

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**050803Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**  
*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use*

NDA NUMBER

(b) (4)

NAME OF APPLICANT / NDA HOLDER

Connetics Corporation

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

Velac Gel

ACTIVE INGREDIENT(S)

clindamycin phosphate 1%, tretinoin 0.025%

STRENGTH(S)

N/A

DOSAGE FORM

Topical Gel

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

5,690,923

b. Issue Date of Patent

25 NOV 1997

c. Expiration Date of Patent

07 JAN 2013

d. Name of Patent Owner  
Yamanouchi Europe, B.V.

Address (of Patent Owner)

Elisabethhof 19

City/State

2353 EW Leiderdorp, The Netherlands

ZIP Code

Not Applicable

FAX Number (if available)

+31715455820

Telephone Number

+31 655 813150

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Connetics Corporation

Address (of agent or representative named in 1.e.)

3290 West Bayshore Road

City/State

Palo Alto, CA

ZIP Code

94303

FAX Number (if available)

650.843.2802

Telephone Number

650.843.2858

E-Mail Address (if available)

shall@connetics.com

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

- Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No
- 2.6 Does the patent claim only an intermediate?  Yes  No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

- Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No
- 3.2 Does the patent claim only an intermediate?  Yes  No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in manufacture, use, or sale of the drug product.  Yes

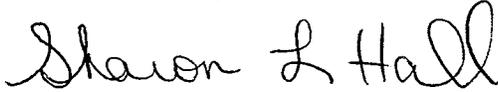
**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed  
28 OCT 2004



**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Sharon L. Hall, Senior Director, Regulatory Affairs

Address

3290 West Bayshore Road

City/State

Palo Alto, CA

ZIP Code

94303

Telephone Number

650.843.2858

FAX Number (if available)

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E-Mail Address (if available)

shall@connetics.com

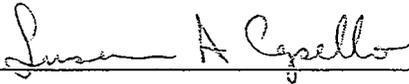
The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

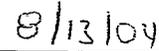
*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

**1.3.1.2 Patent Certifications**

In the opinion and to the best knowledge of Connetics Corporation, there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.



Susan A. Capello  
Vice President  
Intellectual Property



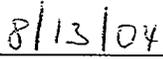
Date

**1.3.1.1 Patent Information**

The undersigned declares that no known patent covers the formulation, composition, and/or method of use of Velac (clindamycin 1% - tretinoin 0.025%) Gel. This product is the subject of this application for which approval is being sought:

  
\_\_\_\_\_

Susan A. Capello  
Vice President  
Intellectual Property

  
\_\_\_\_\_

Date

## EXCLUSIVITY SUMMARY

NDA # 050803

HFD # 540

Trade Name Veltin Gel

Generic Name clindamycin phosphate 1.2%, tretinoin 0.025%

Applicant Name Stiefel Laboratories, Inc.

Approval Date July 16, 2010

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

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  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  NO

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

3 years

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

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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  NO

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

NDA# 050802	Ziana (clindamycin phosphate, tretinoin)
NDA# 050801	Evoclin (clindamycin phosphate)
NDA# 050741	Duac (benzoyl peroxide, clindamycin phosphate)
NDA# 050793	Clindesse (clindamycin phosphate)
NDA# 050782	Clindagel (clindamycin phosphate)
NDA# 050680/050767/050537	Cleocin (clindamycin phosphate)
NDA# 050441	Cleocin Phosphate
NDA# 050639	Cleocin Phosphate in dextrose 5%
NDA# 050600/050615/050537	Cleocin T (clindamycin phosphate)
NDA# 050635	clindamycin phosphate in dextrose 5%
NDA# 050756	Benzaclin (benzoyl peroxide, clindamycin phosphate)
NDA# 050819	Acanya (benzoyl peroxide, clindamycin phosphate)
NDA# 022070	Atralin (tretinoin)
NDA# 020404/020400	Avita (tretinoin)
NDA# 021108/019963	Renova (tretinoin)
NDA# 017955/017579/016921	Retin-A (tretinoin)

NDA# 019049/017522/017340 Retin-A (tretinoin)  
NDA# 020475 Retin-A Micro (tretinoin)  
NDA# 020922 Solage (mequinol, tretinoin)  
NDA# 021112 Tri-luma (fluocinolone acetonide, hydroquinone, tretinoin)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

### **PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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  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 8:

(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

(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

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:

W0265-03, VLC.C.304, VLC.C.305.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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

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"):

W0265-03, VLC.C.304, VLC.C.305.

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: W0265-03

IND # 065369      YES       !  
! NO   
! Explain:

Investigation #2: VLC.C.304

IND # 065369      YES       !  
! NO   
! Explain:  
The previous applicant (Connetics) was identified.  
Transfer of Ownership communication sent 1-5-10.

Investigation #3: VLC.C.305

IND # 065369      YES       !  
! NO   
! Explain:  
The previous applicant (Connetics) was identified.  
Transfer of Ownership communication sent 1-5-10.

(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?

n/a

(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

If yes, explain:

=====

Name of person completing form: Cristina Attinello, M.P.H.  
Title: Regulatory Project Manager, Division of Dermatology and Dental Products  
Date: July 16, 2010

Name of Office/Division Director signing form: Susan J. Walker, M.D., F.A.A.D.  
Title: Director, Division of Dermatology and Dental Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-50803

-----  
ORIG-1

-----  
STIEFEL A GSK CO Veltin

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

CRISTINA Petruccelli Attinello  
07/16/2010

SUSAN J WALKER  
07/16/2010

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 050803 Supplement Number: n/a NDA Supplement Type (e.g. SE5): n/a  
Division Name: Division of Dermatology and Dental Products PDUFA Goal Date: July 16, 2010 Stamp Date: October 16, 2009

Proprietary Name: Veltin

Established/Generic Name: clindamycin phosphate 1.2%, tretinoin 0.025%

Dosage Form: Gel

Applicant/Sponsor: Stiefel, a GSK company

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** topical treatment of acne vulgaris

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
  - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):  
*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

Reason (see below for further detail):

		minimum	Maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit*	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver **(check reason corresponding to the category checked above, and attach a brief justification)**:

**#** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

**1.3.1.3 Debarment Certification**

**Clinical**

Connetics Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Signed by: A. Yarmyly  
Title: VP, Clinical Operations & Biostatistics  
Date: August 19, 2004

**Nonclinical**

Connetics Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Signed by: Kretchen Ansell  
Title: Coordinator, Contract Toxicology  
Date: Aug 19, 2004

**Quality**

Connetics Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Signed by: [Signature]  
Title: VP Quality  
Date: 8/20/04

**Attinello, Cristina**

---

**From:** Greeley, George  
**Sent:** Wednesday, July 14, 2010 3:53 PM  
**To:** Attinello, Cristina  
Stowe, Ginneh D.  
**Subject:** NDA 50-803 Veltin  
**Importance:** High

Hi Cristina,

The Veltin (clindamycin 1%, tretinoin 0.025%) full waiver was scheduled for review by the PeRC PREA Subcommittee on February 24, 2010.

The PeRC has found that the product does not trigger PREA and will not require a review prior to approval. The product is the pharmaceutical equivalent of an already approved product for the same indication and dosage form.

Thank you.

George Greeley  
Regulatory Health Project Manager  
Pediatric and Maternal Health Staff  
FDA/CDER/OND  
7903 New Hampshire Avenue  
Bldg. 22, Room 6467  
Silver Spring, MD 20993-0002  
Phone: 301.796.4025  
Email: [george.greeley@fda.hhs.gov](mailto:george.greeley@fda.hhs.gov)

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**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** Tuesday, March 9, 2010  
**TIME:** 1:00 PM to 2:00 PM EST  
**APPLICATION:** NDA 50-803  
**DRUG NAME:** Veltin (clindamycin and tretinoin) Gel, 1.2%/0.025%  
**SPONSOR:** Stiefel Laboratories, Inc., Research Triangle Park, NC  
Contact: Susanne Wilhelm, Assoc. Dir. Reg. Affairs, Ph: (919) 990-6104  
**TYPE OF MEETING:** Teleconference  
**PHONE NUMBER CALLED:** Call-in number provided by Steifel Laboratories, Inc.

**FDA PARTICIPANTS:**

Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment (ONDQA)  
Jeannie David, M.S., Regulatory Project Manager, ONDQA  
Margo Owens, Project Management Team Leader, Division of Dermatology and Dental Products (DDDP)  
Cristina Attinello, MPH, Regulatory Project Manager, DDDP

**EXTERNAL PARTICIPANTS:**

Stiefel Laboratories, Inc.

**BACKGROUND:**

Per request of Stiefel Laboratories, Inc. (Stiefel), this is a continuation of the discussion from the March 5, 2010, teleconference.

In preparation for this follow-up teleconference, Stiefel sent an email communication to the Agency on March 8, 2010, to address several of the points raised during the March 5, 2010, teleconference. A copy of the email is appended to these minutes.

**POINTS DISCUSSED:**

1. Stiefel asked if the information provided in the March 8, 2010, email helped to clarify the issues raised during the March 5, 2010, teleconference. FDA responded that the key issue regarding the source of opacity has still not been resolved.
2. Regarding the Veltin samples provided prior to the March 5, 2010, teleconference and the samples requested, Stiefel stated that the Veltin samples provided prior to the March 5, 2010, teleconference were representative (b) (4) of apparent viscosity. Stiefel confirmed that the Veltin samples provided were pulled from long-term stability chambers at 25°C, 60% RH (March 5, 2010, minutes: Points Discussed item 6., Action Item 2.). FDA requested a sample that is representative of the commercial product.
3. Regarding Veltin samples requested during the March 5, 2010, teleconference, Stiefel stated that they are in the process of putting the following samples together:
  - Samples from an approx. 7-month old lot, placed under accelerated stability and long-term stability.
  - Clinical trial material of Veltin gel and Velac product, both approx. 40 months old. This age is longer than the proposed shelf-life.
  - Clinical trial material of vehicle for Veltin gel, approximately 29 months old.

- FDA requested that Steifel clearly state whether the samples are commercial product or clinical trial material, and that each sample come with a Certificate of Analysis.
  - Steifel informed the Agency that the clinical trial material had been placed in long-term stability chambers.
  - Steifel is targeting to have the samples received by the Agency by either Friday, March 12 or Monday, March 15, 2010.
4. Steifel stated that they believe they met the definition for gel, as described in the Data Standards Manual. FDA responded that the product did meet the description for gel, but also for cream. The Agency further explained that having these teleconferences is the Agency's effort to obtain information so that a decision can be made regarding the dosage form. Steifel acknowledged that the FDA will make the ultimate decision on dosage form.
  5. FDA continued the discussion on what would be possible causes of turbidity/opacity, and suggested that the following information would be helpful: when the opacity develops and the nature of the opacity (i.e. the physical state of the internal phase) (b) (4)  
[REDACTED]
  6. Steifel described their QC appearance test to designate (b) (4) FDA requested that Steifel submit the information in an amendment.
  7. Steifel agreed that (b) (4) is not an accurate descriptor. However, they re-iterated that they had not observed any (b) (4), and that the proposed product had been very stable.

The call ended.

**ACTION ITEMS FOR SPONSOR:**

1. Provide the samples requested in the March 5, 2010, teleconference with Certificates of Analysis.
2. Submit in an amendment the analytical procedure of the QC appearance test for batch release and stability samples.

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

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/s/

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JEANNIE C DAVID  
06/07/2010

SHULIN DING  
06/07/2010



**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** Friday, March 5, 2010  
**TIME:** 12:15 PM to 1:00 PM EST  
**APPLICATION:** NDA 50-803  
**DRUG NAME:** Veltin (clindamycin and tretinoin) Gel, 1.2%/0.025%  
**SPONSOR:** Stiefel Laboratories, Inc., Research Triangle Park, NC  
Contact: Susanne Wilhelm, Assoc. Dir. Reg. Affairs, Ph: (919) 990-6104  
**TYPE OF MEETING:** Teleconference  
**PHONE NUMBER CALLED:** Call-in number provided by Stiefel Laboratories, Inc.

**FDA PARTICIPANTS:**

Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment (ONDQA)  
Jeannie David, M.S., Regulatory Project Manager, ONDQA  
Margo Owens, Project Management Team Leader, Division of Dermatology and Dental Products (DDDP)  
Jill Merrill, Ph.D., Pharmacology/Toxicology Reviewer, DDDP

**EXTERNAL PARTICIPANTS:**

Stiefel Laboratories, Inc.

**BACKGROUND:**

On October 15, 2009, Stiefel Laboratories, Inc. provided a resubmission of NDA 50-803 for Veltin (clindamycin/tretinoin) Gel, 1.2%/0.025% for the topical treatment of acne vulgaris to the Division of Dermatology and Dental Products. This was acknowledged by the Division on November 20, 2009, as a complete, class 2 response to the Division's June 10, 2005 action letter.

In reviewing the chemistry, manufacturing and controls (CMC) sections of the NDA resubmission, Dr. Shulin Ding noted the discrepancy in appearance between the description given in the NDA and the samples received, and requested to hold a teleconference with Steifel Laboratories, Inc.

The purpose of the March 5, 2010, teleconference was to discuss the appearance and dosage form of the proposed drug product.

**POINTS DISCUSSED:**

1. FDA acknowledged the receipt of Veltin final drug product samples provided by Stiefel Laboratories, Inc (Stiefel) in the Feb. 12, 2010 amendment.

2. FDA inquired on [REDACTED] (b) (4)  
[REDACTED] (b) (4)

3. FDA inquired on the appearance of [REDACTED] (b) (4)  
[REDACTED]

4. The FDA indicated that the Veltin final drug product samples received was considered to be "opaque" in appearance, and inquired what might cause the [REDACTED] (b) (4) turbidity of the gel, and how different might

be in turbidity between the samples received by the Agency and the Phase 3 clinical supplies. (Note: Phase 3 clinical supplies were described as ‘(b) (4)’ in the NDA.) Stiefel responded that the samples and Phase 3 supplies were look-alike in turbidity, and that they had not observed any change in gel appearance in the stability studies including the accelerated temperature stability samples. They believed that the subjectivity of an individual was the reason attributed to the use of different descriptors for the same appearance. Stiefel further indicated that they would not mind changing the descriptor from (b) (4) upon the request the Agency.

(b) (4)

5. FDA explained how ‘opacity’ can impact dosage form designation. FDA stated that opacity could be produced by suspended solid particles or dispersed liquid droplets. If opacity is due to the former, the dosage form could be “gel” for a semisolid. If due to the latter, the dosage form could be “cream” for a semisolid. The Agency agreed that Veltin samples received indicated that they were semisolid. Stiefel replied that it was unclear as to the possible causes for turbidity/opacity, but due to the controls mentioned above, Stiefel was confident (b) (4). The Agency recommends Stiefel to submit more information to assist in dosage form determination.
6. FDA inquired on the source of the Veltin samples provided to the Agency. Stiefel indicated that the (b) (4) (b) (4) Veltin samples may have been from 25°C long-term stability studies conducted to assess for weight loss, and the (b) (4) Veltin samples may have been retrieved from the warehouse. They will confirm and notify the Agency.
7. FDA inquired on the appearance of the vehicle for Veltin gel. Stiefel responded that it was similar in turbidity to the active Veltin gel except for color.
8. FDA inquired on Velac gel and the vehicle for Velac gel:
  - Stiefel stated the appearance of Velac gel was similar to Veltin gel: (b) (4)
  - Stiefel stated the appearance of the vehicle for Velac gel was similar to that of Veltin gel’s vehicle.
  - Stiefel indicated that samples of Velac gel were no longer available.
  - Stiefel will check if samples of vehicle for Velac gel are still available.
9. FDA requested more samples in order to continue the review, and Stiefel agreed to provide:
  - Fresh sample of Veltin gel
  - Six-month, 40°C sample of Veltin gel
  - A representative sample of Veltin gel at (b) (4)
  - Sample of vehicle for Veltin gel
  - Sample of Velac gel
  - Sample of vehicle for Velac gel
10. FDA inquired on the pivotal clinical trial material for Veltin gel:
  - FDA requested that Stiefel provide the age of the clinical material at the time the studies began, and at the time the studies were completed.
  - FDA further requested that Stiefel submit a statement regarding whether the appearance of the clinical trial material remained the same throughout the course of the clinical studies, and if the appearance of the materials were similar to the Veltin samples already provided to the Agency.

11. Stiefel requested to continue these discussions in a follow-up teleconference early the following week, and the Agency concurred (see next page for additional teleconference minutes).

The call ended.

**ACTION ITEMS FOR SPONSOR:**

1. Provide details on the in-process (b) (4) method and how samples are prepared.
2. Confirm from where each of the Veltin samples provided to the Agency was retrieved.
3. Provide the samples listed in Point 9.
4. Provide the ages of the Veltin gel pivotal clinical trial materials at the time the clinical studies began, and at the time the clinical studies were completed.
5. Submit a statement regarding whether the appearance of the Veltin gel pivotal clinical trial materials remained the same throughout the course of the clinical studies, and if the appearance of the materials were similar to the Veltin samples already provided to the Agency.

