

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**050803Orig1s000**

**CHEMISTRY REVIEW(S)**

**NDA 50-803**

**VELTIN™ (Clindamycin Phosphate and Tretinoin) Gel  
1.2%/0.025%**

**Stiefel, a GSK Company**

**CMC Review  
for  
Division of Dermatology and Dental Products**

**Shulin Ding, Ph.D.**

**Branch IV, Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment**

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# Chemistry Review Data Sheet

1. NDA 50-803
2. REVIEW #: 2
3. REVIEW DATE: June 22, 2010
4. REVIEWER: Shulin Ding, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

<u>Submission(s)</u>	<u>Document Date</u>
Original	Aug. 23, 2004
Amendment <sup>1</sup>	Oct. 8, 2004
Amendment <sup>2</sup>	Nov. 22, 2004
Amendment <sup>3</sup>	Dec. 6, 2004
Amendment <sup>4</sup>	Jan. 28, 2005
Amendment <sup>5</sup>	Feb. 17, 2005
Amendment <sup>6</sup>	March 2, 2005
Amendment <sup>7</sup>	March 8, 2005
Amendment <sup>8</sup>	March 22, 2005
Amendment <sup>9</sup>	April 5, 2005
Amendment <sup>10</sup>	April 22, 2005
Amendment <sup>11</sup>	May 12, 2005
Amendment <sup>12</sup>	May 16, 2005

## 6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (Complete response to non-approvable action letter dated June 10, 2005)	Oct. 16, 2009
Amendment <sup>13</sup>	Nov, 27, 2009
Amendment <sup>13</sup>	Dec, 22, 2009
Amendment <sup>14</sup>	Feb. 12, 2010
Amendment <sup>15</sup>	March 12, 2010
Amendment <sup>16</sup>	March 17, 2010
Amendment <sup>17</sup>	May 4, 2010 and May 5, 2010
Amendment <sup>18</sup>	May 24, 2010
Amendment <sup>19</sup>	June 1, 2010
Amendment <sup>20</sup>	June 15, 2010
Amendment <sup>21</sup>	See footnote

<sup>1</sup>The 10/8/04 amendment provides for a response to clinical and CMC questions.

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- <sup>2</sup>The 11/22/04 amendment provides for a response to requests for information contained in the NDA filing Review Letter dated Nov. 5, 2004.
- <sup>3</sup>The 12/6/04 amendment provides for a response to the chemist's request for samples contained in the NDA filing review letter dated Nov. 5, 2004.
- <sup>4</sup>The 1/28/05 amendment provides for an additional comparability protocol.
- <sup>5</sup>The 2/17/05 amendment provides for copies of foreign labels.
- <sup>6</sup>The 3/2/05 amendment provides for two additional proposed proprietary trade names.
- <sup>7</sup>The 3/8/05 amendment provides for supporting data for the proposed trade names.
- <sup>8</sup>The 3/22/05 amendment provides for a response to CMC information request dated March 14, 2005.
- <sup>9</sup>The 4/5/05 amendment provides for a response to CMC information request on comparability protocols dated March 29, 2005.
- <sup>10</sup>The 4/22/05 amendment provides for a partial response to CMC information request dated April 15, 2005.
- <sup>11</sup>The 5/12/05 amendment provides for a response to CMC information request dated April 15, 2005 (b) (4).
- <sup>12</sup>The 5/16/05 amendment provides for a response to CMC information request dated April 15 and 28, 2005 regarding analytical methods and method validation.
- <sup>13</sup>The 11/27/09 and 12/22/09 amendments provide for the addition and deletion of a packaging site, (b) (4)
- <sup>14</sup>The 2/12/2010 amendment provides for a response to the information request letter dated Jan. 26, 2010, and the submission of two drug product samples as requested in the information request letter dated Jan. 26, 2010.
- <sup>15</sup>