Application  
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NDA-50803

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/s/  
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JEANNIE C DAVID

06/02/2010

SHULIN DING

06/04/2010



NDA 050803

**INFORMATION REQUEST**

Stiefel, a GSK company  
Attention: Susanne Wilhelm, M.S., R.A.C.  
Associate Director, Regulatory Affairs  
20 TW Alexander Drive  
Research Triangle Park, NC 27709

Dear Ms. Wilhelm:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Veltin (clindamycin phosphate, tretinoin) Gel, 1.2%/0.025%.

We also refer to your May 3 and May 4, 2010 submissions, containing a quality response to our information request.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comment and information request:

1. Your proposed approach to a qualitative method for the verification of the opacity of the product is acceptable, provided that an appropriate reference standard is selected to serve as the opacity lower limit. Amend all relevant sections of the NDA by May 19, 2010 with the addition of this qualitative opacity specification and its method. The method should include a photograph showing reference standards with various degrees of opacity and a representative drug product sample.

If you have any questions, call Cristina Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, M.D., F.A.A.D.  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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SUSAN J WALKER

05/14/2010

**David, Jeannie C**

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**From:** Susanne R Wilhelm [swilhelm@stiefel.com]  
**Sent:** Tuesday, May 04, 2010 4:21 PM  
**To:** Attinello, Cristina  
**Cc:** David, Jeannie C; Owens, Margo  
**Subject:** RE: NDA 50-803 Information Request CMC 23APR10 - Request for Clarification

**Importance:** High

Cristina,

Please see our response regarding the proposed qualitative method to verify the opacity of Veltin Gel below. Please advise if this approach is acceptable to the Agency.

"Stiefel proposes a qualitative test to verify the opacity of the product that would be based on Chapter 2.2.1 of the European Pharmacopoeia (EP): Clarity and Degree of Opalescence of Liquids, Visual Method.

We propose an adaptation of this method that would employ prepared turbidity reference standards consistent with those described in the EP method or commercially available turbidity standards. As with the compendial method, the Veltin method would include a visual comparison of the test sample to reference standard(s) observed under controlled conditions. Opacity is verified when the opalescence of the test sample is greater than or equal to a specified reference standard."

Thank you.

Sincerely,

Susanne Wilhelm, MS, RAC  
Assoc. Director, Regulatory Affairs  
Stiefel, a GSK company  
Tel: (919) 990.6104  
Fax: (919) 990.6001  
swilhelm@stiefel.com

20 TW Alexander Drive  
Research Triangle Park, NC 27709 USA

<http://www.stiefel.com>

"Attinello, Cristina" <Cristina.Attinello@fda.hhs.gov>  
Tue 04 May 2010 10:48 AM

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To

"Susanne R Wilhelm" <swilhelm@stiefel.com>

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Susanne,

Per your below request for clarification to Question 1, please see the below:

I am open to the idea of a "qualitative test to verify the opacity of this product" if you can quickly let me know via e-mail what in general the

method would look like and if the method would employee turbidity standards such as EP's standards.

Please let me know if you have any questions.

Thank you,

Cristina

-----Original Message-----

From: Susanne R Wilhelm [mailto:swilhelm@stiefel.com]

Sent: Thursday, April 29, 2010 4:47 PM

To: David, Jeannie C

Cc: Attinello, Cristina

Subject: NDA 50-803 Information Request CMC 23APR10 - Request for Clarification

Importance: High

Dear Jeannie,

As indicated in yesterday's email, please see Stiefel's request for clarification regarding question 1 of the Agency's information request attached.

Please let me know if you have any questions. Also, could either you or Cristina please confirm receipt of the electronic response document and attachments that I sent yesterday?

Thanks for your assistance.

(See attached file:

1111-qual-info-amendment-req-clarification-info-req-23APR10.pdf)

Regards,

Susanne Wilhelm, MS, RAC  
Assoc. Director, Regulatory Affairs  
Stiefel, a GSK company  
Tel: (919) 990.6104  
Fax: (919) 990.6001  
swilhelm@stiefel.com

20 TW Alexander Drive  
Research Triangle Park, NC 27709 USA

<http://www.stiefel.com>

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-50803

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STIEFEL A GSK CO Veltin

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/s/  
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JEANNIE C DAVID

05/11/2010

**505(b)(2) ASSESSMENT**

<b>Application Information</b>		
NDA # 050803	NDA Supplement #: S- n/a	Efficacy Supplement Type SE- n/a
Proprietary Name: Veltin Established/Proper Name: clindamycin phosphate 1.2%, tretinoin 0.025% Dosage Form: Gel Strengths: N/A		
Applicant: Stiefel, a GSK company		
Date of Receipt: October 16, 2009		
PDUFA Goal Date: July 16, 2010	Action Goal Date (if different):	
Proposed Indication(s): topical treatment of acne vulgaris		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published Literature	Fertility and peri-/postnatal development Carcinogenicity

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The sponsor relied upon appropriate literature data to provide nonclinical data needed for approval of the drug product which contains two active ingredients (i.e., tretinoin and clindamycin). The use of this literature data was scientifically relevant and provided genetic toxicology data, reproductive toxicology data and carcinogenicity data for tretinoin and reproductive toxicity data for clindamycin. The published literature referenced did not refer to an approved drug product and provided appropriate nonclinical data for each active ingredient in the drug product.

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

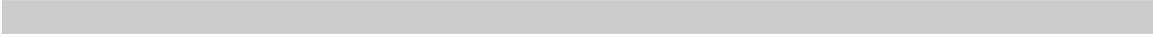
YES  NO

*If “NO”, proceed to question #5.*

*If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO



**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.  
If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

**(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).**

**Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES  NO

If "NO" to (a) proceed to question #11.  
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

NDA 050802 Ziana is a pharmaceutical equivalent and it was approved 11/7/2006, i.e., after this original NDA was submitted.

If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s): NDA 050802 Ziana (clindamycin phosphate 1.2% and tretinoin 0.025%) Gel.

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

**PATENT CERTIFICATION/STATEMENTS**

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

\*\*A Paragraph IV certification was submitted by the sponsor in their original submission; however, we believe this was done in error. In the resubmission received October 16, 2009, the sponsor noted that the above was not applicable and referred back to their original submission.\*\*

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification*

was submitted, proceed to question #15.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

**\*\*A Paragraph IV certification was submitted by the sponsor in their original submission; however, we believe this was done in error. In the resubmission received October 16, 2009, the sponsor noted that the above was not applicable and referred back to their original submission.\*\***

(a) Patent number(s): 5690923

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *n/a*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-50803

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ORIG-1

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STIEFEL A GSK CO Veltin

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/s/  
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CRISTINA Petruccelli Attinello

04/30/2010



NDA 50,803

**INFORMATION REQUEST**

Stiefel, a GSK company  
Attention: Susanne Wilhelm, M.S., R.A.C.  
Associate Director, Regulatory Affairs  
20 TW Alexander Drive  
Research Triangle Park, NC 27709

Dear Ms. Wilhelm:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Veltin (clindamycin, tretinoin) Gel, 1%/0.025%.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Regarding drug product specification, change the acceptance criterion of the test on Appearance [REDACTED] (b) (4) and add a quantitative test on turbidity with an appropriate numeric acceptance criterion.

(b) (4)

4. Your request of categorical exclusion for Environmental Assessment is acceptable. However, you should cite 21 CFR 25.31(b) as the basis. Amend Section 1.12.14 by citing 21 CFR 25.31(b) as the basis.
5. The stress studies (freeze/thaw and cold/warm cycling,) described in Module 3 Section 8 show all samples remain stable and meet the proposed drug product specification at the end of the studies. However, the freezing study reported in Pharmaceutical Development section (3.2.P.2.2.1.7, Table 14) shows [REDACTED] (b) (4)  
[REDACTED] Add a statement of “avoid freezing” or “protect from freezing” to label/labeling. Alternatively, explain what may cause the difference in the results of freeze/thaw studies and provide a strong justification to support the exclusion of “protect from freezing” statement.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality

Assessment (Jeannie.David@fda.hhs.gov), and Cristina Attinello, Regulatory Project Manager the Office of New Drugs (Cristina.Attinello@fda.hhs.gov).

If you have any questions regarding this letter, call Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

*{See appended electronic signature page}*

Moo-Jhong Rhee, Ph.D.  
Chief, Branch III  
Division of Pre-Marketing Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
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Submitter Name

Product Name

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NDA-50803

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ORIG-1

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/s/  
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MOO JHONG RHEE

04/23/2010

Chief, Branch III



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 050803

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Stiefel, a GSK company  
Attention: Susanne Wilhelm, M.S., R.A.C.  
Associate Director, Regulatory Affairs  
20 TW Alexander Drive  
Research Triangle Park, NC 27709

Dear Ms. Wilhelm:

Please refer to your October 15, 2009 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Veltin (clindamycin, tretinoin) Gel, 1%, 0.025%.

On March 19, 2010, we received your March 18, 2010 solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 16, 2010.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 23, 2010.

If you have any questions, call Cristina Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

*{See appended electronic signature page}*

Barbara Gould, M.B.A.H.C.M.  
Chief, Project Management Staff  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Application  
Type/Number

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NDA-50803

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/s/  
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BARBARA J GOULD

03/30/2010

## MEMORANDUM OF TELECONFERENCE

**MEETING DATE:** March 2, 2010  
**TIME:** 1:30 PM  
**LOCATION:** Teleconference  
**APPLICATION:** NDA 050803  
**DRUG NAME:** Veltin Gel

**MEETING CHAIR:** David Kettl

**MEETING RECORDER:** Cristina Attinello

### **FDA ATTENDEES:**

David Kettl, MD, Clinical Team Leader, DDDP  
Gary Chiang, MD, MPH, Clinical Reviewer, DDDP  
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III  
Mat Soukup, PhD, Biostatistics Reviewer, DB III  
Margo Owens, Project Management Team Leader, DDDP  
Cristina Attinello, MPH, Regulatory Project Manager, DDDP

### **SPONSOR ATTENDEES:**

Gavin Corcoran, MD, FACP, Senior Vice President, Stiefel  
Tom Brundage, MS, Global Director, Biometry, Stiefel  
David Angulo, MD, Executive Director, Global Clinical Research, Stiefel  
Beth Zib, BS, Director, Clinical Operations, Stiefel  
Aaron Potts, BA, Associate Director, Clinical Operations, Stiefel  
Devon Allen, MS, RAC, Senior Director, Regulatory Affairs, Stiefel  
Salisa Hauptmann, MPH, RAC, Vice President, Global Regulatory Affairs, Stiefel  
Susanne Wilhelm, MS, RAC, Associate Director, Regulatory Affairs, Stiefel  
Sharon Daly, BSc, CChem, MRSC, Director, Global Portfolio Planning & Management, Stiefel

### **BACKGROUND:**

The Agency requested on January 14, 2010 that the sponsor submit an analysis data set which included data from all Phase 3 trials, namely Studies VLC.C.304, VLC.C.305, and W0265-03. Additionally, the Agency asked the sponsor to provide an analysis data set that included one record per subject per visit per analysis visit type (note that such a structure would thereby include imputation of missing data).

The sponsor submitted an analysis data set (ADSE.XPT) on January 21, 2010; however, this data set does not include one record per subject per visit, nor does it include imputed values of the co-primary endpoints from which the primary efficacy evaluation is based.

The Agency requested this teleconference to provide further clarification of the January 14, 2010 request as the analysis data set for the ISE submitted by the sponsor on January 21, 2010 did not conform to the Agency's request.

## **DISCUSSION POINTS:**

- The Agency reminded the sponsor of the January 14, 2010 Information Request and of their subsequent response on January 21, 2010.
- The Agency explained that the data set corresponding to all Phase 3 trials submitted on January 21, 2010 required restructuring and imputations of all missing data by the Agency statistical reviewer. Based on the restructured data and using LOCF imputation on the ITT population as specified in the protocol, the reviewer was not able to reproduce the lesion count efficacy results as listed in the Study Report.
- In the discussion about the analysis of lesion counts for Study W0265-03, the sponsor stated that subjects with no scheduled post-baseline visits were not included in their reporting of the ITT/LOCF efficacy results. The Agency stated that typically the ITT population consists of all subjects randomized and dispensed medication regardless of whether or not a subject had a post-baseline visit or not. Under this scenario, those subjects with no scheduled post-baseline visits would have their baseline count carried forward when imputing the missing visit data using LOCF.

Addendum: The protocols for Studies VLC.C.304 and VLC.C.305 defined the ITT population as all subjects randomized to a treatment arm. The protocol definition of the ITT population for Study W0265-03 was all subjects randomized and dispensed study product.

- The Agency emphasized that the analysis should be based upon protocol defined methods. Further, the analysis population definitions and imputations approaches should be consistent for all Phase 3 trials to allow exploration of the consistency in efficacy findings for all Phase 3 studies.
- The Agency asked the sponsor if the same approach of excluding subjects with no post-baseline visits for the ITT population for Study W0265-03 was used in Studies VLC.C.304 and VLC.C.305. The sponsor stated they believed this was the case.
- The Agency further clarified their original Information Request, specifying that:
  - The sponsor provide an efficacy data set for all Phase 3 trials which includes one record per subject per visit. As each Phase 3 trial has five planned visits, this data set should contain at least five records per subject (note that the sponsor should also address visits that occurred outside the visit window and how these are treated in the analysis data set).
  - This data set should contain variables for both the raw variable (i.e. include missing values) as well as variables that incorporate imputed values (e.g. LOCF).
  - The sponsor use an imputation approach (e.g. LOCF) which utilizes information for subjects with no post-baseline data; ideally this should correspond to protocol defined methods which were in agreement with the Agency. Alternate imputation approaches may be provided as additional variables in the data set.
  - The sponsor submit a thorough Define file so the Agency can easily understand the content of the electronic data base.

- The sponsor ensure efficacy results based on the revised data set(s) to be submitted are consistent with the efficacy results provided in the Study Reports for all Phase 3 studies.
- The sponsor requested clarification on the February 18, 2010 Information Request regarding bioavailability study W0265-02. The Agency explained that we requested an explanation of why the exposure of clindamycin and its metabolites was higher from the reformulated Veltin Gel than that reported with the original formulation. Additionally, an assessment of how this difference in bioavailability would impact the safety assessments for Veltin Gel compared to the originally submitted formulation should be provided. The Agency reiterated their original request, which has a due date of March 10, 2010.

**ACTION ITEMS:**

The sponsor agreed to submit the data sets, as requested, by March 17, 2010.

Addendum: The sponsor submitted a Desk Copy of the data sets on March 17, 2010.

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

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/s/

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CRISTINA Petruccelli Attinello

03/18/2010

Veltin Memo of T-con for your signature. I added an addendum, stating that the data sets were received 3-17-10. Thanks!

DAVID L KETTL

03/18/2010



NDA 050803

**INFORMATION REQUEST**

Stiefel, a GSK company  
Attention: Susanne Wilhelm, M.S., R.A.C.  
Associate Director, Regulatory Affairs  
20 TW Alexander Drive  
Research Triangle Park, NC 27709

Dear Ms. Wilhelm:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Veltin (clindamycin, tretinoin) Gel, 1%, 0.025%.

We also refer to your October 16, 2009 submission, containing your complete response to the June 10, 2005 Not Approvable letter.

We are reviewing the labeling section of your submission and have the following comments and information requests. We request a prompt written response by Friday, March 12, 2010 in order to continue our evaluation of your NDA.

1. Provide the complete reference and a copy of the journal article describing the lack of teratogenicity of clindamycin at 250 mg/kg after subcutaneous injection in rats and mice.
2. Provide a proper chemical structure in the labeling for clindamycin phosphate. The one provided in the current version of labeling is not appropriate because it does not show bond orientation for all chemical bonds.
3. The established name of the drug substance should be clindamycin phosphate instead of clindamycin. The drug strength for clindamycin phosphate should, therefore, be 1.2% rather than 1%.
4. The two drug strengths should not be inside of the parenthesis which contains the drug substance established names. The two drug strengths should be placed outside of the parenthesis after the dosage form and a comma, and separated by a backslash, i.e., Trade name (clindamycin phosphate and tretinoin) dosage form, 1.2%/0.025%.

If you have any questions, call Cristina Petrucelli Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

*{See appended electronic signature page}*

Margo Owens  
Team Leader, Project Management Staff  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Application  
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NDA-50803

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/s/  
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MARGO L OWENS

03/04/2010

## David, Jeannie C

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**From:** Susanne R Wilhelm [swilhelm@stiefel.com]  
**Sent:** Thursday, March 04, 2010 4:46 PM  
**To:** David, Jeannie C  
**Cc:** Attinello, Cristina; Owens, Margo  
**Subject:** Re: Request for teleconference to discuss CMC

**Importance:** High

Ms. David,

Thank you for your email. This is to confirm the phone call for tomorrow as scheduled in your message below.

Please use the following phone number and passcode to dial in:

Toll Free Dial-In Number (US/CAN):  
(888) 637-4753

Participant Code: 1276 1046 45

We look forward to our discussion tomorrow. Please let me know if you need anything else from our end for this phone call.

Sincerely,

Susanne Wilhelm, MS, RAC  
Assoc. Director, Regulatory Affairs  
Stiefel, a GSK company  
Tel: (919) 990.6104  
Fax: (919) 990.6001  
swilhelm@stiefel.com

20 TW Alexander Drive  
Research Triangle Park, NC 27709 USA

<http://www.stiefel.com>

"David, Jeannie C" <Jeannie.David@fda.hhs.gov>  
Thu 04 Mar 2010 11:46 AM

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Dear Ms. Wilhelm:

Reference is made to NDA 50-803 and our telephone conversations from earlier today.

I would like to confirm that we request to hold a teleconference with your Chemistry, Manufacturing and Controls team to discuss the formulation and dosage form for Veltin Gel (clindamycin 1% - tretinoin 0.025%). Below is the proposed time we had discussed over the phone:

Requested date: Friday, March 5, 2010  
Requested time: 12:15 PM - 1:00 PM EST

Please provide an alternate date/time if the suggested time above does not work for your team. It would be appreciated if you can provide a call-in number for our teleconference.

Thank you, I look forward to our call.

Best regards,

Jeannie

Jeannie David, M.S.  
Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of New Drug Quality Assessment  
10903 New Hampshire Avenue  
Building 22, Mail Room 1491  
Silver Spring, MD 20993  
Phone: (301) 796-4247  
Fax: (301) 796-9877

[jeannie.david@fda.hhs.gov](mailto:jeannie.david@fda.hhs.gov)

Application  
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Submission  
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Submitter Name

Product Name

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NDA-50803

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ORIG-1

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STIEFEL A GSK CO Veltin

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/s/  
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JEANNIE C DAVID

03/04/2010



NDA 050803

**INFORMATION REQUEST**

Stiefel, a GSK company  
Attention: Susanne Wilhelm, M.S., R.A.C.  
Associate Director, Regulatory Affairs  
20 TW Alexander Drive  
Research Triangle Park, NC 27709

Dear Ms. Wilhelm:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Veltin (clindamycin, tretinoin) Gel, 1%, 0.025%.

We also refer to your October 16, 2009 submission, containing your complete response to the June 10, 2005 Not Approvable letter.

We are reviewing the Clinical/Biostatistics section of your submission and have the following comments and information requests. We request a prompt written response by Wednesday, March 10, 2010 in order to continue our evaluation of your NDA.

- In the review of your bioavailability study (W0265-02), it is noted that the confidence intervals of AUC and Cmax for clindamycin and clindamycin sulfoxide are well outside the 80%-125% range. Your reformulated Veltin Gel BA parameters range between 90%-295%, or more than twice the exposure of the original formulation (Velac Gel). Provide a rationale for the higher exposure levels observed in this study and its impact on the systemic and local safety of your combination product.
- The increased bioavailability of clindamycin and its metabolites in Veltin Gel impacts the ability to rely on the previously conducted trials with Velac Gel to support safety assessments for your reformulated product. Address the impact, particularly on systemic safety, of the increased clindamycin exposure from the reformulated Veltin product. Provide a safety analysis comparing the previously conducted clinical trials (VLC.C.304 and VLC.C.305) to the newly conducted Phase 3 clinical trial for Veltin Gel (W0265-03). Include all safety profiles from the clindamycin arms, specifically analyzing systemic safety assessments across all trials.

If you have any questions, call Cristina Petrucelli Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

*{See appended electronic signature page}*

Margo Owens  
Team Leader, Project Management Staff  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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MARGO L OWENS

02/18/2010



NDA 050803

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Stiefel, a GSK Company  
20 TW Alexander Drive  
Research Triangle Park, NC 27709

ATTENTION: Susanne Wilhelm, M.S., R.A.C.  
Associate Director, Regulatory Affairs

Dear Ms. Wilhelm:

Please refer to your New Drug Application (NDA) resubmission dated October 15, 2009, received October 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clindamycin and Tretinoin Topical Gel 1% /0.025%.

We also refer to your November 6, 2009, correspondence, received November 10, 2009, requesting review of your proposed proprietary name, Veltin. We have completed our review of the proposed proprietary name, Veltin, and have concluded that it is acceptable.

We consider this a final review; however, if approval of the NDA is delayed beyond April 16, 2010 the proposed proprietary name, Veltin must be re-evaluated.

If **any** of the proposed product characteristics as stated in your November 6, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-0675. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Cristina Petrucci Attinello at 301-796-3986.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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

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DENISE P TOYER on behalf of CAROL A HOLQUIST  
02/05/2010



NDA 050803

**INFORMATION REQUEST**

Stiefel, a GSK company  
Attention: Susanne Wilhelm, M.S., R.A.C.  
Associate Director, Regulatory Affairs  
20 TW Alexander Drive  
Research Triangle Park, NC 27709

Dear Ms. Wilhelm:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Veltin (clindamycin, tretinoin) Gel, 1%, 0.025%.

We also refer to your October 16, 2009 submission, containing your complete response to the June 10, 2005 Not Approvable letter.

We are reviewing the Clinical/Biostatistics section of your submission and have the following comment and information request. We request a prompt written response by Friday, February 12, 2010 in order to continue our evaluation of your NDA.

The Agency notes that a clinical contact sensitization study with the reformulated Veltin product was not submitted in the NDA application. Provide the results of this study, or provide a waiver request with rationale.

If you have any questions, call Cristina Petruccelli Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

*{See appended electronic signature page}*

Cristina Petruccelli Attinello, MPH  
Regulatory Project Manager  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Application  
Type/Number

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/s/  
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CRISTINA Petruccelli Attinello  
02/04/2010

## **Executive CAC**

**Date of Meeting:** February 2, 2010

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair  
Paul Brown, Ph.D., OND IO, Member  
David Joseph, Ph.D., DGP, Alternate Member  
Barbara Hill, Ph.D., DDDP, Pharm Tox Supervisor  
Jill Merrill, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Jill Merrill

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

**NDA # 50-803**

**Drug Name:** Veltin™ Gel (reformulation of Velac Gel)

**Sponsor:** Stiefel Laboratories Inc.

### **Background**

Velac Gel (1% clindamycin, 0.025% tretinoin) was developed by the sponsor as a dermal treatment for patients with acne vulgaris. The Division of Dermatology and Dental Products previously informed the sponsor that the carcinogenic potential of tretinoin could be supported by the literature, but that it would be necessary to assess the carcinogenic potential of clindamycin in the clinical vehicle. The sponsor then conducted a Tg.AC mouse dermal carcinogenicity study for Velac Gel in which the vehicle alone caused a statistically significant increased incidence of skin papillomas compared to the untreated control. Clindamycin in the Velac Gel vehicle caused a further increase in papillomas. These findings formed the basis of a nonapprovable letter for the associated NDA (50-803). The sponsor subsequently modified the vehicle by (b) (4) polyoxyethylene 4 monolaurate ether. The present study (NPB00012) evaluates the carcinogenicity of the clinical concentration of clindamycin only in the reformulated vehicle.

### **Mouse Carcinogenicity Study**

This study was designed to assess the carcinogenic potential of clindamycin with daily application to the skin of CD-1 mice for up to 104 weeks. The study groups (60 mice/sex/group) included the following: a sham treatment group; the clinical vehicle group (denoted CTG - clindamycin tretinoin gel without either clindamycin or tretinoin); 1% clindamycin in CTG vehicle (32 mg/kg/day). Dosing of either sex in the clindamycin-treated group was discontinued if the number of survivors in that sex reached 20 or less. Treatment of other groups continued. Any given treatment group of either sex was terminated and subjected to a complete necropsy if the number of

surviving animals in that group declined to 15. Therefore, dosing was discontinued on Day 645 (Week 93) for clindamycin treated males and on Day 683 (Week 98) for clindamycin treated females. These groups were euthanized during Week 98 and Week 103, respectively.

The only treatment site specific tumors seen in the CTG vehicle-treated group included a benign squamous papilloma and a squamous cell carcinoma in the males and a fibrosarcoma in a female. These tumors were of an incidence and character of those seen spontaneously in control CD-1 mice at the testing facility. No treatment-related tumors were seen in the skin or in other tissue locations among mice treated with 1% clindamycin in CTG vehicle. The other neoplastic findings were considered spontaneous, incidental lesions commonly observed in aging control CD-1 mice of this stock and are not considered test article related.

#### **Executive CAC Recommendations and Conclusions:**

- The Committee agreed that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded that the study was negative for drug related neoplasms.

Abigail Jacobs, Ph.D.  
Acting Chair, Executive CAC

cc:\

/Division File, DDDP  
/B Hill, DDDP  
/JMerrill, DDDP  
/Cattinello, DDDP  
/ASeifried, OND IO

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

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/s/

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ADELE S SEIFRIED  
02/03/2010

ABIGAIL ABBY C C JACOBS  
02/04/2010



NDA 050803

**INFORMATION REQUEST**

Stiefel, a GSK company  
Attention: Susanne Wilhelm, M.S., R.A.C.  
Associate Director, Regulatory Affairs  
20 TW Alexander Drive  
Research Triangle Park, NC 27709

Dear Ms. Wilhelm:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Veltin (clindamycin, tretinoin) Gel, 1%, 0.025%.

We also refer to your October 16, 2009 submission, containing your complete response to the June 10, 2005 Not Approvable letter.

We are reviewing the Clinical/Biostatistics and Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response by Friday, February 12, 2010 in order to continue our evaluation of your NDA.

**Clinical**

Trial W0265-03

1. Submit a subgroup analysis (ITT) for AEs stratified by age, race, and gender.
2. Include a subgroup analysis (ITT) for local tolerability assessments (erythema, dryness, scaling, burning, and itching) stratified for age, race, and gender.

**Chemistry, Manufacturing and Controls**

Drug Substance

1. The test results presented in Table 1 of p. 55 of Module 3 Volume 1 on tretinoin drug substance Lot DPT 05-005183 are inconsistent with the results shown in the DPT certificate of analysis (p. 56 of Module 3 Volume 1). Clarify and correct errors in Table 1.

Drug Product Manufacturing

1. Provide in-process test results for the four registration stability batches.
2. Your response to FDA's comments regarding the immediate use of tretinoin and clindamycin phosphate mixtures in drug product manufacture is inadequate. Provide (b) (4) information from the four registration stability batches for these two mixtures (b) (4) (b) (4) Propose an acceptable limit (b) (4) based on the actual data from the registration batches, and add this limit to the master batch records.

3. The proposed (b) (4) maximum hold time (b) (4) is not supported by the data provided to-date. Provide the actual hold time information from the four registration stability batches, and re-propose an acceptable maximum hold time based on the actual hold time.
4. Provide weight check control limits which are set according to the statistical sampling plan ANSI/ASCC 1.4-1993 per your statement on p. 1 of Section 3.2.P.3.4.

#### Drug Product Specification

1. Add the test on weight loss back to the drug product specification table in Section 3.2.P.5.1 with an appropriate acceptance criterion as requested in the Information Request Letter dated June 28, 2005. You included this test in the drug product specification table in your original NDA. (b) (4)
2. Viscosity tests should be conducted at batch release and on stability with an acceptance criterion (b) (4). The provided justification to support the proposed acceptance criterion (b) (4) is not deemed acceptable.
3. The degradation peak which is from the vehicle (b) (4) (Section 3.2.P.5.3.3.8.1) should be controlled by the drug product specification with an acceptance criterion of (b) (4).
4. Method numbers should be specified for the in-house methods described in the following sections:
  - 1) Drug Product Specification table on p. 1 of Section 3.2.P.5.1.
  - 2) Table 2 Analytical Procedures on p. 1 of Section 3.2.P.5.2.
  - 3) Table 1 Description of Changes to the Validation Information on p. 2 of Section 3.2.P.5.3 for Apparent Viscosity, and the two HPLC methods.
5. Provide a copy of the current version of all in-house HPLC methods referenced in the drug product specification table.

#### Drug Product Post-approval Stability Protocol

1. Add viscosity and weight loss to the protocol.

#### Drug Product Miscellaneous

1. In order for us to evaluate dosage form, provide a representative sample together with another sample whose viscosity is close to the lower limit of the viscosity acceptance criterion.
2. You have assigned (b) (4) the function for propylene glycol in the proposed formulation. The function (b) (4) suggests a medical claim for which no data have been submitted to the NDA. You should assign functions to excipients such as propylene glycol based on their physicochemical properties (b) (4).

If you have any questions, call Cristina Petruccelli Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

*{See appended electronic signature page}*

Cristina Petruccelli Attinello, MPH  
Regulatory Project Manager  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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

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/s/  
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CRISTINA Petruccelli Attinello  
01/26/2010



NDA 050803

**INFORMATION REQUEST**

Stiefel, a GSK company  
Attention: Susanne Wilhelm, M.S., R.A.C.  
Associate Director, Regulatory Affairs  
20 TW Alexander Drive  
Research Triangle Park, NC 27709

Dear Ms. Wilhelm:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Veltin (clindamycin, tretinoin) Gel, 1%, 0.025%.

We also refer to your October 16, 2009 submission, containing your complete response to the June 10, 2005 Not Approvable letter. We acknowledge your response to our Information Request dated November 17, 2009.

Upon review of the Clinical/Biostatistics section of your submission, we have the following comments and information requests. We request a prompt written response by Thursday, January 21, 2010 in order to continue our evaluation of your NDA.

Design and analytical features of Study WO265-03 differ from those of the two Phase 3 trials submitted in the NDA, namely studies VLC.C.304 and VLC.C.305. Specifically, the following items differ between the resubmission and the original submission:

- dichotomization of the IGA endpoint (i.e. definition of success),
- assessment of change in lesion counts (absolute change versus percent change), and
- method of data imputation

Due to the above differences, and others that may arise during the review process, it is important that the evaluation of efficacy is consistent across studies.

As currently submitted, you provide an electronic data base which differs from that provided in the original submission. Differences occur in the names of the data sets, names of the variables, formats of the dates, and controlled terminology for subject level data (e.g. values for race), amongst others. As such, it is difficult to apply consistent analytical procedures to each of the data bases without significant amounts of time managing the data base.

To facilitate sufficient review of your efficacy data base, you are requested to submit an electronic data base in which the data capture is similar for ALL studies. You might consider using the following two alternatives:

1. Map the data base of the original submission to the structure of the current submission.
2. Create a thorough ISE data base.

A clear and thorough define file is required regardless of the approach you choose.

If you have any questions, you are encouraged to contact Cristina Petruccelli Attinello, Regulatory Project Manager, at (301) 796-3986, to arrange a teleconference.

Sincerely,

{ See appended electronic signature page }

Margo Owens  
Team Leader, Project Management Staff  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

As a guideline, the following example and details are meant to provide guidance to you in the creation of efficacy analysis data sets for the Integrated Summary of Efficacy (ISE). For further details and information about analysis data sets, you are encouraged to consult the following link on the CDISC Analysis Data Model (ADaM); current version 2.0:

<http://www.cdisc.org/models/adam/V2.0/index.html>

While the below example is not all inclusive, the key concept is that FDA reviewers should have access to analysis data sets which provide clear and unambiguous details about the content of all the clinical trials included in the ISE. Note that you should provide a similar table (i.e. Define file) as that in Table 1 with descriptions of the analysis variables included in the data set(s). The example in Table 1 below is an analysis data set which includes one record per subject per visit per analysis visit type (Observed/Impute1/etc.).

**Table 1. Analysis Variable Descriptions**

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes
USUBJID	Unique Subject Identifier	Numeric/Character		Consistent Subject Identifier across <b>ALL</b> data sets
STUDYID	Study Identifier	Numeric/Character		Studies should be limited to those used in the ISE, namely WO265-03 and VLC.C.304, and VLC.C.305
SITEID	Study Site Identifier	Numeric/Character		
AVISIT	Analysis Visit	Numeric/Character		<ul style="list-style-type: none"> <li>▪ If subject did not attend the visit, <i>do not</i> include a row in the dataset for the <i>observed</i> analysis visit type</li> <li>▪ Can also include character visit with levels corresponding to screening, baseline, etc.</li> <li>▪ When subjects do not attend a visit, a value should be included for imputed analysis visits types.</li> </ul>
AVISFLG*	Analysis visit flag denoting the analysis	Character	Observed, Impute1, etc.	<ul style="list-style-type: none"> <li>• Categorical variable with the number of levels driven by the</li> </ul>

	visit type			number of analysis visit types. <ul style="list-style-type: none"> <li>Imputation approaches should be consistent for all trials</li> </ul>
VISITDT	Date subject attended visit	Numeric		
TRTAN	Actual Treatment Group	Numeric	0 = Vehicle, 1 = Active	<ul style="list-style-type: none"> <li>Choice of numeric values may be altered</li> <li>Character variable may also be submitted.</li> <li>Also possible to include a variable for randomized treatment group</li> </ul>
EFFICACY ENDPOINTS**	Endpoints used to assess efficacy of drug product	Numeric		<ul style="list-style-type: none"> <li>If categorical, include decode</li> <li>If derived, provide algorithm</li> </ul>
PSITEID	Pooled Site Identifier	Numeric/Character		
AGE	Subject age at baseline	Numeric		Also optional to include a variable for age category
SEXN	Sex of subject	Numeric	0 = Female, 1 = Male	
RACEN	Race of Subject	Numeric	Provide Decode	
ITT	ITT analysis flag	Numeric	0 = Not ITT, 1 = Yes ITT	
PP	PP analysis flag	Numeric	0 = Not PP, 1 = Yes PP	
WINDOWFL	Visit within protocol specified window flag	Numeric	0 = Not in Window 1 = Yes in Window	Rather than include as a variable, this could also be used as a level for the analysis visit type.

\* All imputation approaches used in the evaluation of efficacy for any of the Phase 3 trials should be incorporated into the data set for all of the studies included in the ISE.

\*\* The following are the efficacy endpoints requested for your completed Phase 3 trials.

1. Baseline IGA score
2. Baseline total lesion count
3. Baseline inflammatory lesion count
4. Baseline non-inflammatory lesion count

5. IGA Success (definition 1): Week 12 score of “clear” or “almost clear”
6. IGA Success (definition 2): Two grade improvement: baseline to Week 12
7. IGA Success (definition 3): Week 12 score of “clear” or “almost clear” AND a two grade improvement
8. Absolute change in total lesion counts
9. Absolute change in inflammatory lesion counts
10. Absolute change in non-inflammatory lesion counts.
11. Percent change in total lesion counts
12. Percent change in inflammatory lesion counts
13. Percent change in non-inflammatory lesion counts.

Examples of a data set for a study with 3 planned visits and two treatment arms and two efficacy endpoints (note that the notation uses subscripts  $i$  and  $j$  which correspond to the value for the  $i$ -th visit and the  $j$ -th subject). In this example Observed and LOCF visit types were defined. Note that in the following example: Subject 0001 attended all visits, Subject 0002 missed visit 2, and Subject 0003 missed visit 3 and the endpoint X was not collected at visit 2 (‘-‘ denoting missing in this example). As such, the data set based upon this structure excludes rows for subjects who did not attend a visit (i.e. the “Observed” visit type) but a row is included for the visit types that rely on data imputation (“LOCF” in this example).

**Table 2. Example Efficacy Data Set**

USUBJID	SITEID	AVISIT	AVISFLG	VISITDT	TRTAN	EFFICACY ENDPOINTS		PSITEID	AGE	SEXN	RACEN	ITT	PP	WINDOW
0001	1	1	Observed		1	X <sub>11</sub>	Y <sub>11</sub>	88						
0001	1	1	LOCF		1	X <sub>11</sub>	Y <sub>11</sub>	88						
0001	1	2	Observed		1	X <sub>21</sub>	Y <sub>21</sub>	88						
0001	1	2	LOCF		1	X <sub>21</sub>	Y <sub>21</sub>	88						
0001	1	3	Observed		1	X <sub>31</sub>	Y <sub>31</sub>	88						
0001	1	3	LOCF		1	X <sub>31</sub>	Y <sub>31</sub>	88						
0002	2	1	Observed		0	X <sub>12</sub>	Y <sub>12</sub>	88						
0002	2	1	LOCF		0	X <sub>12</sub>	Y <sub>12</sub>	88						
0002	2	2	LOCF		0	X <sub>12</sub>	Y <sub>12</sub>	88						
0002	2	3	Observed		0	X <sub>32</sub>	Y <sub>32</sub>	88						
0002	2	3	LOCF		0	X <sub>32</sub>	Y <sub>32</sub>	88						
0003	1	1	Observed		1	X <sub>13</sub>	Y <sub>13</sub>	88						

0003	1	1	LOCF	1	$X_{13}$	$Y_{13}$	88
0003	1	2	Observed	1	-	$Y_{23}$	88
0003	1	2	LOCF	1	$X_{13}$	$Y_{23}$	88
0003	1	3	LOCF	1	$X_{13}$	$Y_{23}$	88
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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-50803

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ORIG-1

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STIEFEL A GSK CO Veltin

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/s/  
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MARGO L OWENS

01/14/2010



NDA 50-803

**ACKNOWLEDGE TRANSFER NDA OWNERSHIP**

Stiefel Laboratories  
Attention: Susanne Wilhelm, M.S., R.A.C.  
Associate Director, Regulatory Affairs  
20 TW Alexander Drive  
Research Triangle Park, NC 27709

Dear Ms. Wilhelm:

We acknowledge receipt on January 11, 2007, of your January 9, 2007, correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug Product: Veltin (clindamycin 1% - tretinoin 0.025%) Gel

NDA Number: 50-803

Name of New Applicant: Stiefel Laboratories

Name of Previous Applicant: Connetics Corporation

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate Stiefel Laboratories, as the applicant of record for this application.

All changes in the NDA from those described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation except that changes in the drug product's label or labeling to change the product's brand or the name of its manufacturer, packer, or distributor may be reported in the next annual report. Refer to the *Guidance for Industry: Changes to an Approved NDA or ANDA* for information on reporting requirements. We request that you notify your suppliers and contractors who have DMFs referenced by your application of the change in ownership so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Dermatology and Dental Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call me at 301-796-3986.

Sincerely,

*{See appended electronic signature page}*

Cristina Petruccelli Attinello  
Regulatory Health Project Manager  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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

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/s/

CRISTINA Petruccelli Attinello  
01/05/2010

**REQUEST FOR CONSULTATION**

TO (Division/Office):

**Mail: OSE**

FROM:

David Kettl, M.D., ODE III/DDDP, 301-796-2105  
Gary Chiang, M.D., ODE III/DDDP, 301-796-5015  
Cristina Petruccelli Attinello, RPM, 301-796-3986

DATE  
12-16-09

IND NO.

NDA NO.  
050803

TYPE OF DOCUMENT  
NDA resubmission

DATE OF DOCUMENT  
10-16-09

NAME OF DRUG  
Veltin (clindamycin – 1% -  
tretinoin, 0.025%) Gel

PRIORITY CONSIDERATION  
S

CLASSIFICATION OF DRUG  
4

DESIRED COMPLETION DATE  
3-23-10  
(4-16-10 PDUFA date)

NAME OF FIRM:

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input checked="" type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input checked="" type="checkbox"/> PAPER NDA    | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- |  |   |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES      | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW         | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):  |   |

**III. BIOPHARMACEUTICS**

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

**IV. DRUG EXPERIENCE**

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

**V. SCIENTIFIC INVESTIGATIONS**

CLINICAL

PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**

NDA 050803 for Veltin Gel received a Not Approvable action on June 10, 2005. The applicant has reformulated their product and submitted a resubmission which contains a new Phase 3 study. The Division would like to request consultation with OSE regarding this NDA resubmission. The PDUFA goal date is April 16, 2010.

Please contact me if you have questions. Thank you.

SIGNATURE OF REQUESTER  
Cristina Petruccelli Attinello

METHOD OF DELIVERY (Check one)  
 EMAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER



Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-50803

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ORIG-1

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STIEFEL A GSK CO Veltin

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/s/  
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CRISTINA Petruccelli Attinello  
12/16/2009

# REQUEST FOR CONSULTATION

TO (Office/Division): **DDMAC**

FROM (Name, Office/Division, and Phone Number of Requestor):

David Kettl, M.D, ODE III/DDDP, 301-796-2105

Gary Chiang, M.D., ODE III/DDDP, 301-796-5015

Cristina Petruccelli Attinello, RPM, 301-796-3986

DATE  
12-16-09

IND NO.

NDA NO.  
050803

TYPE OF DOCUMENT  
NDA resubmission

DATE OF DOCUMENT  
10-16-09

NAME OF DRUG  
**Veltin (clindamycin – 1% -  
tretinoin, 0.025%) Gel**

PRIORITY CONSIDERATION  
**S**

CLASSIFICATION OF DRUG  
**4**

DESIRED COMPLETION DATE  
**3-23-10**  
(4-16-10 PDUFA date)

NAME OF FIRM: **Stiefel, a GSK company**

## REASON FOR REQUEST

### I. GENERAL

- |  |  |  |
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| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING                | <input checked="" type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input checked="" type="checkbox"/> PAPER NDA    | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

### IV. DRUG SAFETY

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|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
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| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

#### COMMENTS / SPECIAL INSTRUCTIONS:

NDA 050803 for Veltin Gel received a Not Approvable action on June 10, 2005. The applicant has reformulated their product and submitted a resubmission which contains a new Phase 3 study. The Division would like to request consultation with DDMAC regarding this NDA resubmission. Please review the draft package insert and carton and container labels. The PDUFA goal date is April 16, 2010. You will be invited to labeling meetings once scheduled.

Please contact me if you have questions. Thank you.

SIGNATURE OF REQUESTOR  
**Cristina Petruccelli Attinello**

METHOD OF DELIVERY (Check one)  
 DARRTS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER  
**Cristina Petruccelli Attinello**

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-50803

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ORIG-1

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STIEFEL A GSK CO Veltin

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/s/  
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CRISTINA Petruccelli Attinello  
12/16/2009

## REQUEST FOR CONSULTATION

TO (Office/Division): OAP/DAIOP  
Frances LeSane, CPMS  
Maureen Dillon-Parker, CPMS

FROM (Name, Office/Division, and Phone Number of Requestor):  
David Kettl, M.D., ODE III/DDDP, 301-796-2105  
Gary Chiang, M.D., ODE III/DDDP, 301-796-5015  
Cristina Petruccelli Attinello, RPM, 301-796-3986

DATE 11-20-09	IND NO.	NDA NO. 050803	TYPE OF DOCUMENT NDA resubmission	DATE OF DOCUMENT 10-16-09
NAME OF DRUG Veltin (clindamycin, 1% - tretinoin, 0.025%) Gel		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG 4	DESIRED COMPLETION DATE 1-15-10

NAME OF FIRM: Stiefel, a GSK company

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input checked="" type="checkbox"/> PAPER NDA    | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

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|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

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|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

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|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
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| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
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#### COMMENTS / SPECIAL INSTRUCTIONS:

NDA 050803 for Veltin Gel received a Not Approvable action on June 10, 2005. The applicant has reformulated their product and submitted a resubmission which contains a new Phase 3 study. Please review this NDA from a clinical microbiology perspective. The PDUFA goal date is April 16, 2010. Please let us know who will be assigned to review this resubmission so that meeting invitations can be sent. If you have any questions, please contact me or the medical officer, Gary Chiang, M.D., at 6-5015 or the clinical team leader, David Kettl, M.D., at 6-2105. Thank you.

SIGNATURE OF REQUESTOR Cristina Petruccelli Attinello	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER Cristina Petruccelli Attinello

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

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/s/

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CRISTINA Petruccelli Attinello  
11/20/2009

Frances V LESANE  
11/20/2009



NDA 050803

**ACKNOWLEDGE CLASS 2 RESPONSE**

Stiefel, a GSK company  
Attention: Susanne Wilhelm, M.S., R.A.C.  
Associate Director, Regulatory Affairs  
20 TW Alexander Drive  
Research Triangle Park, NC 27709

Dear Ms. Wilhelm:

We acknowledge receipt on October 16, 2009 of your October 15, 2009 resubmission to your new drug application for Veltin (clindamycin, tretinoin) Gel, 1%, 0.025%.

We consider this a complete, class 2 response to our June 10, 2005 action letter. Therefore, the user fee goal date is April 16, 2010.

If you have any questions, call me at (301) 796-3986.

Sincerely,

*{See appended electronic signature page}*

Cristina Petruccelli Attinello, M.P.H.  
Regulatory Project Manager  
Division of Dermatology and Dental  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50803	ORIG-1	CONNETICS CORP	VELAC GEL(CLINDAMYCIN 1%/TRETINOIN 0.025

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/s/

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CRISTINA Petruccelli Attinello  
11/20/2009

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** December 18, 2007                      **Time:** 9:00 A.M.  
**Location:** WO 22 Room 1315                      **Meeting ID:** 23115  
**Topic:** IND 65, 369, Velac (clindamycin, 1% - tretinoin, 0.025%) Gel  
**Subject:** Post-SPA Guidance Meeting  
**Sponsor:** Stiefel Laboratories, Inc.  
**Meeting Chair:** Susan J. Walker, M.D./Division Director, DDDP  
**Meeting Recorder:** Margo Owens/Regulatory Project Manager, DDDP



### FDA Attendees:

Susan J. Walker, M.D./Division Director, DDDP  
Jill Lindstrom, M.D./Team Leader, Clinical, DDDP  
Brenda Carr, M.D./Clinical Reviewer, DDDP  
Paul Brown, Ph.D./Supervisor, Pharmacology, DDDP  
Margo Owens/Regulatory Project Manager, DDDP  
Shulin Ding, Ph.D./Pharmaceutical Assessment Lead, ONDQA  
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII  
Kathleen Fritsch, Ph.D./Biostatistician, DBIII

### Sponsor Attendees:

#### **Stiefel Laboratories, Inc.**

Edward Hsia, Ph.D. Scientis, Research and Preclinical Development  
David Angulo, M.D., Senior Director, Global Clinical Research  
Susanne Wilhelm, M.S., RAC, Associate Director, Regulatory Affairs  
Salisa hauptmann, MPH, RAC, Executive Director, Regulatory Affairs  
John Statler, Senior Director, Technical Operations  
Aaron Potts, Senior Director, Clinical Operations  
Tom Brundage, M.S., Director, Global Biometry  
Aida Cancel, Ph.D., RAC, Project Manager

### **Purpose:**

The sponsor wishes to discuss the Agency's November 17, 2005, responses to your September 30, 2005, request for special protocol assessment for Velac (clindamycin 1% - tretinoin, 0.025%) Gel for the treatment of acne vulgaris. The pre-meeting briefing document (submitted November 30, 2007) provides background and questions for discussion.

**Pharmacology/Toxicology:**

The Agency would like to know the status of your carcinogenicity study?

**Meeting Discussion:**

The sponsor stated that they are about 1 year into the study. The draft report will be ready 6 months after study completion.

**Clinical/Biostatistics:**

As the impact of the (b) (4) on the solubility of tretinoin is unclear, new clinical data are needed to demonstrate that the combination product remains effective and that tretinoin continues to contribute to efficacy. This can be accomplished by either of the following paths:

- a three-arm bridging study evaluating the new product, the old product and the new vehicle with an appropriate non-inferiority margin (to establish maintenance of effect of each active with the current formulation)
- a four-arm study of the construct of the previously-conducted Phase 3 trials (i.e. in accordance with 21 CFR 300.50) in which the new product would be compared to tretinoin in the new vehicle, clindamycin in the new vehicle, and the new vehicle.

The efficacy of clindamycin and tretinoin (either singly or in combination) in marketed products does not speak to the efficacy of these ingredients in the sponsor's combination product. Similarly, the demonstrated efficacy of the previous formulation does not alone speak to the efficacy of the current one. Additionally, the demonstrated contribution to efficacy of each active ingredient with the previous formulation does not speak to the maintenance of effect of each active with the current formulation.

Your submission states that a non-inferiority margin of 17% for a 3-arm bridging study is consistent with retention of Velac's effect over vehicle. However, demonstrating only that CT Gel maintains at least some of the effect that Velac had over its vehicle in the original studies, would not adequately demonstrate that CT Gel remains effective and that tretinoin continues to contribute to efficacy. Using a margin that only provides assurance that the combination product retains some effect over vehicle does not provide any additional information beyond what a direct comparison of the combination product to its vehicle would provide. The non-inferiority comparison is only useful if the margin is sufficiently small such that we can have confidence that Velac and CT Gel are truly 'similar' (and that clindamycin and tretinoin both maintain their effect).

**Meeting Discussion:**

The sponsor noted that with a 7% non-inferiority margin as was recommended in the November 17, 2005 SPA letter, a bridging study would have a large sample size and the other alternative of a four-arm study may be more feasible.

The sponsor and the Agency discussed using absolute change instead of percent change for lesion counts, as well as establishing efficacy using inflammatory and non-inflammatory lesions as was discussed at the November 2002 Advisory Committee meeting. The Agency recommended powering the study sufficiently as only one study will be conducted with the new formulation.

The sponsor indicated that the monads may have differential effects on the different lesion types and their study design may reflect this thinking. The Agency acknowledged the sponsor's point and will await submission of the protocol.

**Additional Administrative Comments:**

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the IND might identify additional comments or information requests.

Minutes Preparer: \_\_\_\_\_  
Margo Owens/Regulatory Project Manager DDDP

Chair Concurrence: \_\_\_\_\_  
Susan J. Walker, M.D./Division Director, DDDP

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Linked Applications

Sponsor Name

Drug Name

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IND 65369

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STIEFEL  
LABORATORIES INC

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VELAC GEL(CLINDAMYCIN  
PHOSPHATE/TRETINOI

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/s/

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SUSAN J WALKER  
01/18/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 50-803

Connetics Corporation  
Attention: Michael S. Eison, Ph.D.  
Vice President, Regulatory Affairs  
3160 Porter Drive  
Palo Alto, CA 94304

Dear Dr. Eison:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME (clindamycin , 1% - tretinoin, 0.025%) Gel.

We also refer to the meeting between representatives of your firm and the FDA on August 17, 2005. The purpose of the meeting was to discuss the requirements for approval of TRADENAME (clindamycin, 1% - tretinoin, 0.025%) Gel in light of the Agency's action letter dated June 10, 2005.

We also refer to your submission dated August 22, 2005, which contained your minutes of the August 17, 2005 Post-Action meeting.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure

## MEMORANDUM OF MEETING MINUTES



**Meeting Date:** August 17, 2005      **Time:** 10:30 A.M.  
**Location:** S200 A      **Meeting ID:** 15787  
**Topic:** NDA 50-803, TRADENAME (clindamycin, 1% - tretinoin, 0.025%) Gel for the treatment of acne vulgaris  
**Subject:** Post-NA Meeting  
**Sponsor:** Connetics Corporation  
**Meeting Chair:** Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540  
**Meeting Recorder:** Margo Owens/Regulatory Management Officer, DDDDP, HFD-540

### **FDA Attendees:**

Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540  
Stanka Kukich, M.D./Deputy Director, DDDDP, HFD-540  
Ramesh Sood, Ph.D./Team Leader, Chemistry, DNDCIII, HFD-830  
Joel S. Hathaway, Ph.D./Chemistry Reviewer, DNDCIII, HFD-830  
Paul Brown, Ph.D./Supervisor, Pharmacology, DDDDP, HFD-540  
Jill Merrill, Ph.D./Pharmacology Reviewer, DDDDP, HFD-540  
Dennis Bashaw, Pharm.D./Team Leader, Pharmacokinetics, DPEIII, HFD-880  
Markham Luke, M.D., Ph.D./Team Leader, Clinical, DDDDP, HFD-540  
Bindi Nikhar, M.D./Clinical Reviewer, DDDDP, HFD-540  
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII, HFD-725  
Matthew Soukup, Ph.D./Biostatistician, DBIII, HFD-725  
Donald Hare, Ph.D./Special Assistant to the Director, OGD, HFD-604  
Margo Owens/Regulatory Project Manager, DDDDP, HFD-540  
Maria Anderson/Regulatory Project Manager, DDDDP, HFD-540

### **Sponsor Attendees:**

#### **Connetics**

Michael Eison, Vice President, Regulatory Affairs  
Alex Yaroshinsky, Ph.D., Senior Director, Biostatistics  
Matt Foehr, Technical Operations  
Greg Vontz, President, Operations  
Katy Morton, Director, Regulatory Affairs, CMC  
Hans Hofland, Director, Pharmacology  
Diana Chen, Vice President, Medical Affairs  
Prema Vijayakumar, Senior Director, Process Development & Manufacturing  
Zane Rogers, M.A., Senior Associate, Regulatory Affairs  
Lincoln Krochmal, M.D., Executive Vice President, Research and Product Development  
Wendy Chern, Ph.D., Vice President, Research and Preclinical Development

#### **Purpose:**

The pre-meeting briefing document (submitted July 15, 2005) provides background and questions for discussion. The sponsor requests input from the Agency on the requirements for approval of

TRADENAME (clindamycin, 1% - tretinoin, 0.025%) Gel in light of the Agency's action letter dated June 10, 2005.

**Chemistry, Manufacturing and Controls:**

**Sponsor's Question:**

Does the Agency agree that we can utilize the test requirements as described for a SUPAC Level 3 Change to support a bridge to the original formulation?

**Agency Response:**

The (b) (4) amount of POE-4 excipient from the formulation could be treated as equivalent to a Level 3 change under SUPAC-SS. The data requirements outlined in the Guidance would be expected in the resubmission.

**Sponsor's Question:**

Stability data: Connetics plans to manufacture 3 batches of drug product with the new formulation. Connetics will package the reformulated product in a container-closure system identical to the container-closure system of our original drug product ((b) 30 (b) (4) gram tubes), and place them on accelerated and long-term stability. We propose to submit 6-month stability data on the reformulated product stored at room temperature and under accelerated conditions, and to demonstrate the comparability of the reformulated product's stability to the stability of the original formulation.

Does the Division agree that the above information will adequately support registration, and agree to grant Connetics the opportunity to discuss the open CMC issues in a separate meeting?

**Agency Response:**

The proposal to provide 6 months of stability at the time of submission is not desirable. Six months of stability data under accelerated storage conditions on three batches and twelve months of room temperature stability data are preferred at the time of submission, since this is a new formulation.

With regard to your request for a CMC teleconference, the sponsor may submit a meeting request for this teleconference to discuss product specification issues and any remaining open issues from our June 28, 2005, CMC deficiencies letter.

**Pharmacology/Toxicology:**

**Sponsor's Question:**

Connetics believes that no preclinical toxicological assessments of the reformulated vehicle or product (including carcinogenicity testing) are required prior to product approval for the following reasons:

- The reformulated clindamycin-tretinoin gel product contains only I.I.G.-listed excipients (with the exception of purified water)
- The excipients are used at levels below those established as safe (as defined by the I.I.G.)
- Each excipient is administered by the I.I.G.-listed route of administration (topical)
- The safety profiles of the active ingredients, clindamycin and tretinoin, are well established.

Does the Division agree that as the (b) (4) from the original formulation, and the reformulation contains only I.I.G.-listed ingredients, that no additional preclinical assessments are required?

**Agency Response:**

Although the Inactive Ingredient Database lists laureth-4 in approved topical products at up to 5.2%, that particular product is not for chronic use and as such did not require carcinogenicity testing for approval. Therefore the Division will require data on the carcinogenicity testing of laureth-4. This can be achieved by testing the product in a 2 year dermal carcinogenicity test, either performed by the sponsor or obtained by right of reference.

The sponsor proposed conducting a dermal carcinogenicity study with the reformulated vehicle and including a clindamycin (1%) arm. The carcinogenicity of clindamycin itself would be addressed by the sponsor obtaining right-of-reference to a pre-existing dermal carcinogenicity study. The division responded that it would be preferable to include clindamycin at three different doses with the high dose being the maximum tolerated or maximum feasible dose, but that a single arm at 1% would be minimally acceptable. The division left the choice of carcinogenicity model to the sponsor. The sponsor confirmed that they would submit the protocol to the IND so that the division could take it to the eCAC.

**Sponsor's Question:**

Connetics acknowledges that carcinogenicity data on clindamycin phosphate was an original requirement for NDA 50-803. If required, Connetics is prepared to provide carcinogenicity data on clindamycin phosphate by right of reference to data generated in a Tg.AC mouse model, or by agreeing to perform a post-approval 2-year carcinogenicity study of clindamycin phosphate.

Does the Division require carcinogenicity data on clindamycin as a condition of approval of our reformulated product?

**Agency Response:**

Under the conditions of the 26-Week dermal carcinogenicity study in Tg.AC mice (AA81EW.7D8T.BTL) conducted with the original formulation there was a vehicle effect on papilloma formation which was accentuated by the administration of clindamycin phosphate in Velac Gel vehicle at 3% and 5%. The incidence of papillomas was comparable in the vehicle control and 1% groups.

Although the sponsor believes that (b) (4) the Division is not convinced that this is the case. Obtaining right of reference to a carcinogenicity study with clindamycin phosphate in a different vehicle than what is in the reformulated product would be acceptable if potential carcinogenicity of the vehicle and the 1% clindamycin was being addressed in another study.

All carcinogenicity data is required prior to approval.

**Clinical Pharmacology:**

**Agency:**

The "outline" of the proposed in vivo biopharmaceutical study comparing the re-formulated to the original product appears to be sufficient to address the issue of systemic bioavailability. The study should use subjects with acne towards the upper limit of severity (in terms of area of involvement) and doses sufficient to cover the face, upper chest and back. The sponsor is encouraged to submit the protocol for review prior to initiation. As for the in vitro study, the study as outlined in the meeting package appears to follow the FDA SUPAC-SS guidance document. Taken together these two studies should be sufficient, taken with the pharmacology/toxicology information, to address the issue of systemic bioavailability.

**Clinical:**

**Sponsor's Questions:**

Does the Division agree that Connetics' approach to satisfying the in vitro release and in vivo bioequivalence documentation requirements of SUPAC would constitute an adequate bridge from the reformulated product to the original product, and that such a bridge will permit Connetics to fully utilize and rely upon the clinical and non-clinical safety data generated with the original formulation?

Does the Division agree that the proposed battery with the to-be-marketed product will provide adequate photosafety data to support approval?

**Agency Response:**

Since the change proposed by the sponsor (b) (4) would constitute a level 3 change per the logic/concept of the SUPAC-SS document guidelines (see also 21 CFR 320.24(b)(4)), the sponsor would have to perform bridging clinical studies in order to document safety and efficacy of Velac gel Revised Formulation (RF) in patients with acne vulgaris as compared to Velac gel Old Formulation (OF) and also demonstrate superiority to the component arms as per 21 CFR 300.50. For these purposes, it is recommended that a single 4-armed, Phase 3 clinical study be performed comparing Velac gel (RF): Velac gel (OF): Clindamycin gel (RF): Tretinoin gel (RF). Demonstration of efficacy in this study would require Velac gel (RF) to be non-inferior to Velac gel (OF) and superior to Clindamycin gel (RF) and Tretinoin gel (RF). Please see also Biostat comments regarding power calculations.

The sponsor mentioned that (b) (4) and it was unlikely that the overall safety and efficacy of the drug product would be affected. They also mentioned that they could submit supportive chemistry and pharmacokinetic information in this regard, and that ultimately, (b) (4) would not have a major impact on the efficacy profile of their drug product. The Agency discussed that efficacy may still be affected if usage conditions subvert the solubility or activity of the active drug substances. The Agency mentioned that supportive information to this regard should be submitted prior to agreement regarding the structure of the pivotal bridging clinical study.

The sponsor proposed a study comparing Velac gel (RF): Velac gel (OF): Vehicle (RF); demonstration of efficacy in this study would require Velac gel (RF) to be non-inferior to Velac gel (OF) and superior to Vehicle (RF). In addition, since this would be a bridging clinical trial, there was discussion that different non-inferiority margins for the two co-primary efficacy endpoints might be proposed, i.e. the IGA scale and lesion counts. However, for any superiority comparison, whether to Vehicle (RF) or to either of the active monads (RF), the Agency would be interested in strict co-primaries of dichotomized IGA (to clear and almost clear) and lesion counts. The Agency emphasized that the strength of this clinical 'bridge' between the old and new formulations of Velac gel would be crucial in determining approvability of their revised drug product.

Please also see Biostat comments regarding protocol design.

The Division agrees that dermal photo-safety studies, i.e. photoirritation (n = 30) and photoallergenicity (n = 50) performed with Velac gel (RF) would provide adequate photosafety data to support approval. The sponsor should submit protocols for these studies, ensuring that the lamps emit at the appropriate spectra (UVA, UVB and visible spectra, i.e. 290-700 nm).

The sponsor should propose how ICH E1A will be addressed with use of the product as acne vulgaris is a chronic indication.

**Biostatistics:**

**Agency:**

To establish non-inferiority of the new formulation compared to the original formulation the Division recommends that the sponsor plans a Phase 3 trial with the following treatment arms:

- new formulation
- original formulation
- clindamycin 1% in the new formulation
- tretinoin 0.025% in the new formulation
- 

The study should be powered to establish (i) non-inferiority of the new formulation compared to the original formulation and (ii) superiority of the new formulation to its active ingredients (clindamycin and tretinoin). The study should be planned to establish such comparisons for each of the co-primary endpoints.

Taking into account that the response rates for clindamycin and tretinoin varied greatly in the sponsor's completed Phase 3 trials, the new study should be powered conservatively to reduce the chance of under-powered trial. Specifically, the study should be powered for superiority against the active ingredients high response rates observed in the sponsor's completed study VLC.C.305. In addition, the study should be powered to maintain 75% of the treatment effect against the vehicle. If the non-inferiority comparison is the driving factor for the (b) (4) the sponsor might investigate the impact of using different non-inferiority margins (b) (4) for the division's comments.

**Project Management:**

**Agency:**

1. For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.
2. The sponsor is reminded of the Pediatric Research Equity Act of 2003 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.
3. The sponsor is encouraged to submit its revised protocols as Special Protocols through the 45-day Special Protocol Assessment (SPA) mechanism for Agency review, comment and agreement, prior to study initiation.

The meeting ended amicably.

**ADDENDUM:** The sponsor submitted their record of the August 17, 2005, Post-NA meeting via facsimile and officially to their NDA on August 22, 2005 (see attached). The Agency has the following clarifications in response to this submission:

**Chemistry, Manufacturing and Control:**

**Sponsor's Comment 1 - Modification of the Original Vehicle**

The applicant's minutes state "As the identity and amount of active ingredients is not changed in the modified formulation, and no manufacturing process changes are required, the Sponsor considers the modification a minor change that should not result in a statistically or clinically meaningful difference between the modified and original products. ... "The Division and the Sponsor agree that the application of SUPAC logic for a Level 3 change is appropriate for consideration of this modification to the vehicle."

**FDA Clarification:** We characterize this change as a major change, similar to a Level 3 change under SUPAC-SS, and likely to have a significant impact on formulation quality and performance. In addition, the agreement that the principles of SUPAC-SS are appropriate to this change was limited only to the CMC information outlined under the Level 3 change for a drug without a significant body of information. SUPAC-SS officially applies only to approved products, and additional information has been deemed necessary when it is applied to a not-yet-approved product. This new formulation would require a minimum of twelve months of stability data for three batches under standard storage conditions, and at least six months of data under accelerated conditions, to support the desired expiration dating period. Note that the filing documentation must be submitted in the resubmission, not in a Prior Approval Supplement or Annual Report, as stated in SUPAC-SS.

Other necessary data may be identified by other reviewers.

**Clinical Pharmacology/Biopharmaceutics:**

**Sponsor's Comment 3 - Clinical Pharmacokinetic and Bridging Studies**

The sponsor's proposal to solely follow SUPAC guidance to establish a clinical bridge is not appropriate. The sponsor must establish clinical comparability/bioequivalence of the modified formulation to the original product. The proposed pharmacokinetic (PK) study is adequate for comparing the systemic exposure of the drug products and to establish the safety of the modified formulation. [Post-Meeting Note: The sponsor intends that the duration of treatment (28 days) and the schedule for blood sampling (day 5 and 28) be similar to those used in Study VLC.C.201 as submitted in the original NDA]. The sponsor agreed to provide PK data in acne patients as requested in the FDA Reviewers' Comments dated August 16, 2005. A clinical bridging trial will allow reference to all safety and efficacy data from the clinical trials conducted with the original formulation.

**FDA Clarification:** The proposed PK/bridging study will only identify any potential safety concerns by comparing the systemic exposure. It will not, in and of itself, "establish safety".

Minutes Preparer: \_\_\_\_\_  
Margo Owens/Regulatory Project Manager DDDDP, HFD-540

Chair Concurrence: \_\_\_\_\_  
Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540

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/s/

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Jonathan Wilkin  
9/15/2005 10:45:02 AM

## MEMORANDUM OF TELECON

DATE: June 10, 2005, 3:55 P.M.

APPLICATION NUMBER: NDA 50-803

DRUG PRODUCT: TRADENAME (clindamycin 1% - tretinoin 0.025%) Gel

BETWEEN:

Name: Michael Eisen, Vice President, Regulatory Affairs  
Representing: Connetics Corporation

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540  
Stanka Kukich, M.D., Deputy Division Director  
Margo Owens, Regulatory Project Manager

SUBJECT: NDA 50-803

This teleconference was initiated by the Agency to inform the Applicant that a Not Approvable action was taken on NDA 50-803 TRADENAME (clindamycin 1% - tretinoin 0.025%) Gel today.

The following discussion took place:

The Agency stated that a Not Approvable letter was signed off today. The Agency further stated that the Not Approvable action was taken due to the carcinogenic potential in the vehicle.

*The Applicant asked if there was discussion on how they might address this issue.*

The Agency stated that a reformulation of the product will be needed so that the vehicle is safe and not carcinogenic. Because this is a complex issue, it was recommended that the Applicant request a meeting to discuss further. The Agency stated that a facsimile of the Not Approvable letter listing the deficiencies and how to resolve them will be sent today.

The teleconference ended amicably.

**Addendum:** The Not Approvable letter was sent via facsimile to the Applicant on 6/10/05. The Applicant confirmed receipt of the fax via telephone on June 10, 2005 at 4:18 P.M.

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/s/  
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Margo Owens  
6/20/05 01:20:11 PM  
CSO

Stanka Kukich  
6/20/05 01:35:27 PM  
MEDICAL OFFICER

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/s/

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Margo Owens  
7/18/05 04:11:47 PM  
CSO



NDA 50-803

Connetics Corporation  
Attention: Darlene O'Banion  
Senior Manager, Regulatory Affairs  
3160 Porter Drive  
Palo Alto, California 94304

Dear Ms. O'Banion:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (clindamycin, 1% - tretinoin, 0.025%) Gel.

We also refer to the action letter dated June 10, 2005.

The following comments are based on the CMC information reviewed with your application submitted on August 23, 2004. Please respond to the following items in your resubmission:

Drug Product Manufacturing

It is indicated in the amendment dated April 22, 2005, that the tretinoin and clindamycin mixtures would be used immediately, and a (b) (4) hold time would be validated during process validation. The immediate use of tretinoin and clindamycin mixtures should be indicated in the master batch record with a time limitation (for example, not more than X minutes or hours). The hold time (b) (4) should also be indicated in the master batch record once it is established through manufacturing process validation.

Drug Product Specification

- The drug product specification on butylated hydroxytoluene should be (b) (4) of the target concentration as agreed upon in the amendment dated March 22, 2005 not (b) (4) of the target as indicated in Attachment 7 of the amendment dated April 22, 2005.
- The proposed limit for (b) (4) is too broad (b) (4). The specification should be revised based on batch release and primary stability data.
- The proposed acceptance criterion for weight loss is inadequate. The addition of a limit on maximum weight loss in addition to a limit on the average is recommended.
- The acceptance criteria on clindamycin related substances (specifically, (b) (4) (b) (4) substances) should be considered to be tentative due to the lack of valid data to support specification setting.

According to p. 12 of 79 of Section 3.2.P.8, the data in question were generated using a non-stability indicating method 73.5556 instead of the proposed regulatory method R0252. Although a retrospective analysis was conducted on all lots placed on stability, there is no explanation provided for this retrospective analysis. It is unclear whether it is a data treatment or an actual, physical HPLC run. Consequently, the validity of the data can not be established based on the information submitted to-date.

To support the acceptance criteria, valid data generated using the proposed regulatory method R0252 from all primary stability lots should be provided.

Drug Product Batch Analysis and Stability

You should provide valid related substance data using Method R0252 for all primary stability lots.

Due to the significant drug degradation observed in the accelerated stability studies, and also due to the lack of data generated from the proposed regulatory method R0252, the expiry period is recommended to be based on real time data (b) (4)

If you have any questions, please call Margo Owens, Project Manger, at 301-827-2020.

Sincerely,

*{See appended electronic signature page}*

Jonathan K. Wilkin, M.D.  
Director  
Division of Dermatologic and Dental Drug  
Products, HFD-540  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Stanka Kukich  
6/28/05 08:48:34 AM  
sign off for Dr. Wilkin, Division Director



**NDA 50-803**

Connetics Corporation  
Attention: Michael S. Eison, Ph.D.  
Vice President, Regulatory Affairs  
3160 Porter Drive  
Palo Alto, CA 94304

Dear Dr. Eison:

We received your June 15, 2005 correspondence, requesting an End of Review (Post-action) Conference for **Velac Gel**.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February, 2000). The meeting is scheduled for:

**Date:** Wednesday, August 17, 2005  
**Time:** 10:30-11:30 AM, EDT  
**Location:** 9201 Corporate Blvd., Rockville, MD 20850

Provide the background information for this meeting at least 1 month prior to the meeting. Submit the **original copy** to your NDA, and **15 bound copies**, each marked "DESK COPY", directly to Sandy Childs at the above address. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by July 17, 2005, we may have to cancel the meeting.

If you have any questions, call Sandy Childs, Consumer Safety Technician, at 301-827-2061.

Sincerely,

*{See appended electronic signature page}*

Mary Jean Kozma-Fornaro  
Supervisor, Project Management Staff  
Division of Dermatologic & Dental Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Suzanne Childs  
6/28/05 08:18:01 AM  
Signed for Mary Jean Kozma-Fornaro

## MEMORANDUM OF TELECON

DATE: June 10, 2005, 3:55 P.M.

APPLICATION NUMBER: NDA 50-803

DRUG PRODUCT: TRADENAME (clindamycin 1% - tretinoin 0.025%) Gel

BETWEEN:

Name: Michael Eisen, Vice President, Regulatory Affairs  
Representing: Connetics Corporation

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540  
Stanka Kukich, M.D., Deputy Division Director  
Margo Owens, Regulatory Project Manager

SUBJECT: NDA 50-803

This teleconference was initiated by the Agency to inform the Applicant that a Not Approvable action was taken on NDA 50-803 TRADENAME (clindamycin 1% - tretinoin 0.025%) Gel today.

The following discussion took place:

The Agency stated that a Not Approvable letter was signed off today. The Agency further stated that the Not Approvable action was taken due to the carcinogenic potential in the vehicle.

*The Applicant asked if there was discussion on how they might address this issue.*

The Agency stated that a reformulation of the product will be needed so that the vehicle is safe and not carcinogenic. Because this is a complex issue, it was recommended that the Applicant request a meeting to discuss further. The Agency stated that a facsimile of the Not Approvable letter listing the deficiencies and how to resolve them will be sent today.

The teleconference ended amicably.

**Addendum:** The Not Approvable letter was sent via facsimile to the Applicant on 6/10/05. The Applicant confirmed receipt of the fax via telephone on June 10, 2005 at 4:18 P.M.

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/s/

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Margo Owens  
6/20/05 01:20:11 PM  
CSO

Stanka Kukich  
6/20/05 01:35:27 PM  
MEDICAL OFFICER

## MEMORANDUM OF TELECON

DATE: June 10, 2005, 4:18 P.M.

APPLICATION NUMBER: NDA 50-803

DRUG PRODUCT: TRADENAME (clindamycin 1% - tretinoin 0.025%) Gel

BETWEEN:

Name: Michael Eisen, Vice President, Regulatory Affairs  
Representing: Connetics Corporation

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540  
Margo Owens, Regulatory Project Manager

SUBJECT: NDA 50-803

This teleconference was initiated by the Agency to determine if today's facsimile transmittal of the Not Approvable letter for TRADENAME (clindamycin 1% - tretinoin 0.025%) Gel had been received.

The Applicant confirmed that the facsimile of the Not Approvable letter for NDA 50-803 had been received.

The teleconference ended amicably.

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/s/

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Margo Owens  
6/17/05 03:29:14 PM  
CSO

## FDA Facsimile Memorandum

**Date:** April 28, 2005  
**To:** Darlene O'Banion, Senior Manager, Regulatory Affairs  
Connetics Corporation  
**From:** Margo Owens, Project Manager  
**Subject:** NDA 50-803 TRADENAME (clindamycin, 1% - tretinoin 0.025%)

Ms. O'Banion,

The Chemistry, Manufacturing and Control (CMC) reviewer has the following informational request regarding your NDA 50-803 TRADENAME (clindamycin, 1% - tretinoin, 0.025%).

**CMC Reviewer's Information Request:**

We have the following additional comments after further review of NDA 50-803 and its CMC amendments to-date:

**Drug Product Batch Analysis and Stability**

Provide bridging data to link Method 73.5556 to the proposed regulatory method R0252. The bridging study must be a side-by-side direct comparison of the two methods for all assays intended by Method R0252.

We have noted that the batch release and registration stability data provided in the original NDA and its amendments to-date for (b) (4) were generated using Method 73.5556 rather than the proposed regulatory method R0252 (pp. 16 and 22 of 36, Section 3.2.P.5). In the absence of the bridging data to show that Method R0252 is equivalent or superior to Method 73.5556, submitted analytical data (release and stability) will not support your proposed specifications (b) (4) as well as your proposed expiry period.

**Drug Product Method R0252**

Clarify what is the vehicle used in the gel sample preparation. (b) (4)

Respectfully,

Margo Owens  
Project Manager

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/s/

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Margo Owens  
4/28/05 12:33:06 PM  
CSO  
Faxed to applicant 4/28/05.



NDA 50-803

Connetics Corporation  
Attention: Darlene O'Banion  
Senior Manager, Regulatory Affairs  
3160 Porter Drive  
Palo Alto, CA 94304

Dear Ms. O'Banion:

Reference is made to your new drug application (NDA) for TRADENAME (clindamycin, 1% - tretinoin, 0.025%) Gel which was submitted on August 23, 2004.

We also refer to your carcinogenicity study results for the 26-week Tg.AC mouse dermal carcinogenicity study ( (b) (4) A81EW.7D8T.BTL) submitted as part of your original NDA submission.

Our (Executive) Carcinogenicity Assessment Committee (ECAC) reviewed your protocol study report on March 29, 2005. As requested in your April 14, 2005, submission, a copy of the final report of the ECAC regarding TRADENAME (clindamycin, 1% - tretinoin, 0.025%) Gel is enclosed.

Please note that the recommendations made by the ECAC are advisory in nature and should not be interpreted as a measure of the approvability of any application for this drug.

If you have any questions, call Margo Owens, Project Manager, at 301-827-2020.

Sincerely,

*{See appended electronic signature page}*

Mary Jean Kozma-Fornaro.  
Chief, Project Management Staff  
Division of Dermatologic and  
Dental Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

Enclosure

Executive CAC

Date of Meeting: March 29, 2005

Committee: Abby Jacobs, Ph.D., HFD-024, Acting Chair  
Joseph Contrera, Ph.D., HFD-901, Member  
Lois Freed, Ph.D., HFD-120, Alternate Member  
Paul Brown, HFD-540 Supervisor  
Jill Merrill, HFD-540 Presenting Reviewer

Author of Draft: Jill Merrill

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA 50-803

Drug Name: Velac Gel® (clindamycin phosphate 1%, tretinoin 0.025%)

Sponsor: Connetics Corporation

Background: Velac Gel® contains the antibiotic clindamycin phosphate and the retinoid tretinoin in a gel vehicle and is being considered for the topical treatment of acne vulgaris. The protocol for the Tg.AC mouse study for clindamycin phosphate was reviewed and concurred with by the Executive CAC (12-16-03). Results from the 26-week Tg.AC mouse dermal carcinogenicity study (b) (4) AA81EW.7D8T.BTL) were received as part of the NDA submission.

Tg.AC Mouse Carcinogenicity Study:

DOSING COMMENTS: 5% is the maximum feasible dose

NUMBER OF MICE: 20/sex/group, except TPA positive control which was 15/sex

MOUSE DOSE LEVELS: see table

Group	Test Article	Volume (mL/day)	Dose clindamycin phosphate (mg/kg)
1	Velac gel vehicle control	0.1	0
2	Shaved, untreated control	0	0
3	50 µg TPA in Velac gel vehicle	0.1 mL 3x/week	0
4	1% clindamycin phosphate in Velac gel vehicle	0.1	40
5	3% clindamycin phosphate in Velac gel vehicle	0.1	120
6	5% clindamycin phosphate in Velac gel vehicle	0.1	200

TPA = 12-O-tetradecanoylphorbol 13-acetate

MOUSE TUMOR FINDINGS: At the end of the study (week 27)

Group #	Sex (M or F)	Incidence	Burden (all papillomas)	
		Animals bearing at least one latent or actual papilloma per effective # of animals (% incidence)	All papillomas per papilloma bearing animal	All papillomas per effective animal
		SOA	SOA only	SOA only
1	M	9/20 ** (45)	1.8	0.8
1	F	5/20 ** (25)	2.0	0.5
2	M	0/18 (0)	0.0	0.0
2	F	0/16 (0)	0.0	0.0
3	M	NA	NA	NA
3	F	NA	NA	NA
4	M	12/20 ** (60)	2.2	1.3
4	F	6/20 ** (30)	1.7	0.5
5	M	15/20** (75)	2.7	2.0****
5	F	12/20 * ** (60)	1.8	1.1****
6	M	16/20 * ** (80)	3.4	2.8 *** ****
6	F	16/20 * ** (80)	2.2	1.8 *** ****

\*  $p \leq 0.05$ , Fisher's exact Test, when compared to vehicle (Group 1)

\*\*  $p \leq 0.05$ , Fisher's exact Test, when compared to untreated (Group 2)

\*\*\*  $p \leq 0.05$ , ANOVA and Dunnett's t-test, when compared to vehicle (Group 1)

\*\*\*\*  $p \leq 0.05$ , ANOVA and Dunnett's t-test, when compared to untreated (Group 2)

NOTE: Papillomas were scored as "latent" after attaining a size of 2 mm in diameter and protruding from the skin. Papillomas were scored as "actual" when they remained countable for 3 consecutive weekly scoring sessions. Group 3 (positive control) incidence is listed as NA since by week 27 all animals in this group were removed from the study due to tumor burden.

At study termination, the incidence of papillomas was 45%, 0%, 60%, 75%, and 80% in the males and 25%, 0%, 30%, 60%, and 80% in the females from the vehicle control, untreated control, low-, mid-, and high-dose groups, respectively. The incidence was 100% in the positive control animals. These results indicate a positive, statistically significant response in the incidence of papillomas in all treatment groups, including the vehicle control.

Executive CAC Recommendations and Conclusions:

\* The Committee had previously agreed on the doses, and the Committee agreed that the study was adequate.

\* The Committee concurred that the vehicle of Velac gel alone caused a statistically significant increased incidence of skin papillomas compared to the untreated controls and that clindamycin in Velac gel caused further significant dose-related increases in papillomas relative to the vehicle controls and untreated animals.

The Committee noted that positive results in the Tg.AC assay indicate that a substance may be either a promoter or a complete carcinogen.

\* It was noted that the sponsor believes that application site irritation led to papilloma formation. However, the Committee is aware of other studies in Tg.AC mice in which irritation alone was not sufficient to cause papillomas. Therefore, the Committee cannot concur with the sponsor's position that the increase in papillomas with vehicle and clindamycin represents a nonspecific response to irritation.

Abigail Jacobs, Ph.D.  
Acting Chair, Executive CAC

cc:\  
NDA 50-803/ Division File, HFD-540  
P Brown/ Team leader, HFD-540  
J Merrill/ Reviewer, HFD-540  
M Owens/ PM, HFD-540  
A Seifried, HFD-024

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/s/

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Abby Jacobs

4/4/05 09:08:11 AM

## FDA Facsimile Memorandum

**Date:** April 15, 2005  
**To:** Darlene O'Banion, Senior Manager, Regulatory Affairs  
Connetics Corporation  
**From:** Margo Owens, Project Manager  
**Subject:** NDA 50-803 TRADENAME (clindamycin, 1% - tretinoin 0.025%) Gel

Ms. O'Banion,

The Chemistry, Manufacturing and Control (CMC) reviewer has the following informational request regarding your NDA 50-803 TRADENAME (clindamycin, 1% - tretinoin, 0.025%) Gel.

**CMC Reviewer's Information Request:**

We have the following additional comments after further review of NDA 50-803 and its CMC amendments to-date:

**Drug Product Manufacture**



- 2 The flow diagram provided in the amendment dated March 22, 2005 does not accurately reflect the addition sequence conveyed in the manufacturing description (Attachment 2, amendment dated March 22, 2005) and the executed batch record of Batch SIAC-C (p. 28 of 112, Section 3.2.R.2.P.1). For example:



(b) (4)

Submit a revised flow diagram which accurately reflects the actual manufacturing process.

(b) (4)

Provide Master Batch Record for review.

(b) (4)

- 6 No information is provided concerning critical manufacturing steps. Identify critical manufacturing steps with justification.
- 7 Provide maximum hold time and storage condition (b) (4)
- 8 No in-process control data are provided for Velac gel batches manufactured to-date. Provide batch analysis on the in-process control test results.
- 9 The executed batch record of Batch SIAC-C indicated that samples were removed for (b) (4) uniformity test but it was not clear which tests were performed on the (b) (4) uniformity samples. Add (b) (4) uniformity test to the in-process control. Provide sampling plan, list of tests and limits for the (b) (4) uniformity test.

(b) (4)



The above information should be provided in the NDA or by reference in a DMF filed by (b) (4). A letter of authorization (b) (4) should accompany to any cross referenced DMF.

Drug Product Specification

Your proposal to retain the acceptance criteria (b) (4) for (b) (4) is unacceptable. Since you have proposed an in-process limit (b) (4) for (b) (4) and since your drug product stability data (long term and accelerated) show (b) (4) is very stable throughout the study periods, we recommend the same limit (b) (4) for the finished drug product. Any significant deviation from this limit would pose a risk in chemical integrity.

Drug Product Method

(b) (4) provide method number and procedure for this ID test for each active ingredient.

Drug Product Method Validation

- 1 The method validation report VA-VEL-033R (for Method R0252) does not contain the following data/information for related substances (b) (4): linearity, LOD/LOQ, stability of standards and sample solutions, and specificity. The accuracy data are also very limited for related substances. Consequently, the method is not considered to be adequate to support the quantitation of (b) (4). Provide the aforementioned missing data to support your claim that Method R0252 is adequately validated to support the proposed drug product specification.

- 2 The method validation report 54.0983 (for Method R0253) does not contain the following data/information for (b) (4): precision, linearity, LOD/LOQ, stability of standards and sample solutions, and specificity. The accuracy data are also very limited for (b) (4). Consequently, the method is not considered to be adequate to support the quantitation of (b) (4). Provide the aforementioned missing data to support your claim that Method R0253 is adequately validated to support the proposed drug product specification.

Please provide this information by April 22, 2005, via facsimile and in a formal submission to your NDA.

Respectfully,

Margo Owens  
Project Manager

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/s/

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Margo Owens  
4/15/05 02:54:50 PM  
CSO  
Faxed to sponsor 4/15/05.

## FDA Facsimile Memorandum

**Date:** April 5, 2005  
**To:** Darlene O'Banion, Senior Manager, Regulatory Affairs  
Connetics Corporation  
**From:** Margo Owens, Project Manager  
**Subject:** NDA 50-803 Velac Gel (clindamycin, 1% - tretinoin, 0.025%)

Ms. O'Banion,

The clinical reviewer has the following comments regarding your NDA 50-803 Velac Gel (clindamycin, 1% - tretinoin, 0.025%), amendment 012.

**Clinical Reviewer's Comments:**

On reviewing your reply dated March 4, 2005, amendment 012, it is recommended that further photosafety studies be conducted with the to-be-marketed formulation of Velac gel with sufficient numbers of subjects. Please submit a plan of action to address these concerns. Please indicate why such studies are not needed pre-approval based on the data at hand.

Respectfully,

Margo Owens  
Project Manager

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/s/

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Margo Owens  
4/5/05 11:45:51 AM  
CSO  
Faxed to applicant 4/5/05.

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and  
Technical Support (DMETS), HFD-420  
PKLN Rm. 6-34**

FROM:

**Margo Owens  
Project Manager  
Division of Dermatologic and Dental Drug Products,  
HFD-540**

DATE 3/30/05	IND NO.	NDA NO. 50-803	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 3/2/05
NAME OF DRUG TRADENAME Gel (clindamycin, 1% - tretinoin, 0.025%)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG 3S	DESIRED COMPLETION DATE ASAP if objections with <b>revised</b> tradenames PDUFA date 6/25/05 Labeling mtg – May 16, 2005

NAME OF FIRM: Connetics Corporation

REASON FOR REQUEST

I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE--NDA MEETING        | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                           |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                                  |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                                       |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                             |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                                      |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): 2nd Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Per your determination of unacceptable for the originally proposed tradename, Velac. The Applicant has submitted two additional tradenames (one primary and one alternate) for your review. Please review the requested tradenames (b) (4) with the alternate name of "Veltin". The draft package insert, carton and container labels for both names are attached. The Applicant has not submitted a Patient Package Insert. I will also send a hard copy along with supporting information submitted by the Applicant.

Thank you.

PDUFA DATE: June 25, 2005

ATTACHMENTS: Draft package insert, Container and Carton Labels

CC:

Archival NDA 50-503

HFD-540/Division File

HFD-540/RPM, Margo Owens

HFD-540/Bindi Nikhar, M.D., Clinical Reviewer

Markham Luke, M.D., Ph.D., Clinical Team Leader

SIGNATURE OF REQUESTER

Margo Owens

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

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Margo Owens

3/30/05 04:58:01 PM

## FDA Facsimile Memorandum

**Date:** March 29, 2005  
**To:** Darlene O'Banion, Senior Manager, Regulatory Affairs  
Connetics Corporation  
**From:** Margo Owens, Project Manager  
**Subject:** NDA 50-803 TRADENAME Gel (clindamycin, 1% - tretinoin 0.025%)

Ms. O'Banion,

The Chemistry, Manufacturing and Control (CMC) reviewer has the following comments regarding the (b) (4) comparability protocols submitted to your NDA 50-803 TRADENAME Gel (clindamycin, 1% - tretinoin, 0.025%).

**CMC Reviewer's Comments:**

We have reviewed the (b) (4) comparability protocols provided in the NDA 50-803 (b) (4) [REDACTED], below is our comments for each of the protocols:

(b) (4)

(b) (4)



The proposed changes are too general to allow for a specific development plan. In such a case, a comparability protocol is not considered to be appropriate for filing level reduction.

Please call if you have questions.

Respectfully,

Margo Owens  
Project Manager

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/s/

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Margo Owens  
3/29/05 09:46:17 AM  
CSO  
Faxed to sponsor 3/29/05.

## FDA Facsimile Memorandum

**Date:** March 14, 2005  
**To:** Darlene O'Banion, Senior Manager, Regulatory Affairs  
Connetics Corporation  
**From:** Margo Owens, Project Manager  
**Subject:** NDA 50-803 Velac Gel (clindamycin, 1% - tretinoin 0.025%)

Ms. O'Banion,

The Chemistry, Manufacturing and Control (CMC) reviewer has the following informational request regarding your NDA 50-803 Velac Gel (clindamycin, 1% - tretinoin, 0.025%).

**CMC Reviewer's Information Request:**  
**Drug Substance**

The executed batch record of Lot SIAC-C (3.2.R.2.P pages 35, 37, 67, and 88 of 112) indicates that HPLC assays (b) (4)

However, it is unclear if this would be a standard practice for every commercial batch of drug product since you did not provide the agency a copy of master batch record. Additionally, your proposed in-coming specifications of the two active ingredient do not include HPLC assays (b) (4) (Table 2, p. 9 of 20 of 3.2.S.4, and Table 2, p.7 of 24 of 3.2.S.4). You should either revise your in-coming specifications for the two active ingredients (b) (4) or submit a standard operation procedure (SOP) to ensure that assays (b) (4) will be performed (b) (4).

**Drug Product Manufacture:**

1. What is the proposed commercial batch size?

(b) (4)

Excipients

(b) (4)

(b) (4)

Drug Product Specification:

1. Add an additional identification test which employs a technology different from HPLC for both active ingredients (see ICH Q6A).
2. Revise the specifications of methyl paraben and BHT to be consistent with the submitted data. We recommend a (b) (4) of the target concentration based on the data seen in batch analysis and stability study.

Drug Product Analytical Methods:

1. Provide manufacturing records and gel compositions for the two vehicle gels used in the forced degradation studies of clindamycin Method R0252 (p. 18 of 66 of the method validation report, Document #: VA-VEL-033R).
2. Provide manufacturing records and gel compositions for the following vehicle gels cited in the method validation report for the tretinoin HPLC method (method validation report, Document #: 54.0983):

- Vehicle gel lot 348-0719S02 (p. 8 and p. 11 of 54 of the report)
- Vehicle gel lot 337-0726S01 (p. 11 of 54 of the report)
- Vehicle gel lot 348-0726S02 (p. 11 of 54 of the report)
- Vehicle gel lot 337-0806S01 (p. 12 of 54 of the report)
- Vehicle gel lot 337-0726S01 (p. 12 of 54 of the report)
- Vehicle gel lot 337-0808S01 (p. 12 of 54 of the report)

Comparability Protocols:

We will provide comments in a separate letter for the comparability protocols submitted in the original submission and the amendment dated Jan. 28, 2005.

Others:

Provide copies of the letters from the (b) (4) drug substance suppliers certifying their commitment to you for notification of future changes.

Please provide this information by March 22, 2005, via facsimile and in a formal submission to your NDA.

NDA 50-803

Respectfully,

Margo Owens  
Project Manager

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/s/

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Margo Owens  
3/14/05 03:57:42 PM  
CSO  
Faxed to sponsor 3/14/05.

## FDA Facsimile Memorandum

**Date:** March 7, 2005  
**To:** Darlene O'Banion, Senior Manager, Regulatory Affairs  
Connetics Corporation  
**From:** Margo Owens, Project Manager  
**Subject:** NDA 50-803 Velac Gel (clindamycin, 1% - tretinoin 0.025%)

Ms. O'Banion,

The clinical reviewer has the following informational request regarding your NDA 50-803 Velac Gel (clindamycin, 1% - tretinoin, 0.025%).

**Clinical Reviewer's Information Request:**

For those patients who discontinued treatment with the combination product (Velac) due to adverse reactions, were any medications such as topical steroids, etc used to alleviate local reactions such as dryness, erythema, etc., and if so please elaborate and describe the extent to which this occurred.

Please provide this information by March 14, 2005, via facsimile and in a formal submission to your NDA.

Respectfully,

Margo Owens  
Project Manager

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/s/

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Margo Owens

3/7/05 04:44:25 PM

CSO

Faxed to sponsor 3/7/05.

## FDA Facsimile Memorandum

**Date:** March 1, 2005  
**To:** Darlene O'Banion, Senior Manager, Regulatory Affairs  
Connetics Corporation  
**From:** Margo Owens, Project Manager  
**Subject:** NDA 50-803 Velac Gel (clindamycin, 1% - tretinoin 0.025%)

Ms. O'Banion,

The clinical reviewer has the following informational request regarding your NDA 50-803 Velac Gel (clindamycin, 1% - tretinoin, 0.025%).

**Clinical Reviewer's Information Request:**

The spectrophotometric analysis for Velac gel (to be marketed formulation) showed that it absorbs in the wavelengths between 280 and 700 nm. The Yamanouchi phototesting studies included only 10 for irritation and 26 for photosensitization. The Agency requires that phototoxicity (in 30 subjects) and photallergenicity (50 evaluable subjects) be conducted with the final to be marketed formulation if there is absorption in the 280 to 700 nm range. This had been conveyed to you in previous correspondences.

Please indicate when you intend to perform these studies. It is recommended that these studies be performed prior to completion of NDA review time in order to facilitate a complete review of their product.

Please provide this information by March 4, 2005, via facsimile and in a formal submission to your NDA.

Respectfully,

Margo Owens  
Project Manager

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/s/

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Margo Owens  
3/1/05 03:27:31 PM  
CSO  
Faxed to sponsor 3/1/05.

## FDA Facsimile Memorandum

**Date:** February 24, 2005  
**To:** Darlene O'Banion, Senior Manager, Regulatory Affairs  
Connetics Corporation  
**From:** Margo Owens, Project Manager  
**Subject:** NDA 50-803 Velac Gel (clindamycin, 1% - tretinoin 0.025%)

Ms. Hall,

The clinical reviewer has the following informational request regarding your NDA 50-803 Velac Gel (clindamycin, 1% - tretinoin, 0.025%).

**Clinical Reviewer's Information Request:**

1. Provide the pregnancy outcomes of the following 3 patients.  
In study 304, there are 2 patients, # 146-4007 and # 118-4018. In study 305, there is 1 patient # 110-5372.
2. Also provide pregnancy outcomes for any other patients who may have been pregnant and whose outcome was awaited and not reported in the NDA.
3. Patient # 105-3034, SAE Case ID 2003S1000060 (study 304) was a 25 year old female in the Clindamycin arm who had gastroenteritis. Was the patient checked for Clostridium difficile? If so, provide the results.

Please provide this information by February 28, 2005, via facsimile and in a formal submission to your NDA.

Respectfully,

Margo Owens  
Project Manager

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/s/

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Margo Owens  
2/24/05 02:15:43 PM  
CSO  
Faxed to sponsor 2/24/05.

## FDA Facsimile Memorandum

**Date:** November 23, 2004  
**To:** Sharon L. Hall, Senior Director, Regulatory Affairs  
Connetics Corporation  
**From:** Margo Owens, Project Manager  
**Subject:** NDA 50-803 Velac Gel (clindamycin, 1% - tretinoin 0.025%)

Ms. Hall,

The Chemistry reviewer has provided the following responses to your questions sent to the Project Manager on November 18, 2004, via email (see attached) regarding your NDA 50-803 Velac Gel (clindamycin, 1% - tretinoin, 0.025%). Our requests from the November 5, 2004, filing letter and your questions from the November 18, 2004, email correspondence have been provided below for ease of review.

**Agency's Informational Request from November 5, 2004 filing letter:**

2. Provide drug product samples. The samples should include all packaging components and all sizes proposed in the NDA.

**Applicant's Question from November 18, 2004 email:**

Can you clarify if you are referring to the method validation samples that are described in NDA section 3.2.P.R.4.P? If these are for methods validation, please provide the address to where the samples should be sent. If you would like samples for your Division's use, please let me know how many samples (b) (4) you would like. Also, would you like us to prepare mock labeling and apply it to the tubes?

**Agency's Response:**

The samples requested are not method validation samples. These samples are for the reviewer. Please provide 3 samples (b) (4) and place a mock label placed on each tube.

**Agency's Informational Request from November 5, 2004 filing letter:**

(b) (4)

(b) (4) We would like to know if the Agency would accept a modification to the

comparability protocol as an amendment to the NDA without resetting the NDA review clock.

**Agency's Response:**

We can accept the modified comparability protocol without changing the review clock as long as it is received no later than the end of January, 2005. (b) (4)

Please feel free to contact me should you have any questions.

Respectfully,

Margo Owens  
Project Manager

ATTACHMENT

-----Original Message-----

**From:** Hall, Sharon [mailto:SHall@connetics.com]

**Sent:** Thursday, November 18, 2004 2:59 PM

**To:** 'owensm@cder.fda.gov'

**Cc:** Morton, Katy

**Subject:** FW: Velac NDA 50-803

Margo,

Per our conversation, can you please clarify the following regarding the 5 NOV 2004 request for information. (Original FDA questions are provided for ease of review followed by our request for clarification.)

Chemistry Manufacturing and Controls:

2. Provide drug product samples. The samples should include all packaging components and all sizes proposed in the NDA.

Can you clarify if you are referring to the method validation samples that are described in NDA section 3.2.P.R.4.P? If these are for methods validation, please provide the address to where the samples should be sent. If you would like samples for your Division's use, please let me know how many samples (b) (4) you would like. Also, would you like us to prepare mock labeling and apply it to the tubes?

(b) (4)

(b) (4) We would like to know if the Agency would accept a modification to the comparability protocol as an amendment to the NDA without resetting the NDA review clock.

Please feel free to contact me if you have any questions. I can be reached at (650) 843-2860.

Regards, Katy

Katy Morton  
Director, Regulatory Affairs  
Connetics Corporation

(650) 843-2860

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/s/

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Margo Owens  
11/23/04 03:53:16 PM  
CSO  
Faxed to sponsor 11/23/04.



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 50-803

Connetics Corporation  
Attention: Sharon L. Hall  
Senior Director, Regulatory Affairs  
3290 West Bayshore Road  
Palo Alto, CA 94303

Dear Ms. Hall:

Please refer to your New Drug Application (NDA) submitted August 23, 2004, under the Federal Food, Drug, and Cosmetic Act for Velac (clindamycin, 1% - tretinoin, 0.025%) Gel.

The Velac (clindamycin, 1% - tretinoin, 0.025%) Gel application that was previously numbered (b) (4) has been re-numbered to NDA 50-803.

We refer to the guidance document issued by the Agency in May 1998, *Guidance for Industry and Reviewers Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act*. This guidance document defines the administrative actions required by the Agency for reviewing and approving antibiotic drug applications that were submitted after November 21, 1997. We also refer to the *Federal Register* notice Docket Number: 99N-3088, *Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs* issued January 24, 2000, which lists the active drug substances, including any derivative thereof, that are directly affected by the repeal of Section 507.

All documentation regarding this application should be directed to NDA 50-803 from this date forward.

If you have any questions, call Margo Owens, Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

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

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/s/

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Stanka Kukich  
11/23/04 02:53:28 PM  
sign off for Dr. Jonathan Wilkin, Division Director

## FDA Facsimile Memorandum

**Date:** November 9, 2004  
**To:** Sharon L. Hall, Senior Director, Regulatory Affairs  
Connetics Corporation  
**From:** Margo Owens, Project Manager  
**Subject:** (b) (4) Velac Gel (clindamycin, 1% - tretinoin 0.025%)

Ms. Hall,

Per my discussion with Darlene O'Banyon on November 3, 2004, the statistical reviewer has the following informational request regarding your (b) (4) Velac Gel (clindamycin, 1% - tretinoin, 0.025%).

**Statistical Reviewer's Information Request:**

Please submit the VIT dataset for Study VLC.C.305.

Please provide this information in a formal submission to your NDA as soon as possible.

Respectfully,

Margo Owens  
Project Manager

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/s/

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Margo Owens  
11/9/04 01:00:08 PM  
CSO  
Faxed to sponsor 11/9/04.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

(b) (4)

Connetics Corporation  
Attention: Sharon L. Hall, Senior Director, Regulatory Affairs  
3290 West Bayshore Road  
Palo Alto, California 94303

Dear Ms. Hall:

Please refer to your August 23, 2004 new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Velac (clindamycin, 1% - tretinoin, 0.025%) Gel.

We also refer to your submission dated October 8, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 5, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

1. Insufficient details of interim analysis results are submitted.

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

Chemistry, Manufacturing and Controls:

1. Provide a specific date when the new drug product stability testing site will be ready for inspection since it is scheduled to be moved in January 2005.
2. Provide drug product samples. The samples should include all packaging components and all sizes proposed in the NDA.

(b) (4)

Biostatistics:

Provide the following information regarding the interim analysis in Study VLC.C.304:

- a. Efficacy results at the interim along with the number of subjects.
- b. Whether any “Special Situations” as defined in the Interim Statistical Analysis Plan (Section 16.1.13) occurred and if any action was taken.
- c. Any related information that ensured adequate blinding in the conduct of the interim analysis.

Clinical Microbiology:

Provide information regarding the *in vitro* activity of clindamycin and tretinoin as a fixed-combination product against *P. acnes* from published literature.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Jonathan Wilkin  
11/5/04 04:27:34 PM

## REQUEST FOR CONSULTATION

TO (Division/Office):

**Division of Drug Marketing, Advertising and  
Communications, HFD-42  
PKLN Rm. 17B04**

FROM:

**Margo Owens  
Project Manager  
Division of Dermatologic and Dental Drug Products,  
HFD-540**

DATE 10/20/04	IND NO.	NDA NO. (b) (4)	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 8/23/04
NAME OF DRUG Velac Gel (clindamycin, 1% - tretinoin, 0.025%)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG 3S	DESIRED COMPLETION DATE Labeling Day will be scheduled in April 2005 PDUFA date 6/25/05

NAME OF FIRM: **Connetics Corporation**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                           |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                                  |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                                       |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                             |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                                      |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <b>New NDA Labels</b> |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- |  |   |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES      | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW         | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):  |   |

#### III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

#### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

#### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

#### COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Please review the attached draft package insert and carton and container labels. The Sponsor has not submitted a Patient Package Insert. I will also send a hard copy.

A Labeling Day will be scheduled for April 2005. Please provide comments in a sufficient amount of time prior to the meeting.

**ATTACHMENTS:** Draft Package Insert, Container and Carton Labels

**CC:**

Archival (b) (4)

HFD-540/Division File

HFD-540/RPM, Margo Owens

HFD-540/Bindi Nikhar, M.D., Clinical Reviewer

Markham Luke, M.D., Ph.D., Clinical Team Leader

SIGNATURE OF REQUESTER

**Margo Owens**

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

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/s/

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Margo Owens

10/20/04 11:31:24 AM

**REQUEST FOR CONSULTATION**

TO (Division/Office):

**Director, Division of Medication Errors and  
Technical Support (DMETS), HFD-420  
PKLN Rm. 6-34**

FROM:

**Margo Owens  
Project Manager  
Division of Dermatologic and Dental Drug Products,  
HFD-540**

DATE  
10/19/04

IND NO.

NDA NO.  
(b) (4)

TYPE OF DOCUMENT  
New NDA

DATE OF DOCUMENT  
8/23/04

NAME OF DRUG  
Velac Gel (clindamycin, 1% -  
tretinoin, 0.025%)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
3S

DESIRED COMPLETION DATE  
ASAP if objections with  
tradename  
PDUFA date 6/25/05

NAME OF FIRM: Connetics Corporation

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                       |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                              |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                                   |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                         |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                                  |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- |  |   |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES      | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW         | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):  |   |

**III. BIOPHARMACEUTICS**

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

**IV. DRUG EXPERIENCE**

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

**V. SCIENTIFIC INVESTIGATIONS**

CLINICAL

PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

**Please review the requested tradename "Velac". The draft package insert and carton and container labels are attached. The Sponsor has not submitted a Patient Package Insert. I will also send a hard copy.**

PDUFA DATE: **June 25, 2005**

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

CC:

Archival (b) (4)

HFD-540/Division File

HFD-540/RPM, Margo Owens HFD-540/Bindi Nikhar, M.D., Clinical Reviewer Markham Luke, M.D., Ph.D., Clinical Team Leader	
SIGNATURE OF REQUESTER Margo Owens	METHOD OF DELIVERY (Check one) X MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

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Margo Owens  
10/19/04 02:49:38 PM

## FDA Facsimile Memorandum

**Date:** October 7, 2004  
**To:** Sharon L. Hall, Senior Director, Regulatory Affairs  
Connetics Corporation  
**From:** Margo Owens, Project Manager  
**Subject:** (b) (4) Velac Gel (clindamycin, 1% - tretinoin 0.025%)

Ms. Hall,

The Statistical and CMC reviewers have the following informational requests regarding your (b) (4) Velac Gel (clindamycin, 1% - tretinoin, 0.025%).

### **Statistical Reviewer's Information Request:**

In reference to the TUMOR SAS transport data set sent by the Sponsor, please confirm that the codes in the Week1 - Week27 variables are as follows:

ASOA = Actual Site of Application count  
ADSOA = Actual Site of Application count of tumors that disappeared (when? At that week?)  
ANSOA = Actual Non Site of Application count  
ADNSOA = Actual Non Site of Application count of tumors that disappeared (when?)  
LSOA = Latent Site of Application count  
LNSOA = Latent Non-Site of Application count

Define exactly how the numbers in the Week1-Week27 variables in the TUMOR data set are associated with the variables above. In particular, indicate if they correspond to current tumor counts at that week.

### **Additional Statistical Request to the Sponsor:**

Please provide a data set similar to the current TUMOR data set but instead of having tumor count implicit in the Week1-Week27 variables, have each tumor type above explicitly represented with its own week value. That is, weekly tumor counts for the corresponding site are represented as variables similar to the following:

ASOA1-ASOA27  
ADSOA1-ADSOA27  
ANSOA1-ANSOA27  
ADNSOA1-ADNSOA27  
LSOA1-LSOA27  
LNSOA1-LNSOA27

Also, please add variables corresponding to week of sacrifice or death, scored 0 or 1, corresponding to 'no' or 'yes' respectively. Names like SAC1-SAC27 and DEAD1-DEAD27 would be appropriate. Include variables for animal id, gender, dose, etc.

**CMC Reviewer's Information Request:**

Is the response to a comment made by the FDA in the pre-NDA meeting (top paragraph of page 31 of Module 1, Section 1.3.4) included in the NDA. If yes, where is it located in the application? The comment is regarding interferences in each assay by the other active pharmaceutical ingredient and its degradants/impurities.

Please provide the CMC information via facsimile to my attention and in a formal submission to your NDA by October 8, 2004.

The statistical information should be submitted formally to your NDA by October 15, 2004.

Respectfully,

Margo Owens  
Project Manager

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/s/

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Margo Owens  
10/7/04 03:39:45 PM  
CSO  
Faxed to sponsor 10/7/04.

## FDA Facsimile Memorandum

**Date:** October 7, 2004  
**To:** Sharon L. Hall, Senior Director, Regulatory Affairs  
Connetics Corporation  
**From:** Margo Owens, Project Manager  
**Subject:** (b) (4) Velac Gel (clindamycin, 1% - tretinoin 0.025%)

Ms. Hall,

The clinical reviewer has the following informational request regarding your (b) (4) Velac Gel (clindamycin, 1% - tretinoin, 0.025%).

**Clinical Reviewer's Information Request:**

Dermal safety studies - Were irritation, contact sensitization, photorritation and photoallergenicity studies done with the final to be marketed formulation (TBMF) i.e. the formulation with (b) (4) methylparaben concentration ?

Has the spectrophotometric analysis been done with the final TBMF ? If so, where is it located ?

Please provide this information via facsimile to my attention and in a formal submission to your NDA by October 8, 2004.

Respectfully,

Margo Owens  
Project Manager

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/s/

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Margo Owens  
10/7/04 11:59:27 AM  
CSO  
Faxed to sponsor 10/7/04.

(b) (4)

## FDA Facsimile Memorandum

**Date:** October 5, 2004  
**To:** Sharon L. Hall, Senior Director, Regulatory Affairs  
Connetics Corporation  
**From:** Margo Owens, Project Manager  
**Subject:** (b) (4) Velac Gel (clindamycin, 1% - tretinoin 0.025%)

Ms. Hall,

The clinical reviewer has the following informational request regarding your (b) (4)  
(b) (4) Velac Gel (clindamycin, 1% - tretinoin, 0.025%).

**Clinical Reviewer's Information Request:**

Please clarify whether \$29,711.29 is a study specific payment that all investigators received or was this payment only issued to the following investigators: (b) (6)

Please provide this information in a formal submission to your NDA by October 8, 2004.

Respectfully,

Margo Owens  
Project Manager

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/s/

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Margo Owens  
10/5/04 02:41:40 PM  
CSO  
Faxed to sponsor 10/5/04.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Frances LeSane, Supervisory Project Manager, DAIDP, HFD-520</b>		FROM: <b>HFD-540 (Division of Dermatologic and Dental Drug Products)</b> <b>Margo Owens, Project Manager</b> <b>Bindi Nikhar, M.D., Medical Officer</b>		
DATE August 31, 2004	IND NO.	NDA NO. (b) (4)	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT 8/23/04
NAME OF DRUG Velac (clindamycin 1% - tretinoin, 0.025%) Gel	PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG 4	DESIRED COMPLETION DATE 4/23/05	
NAME OF FIRM: Connetics Corporation				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Please review this new NDA in terms of Clinical Microbiology.  If you have any questions, please feel free to contact me at 301-827-2046 or email at owensm or Bindi Nikhar at 301-827-2073 or email at nikharb.  Thank you.				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

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Frances LeSane  
9/13/04 04:27:46 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

(b) (4)

Connetics  
Attention: Sharon L. Hall  
Senior Director, Regulatory Affairs  
3290 West Bayshore Road  
Palo Alto, CA 94303

Dear Ms. Hall:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Velac (clindamycin, 1% / tretinoin, 0.25%) Gel

Review Priority Classification: Standard

Date of Application: August 23, 2004

Date of Receipt: August 25, 2004

Our Reference Number: (b) (4)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 22, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 25, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

Page 2

U.S. Postal Service:

Center for Drug Evaluation and Research  
Division of Dermatologic & Dental Drug Products, HFD-540  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

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

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

*{See appended electronic signature page}*

MARY JEAN KOZMA-FORNARO  
SUPERVISOR, PROJECT MANAGEMENT  
Division of Dermatologic & Dental Drugs  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Mary Jean Kozma Fornaro  
9/7/04 11:20:21 AM

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 50-803 Supplement # Efficacy Supplement Type SE-

Trade Name: Velac Gel  
Established Name: clindamycin - tretinoin  
Strengths: 1% - 0.025%

Applicant: Connectics Corporation  
Agent for Applicant: n/a

Date of Application: August 23, 2004  
Date of Receipt: August 25, 2004  
Date clock started after UN: N/A  
Date of Filing Meeting: October 13, 2004  
Filing Date: November 5, 2004  
Action Goal Date (optional):

User Fee Goal Date: June 25, 2005

Indication(s) requested: treatment of acne vulgaris

Type of Original NDA: (b)(1)  (b)(2)   
OR  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR  NDA is a (b)(2) application

Therapeutic Classification: S  P   
Resubmission after withdrawal?  Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.) 3  
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A  YES  NO   
**If an electronic NDA, all forms and certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format?

Additional comments: Review aids were submitted in electronic format to include published literature, photographs, labeling, case report forms and SAS datasets.

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A  YES  NO
- Is it an electronic CTD (eCTD)? N/A  YES  NO   
**If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments: This is a paper CTD.

- Patent information submitted on form FDA 3542a? YES  NO
- Exclusivity requested? YES, 3 Years NO   
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

**NOTE:** Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge . . .”

- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
**NOTE:** Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y  NO
- PDUFA and Action Goal dates correct in COMIS? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 65,369
- End-of-Phase 2 Meeting(s)? Date(s) 8/26/02 NO   
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 5/27/04 NO   
If yes, distribute minutes before filing meeting.

**Project Management**

- Was electronic “Content of Labeling” submitted? YES  NO   
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES  NO
- Risk Management Plan consulted to ODS/IO? N/A  YES  NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y  NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A  YES  NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A  YES  NO
- Has DOTCDP been notified of the OTC switch application? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES  NO

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: October 13, 2004

**BACKGROUND:** Velac Gel (clindamycin, 1% - tretinoin, 0.025%) is a 505(b)(2) application for the treatment of acne vulgaris. This NDA is being filed under section 505(b)(2) of the FD&C Act because it is supported in part by reference to published literature for fertility and peri-postnatal development for which the Applicant does not have rights of reference to the underlying data. There is currently no approved product that is a combination of clindmycin phosphate and tretinoin that may serve as a reference listed drug. (Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

**ATTENDEES:** Stanka Kukich, M.D., Sandra Kweder, M.D., Jonca Bull, M.D., Terri Rumble, Bindi Nikhar, M.D., Markham Luke, M.D., Ph.D., Ramesh Sood, Ph.D., Shulin Ding, Ph.D., Paul Brown, Ph.D., Jill Merrill, Ph.D., Chandra Chaurasia, Ph.D., Mat Soukpu, Ph.D., Mohamed Alish, Ph.D., Kathleen Fritsch, Ph.D., Steve Thomson, Ph.D., Margo Owens, Roy Blay, Ph.D., Connie Mahon, Ph.D., Fred Marsik, Ph.D.

**ASSIGNED REVIEWERS** (including those not present at filing meeting) :

<b><u>Discipline</u></b>	<b><u>Reviewer</u></b>
Medical:	Bindi Nikhar, M.D.
Secondary Medical:	Markahm Luke, M.D., Ph.D
Statistical:	Matthew Soukup, Ph.D. Kathleen Fritsch, Ph.D.
Pharmacology:	Jill Merrill, Ph.D.
Statistical Pharmacology:	Steve Thomson, Ph.D.
Chemistry:	Shulin Ding, Ph.D.
Environmental Assessment (if needed):	n/a
Biopharmaceutical:	Chandra Chaurasia, Ph.D.
Microbiology, sterility:	n/a
Microbiology, clinical (for antimicrobial products only):	Connie Mahon, Ph.D.
DSI:	Roy Blay, Ph.D.
Regulatory Project Management:	Margo Owens
Other Consults:	

Per reviewers, are all parts in English or English translation? YES  NO

If no, explain:

CLINICAL FILE  REFUSE TO FILE

• Clinical site inspection needed? YES  NO

• Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Biopharm. inspection needed?		YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
PHARMACOLOGY	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• GLP inspection needed?		YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Establishment(s) ready for inspection?		YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>
	• Microbiology		YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>

ELECTRONIC SUBMISSION:  
Any comments: n/a

**REGULATORY CONCLUSIONS/DEFICIENCIES:  
(Refer to 21 CFR 314.101(d) for filing requirements.)**

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
  - No filing issues have been identified.
  - Filing issues to be communicated by Day 74. List (optional):
    1. Biostatistics - Insufficient results of interim analysis were submitted.

**ACTION ITEMS:**

1.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3.  Convey document filing issues/no filing issues to applicant by Day 74.

Filing review issues identified. Biostatistics. Letter issued 11/5/04  
Note: NDA renumbered to 50-803 per the guidance document issued by the Agency in May 1998, Guidance for Industry and Reviewers Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act. This guidance document defines the administrative actions required by the Agency for reviewing and approving antibiotic drug applications that were submitted after November 21, 1997. Also per the Federal Register notice Docket Number: 99N-3088, Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs issued January 24, 2000, which lists the active drug substances, including any derivative thereof, that are directly affected by the repeal of Section 507.

Margo Owens  
Regulatory Project Manager, HFD-540

## Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): The applicant has not provided a referenced listed drug. The application is filed as a 505(b)(2) because they are referencing published literature for fertility and peri-posnatal development for which they do not have rights of reference the underlying data.
3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES  NO

**(Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "No," skip to question 4. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO   
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES  NO

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

**(Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "No," skip to question 5. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO

(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

**NOTE:** *If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If “Yes,” skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES  NO

*If “No,” please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of “pharmaceutical equivalent” or “pharmaceutical alternative,” as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES  NO

*If “No,” skip to question 6.*

*If “Yes,” please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

**\*\*This application provides for a combination of clindamycin, 1% and tretinoin, 0.025%.**

- (b) Is the approved drug product cited as the listed drug? YES  NO
6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”). n/a as there is no listed drug.
7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES  NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES  NO
9. Is the rate at which the product’s active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES  NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES  NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s): 5,690,923

**NOTE:** *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?  
YES  NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?  
YES  NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?  
N/A  YES  NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?  
N/A  YES  NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).  
YES  NO
- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.  
YES  NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# 65,369 NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES  NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES  NO

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

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Margo Owens  
5/11/2006 02:38:01 PM  
CSO

Mary Jean Kozma Fornaro  
5/11/2006 03:34:55 PM  
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	<b>PRESCRIPTION DRUG USER FEE COVER SHEET</b>	Form Approved: OMB No. 0910-0297 Expiration Date: December 31, 2006.
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**See Instructions on Reverse Side Before Completing This Form**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Connetics Corporation 3290 West Bayshore Road Palo Alto, CA 94303	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER (b) (4)
2. TELEPHONE NUMBER (Include Area Code)  ( 650 ) 843.2858	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:  _____ (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME Velac (clindamycin 1% - tretinoin 0.025%) Gel	6. USER FEE I.D. NUMBER 4826

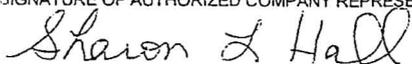
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?  
 YES     NO  
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and 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:

Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	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.
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Sharon L. Hall Senior Director, Regulatory Affairs	DATE 23 AUG 2004
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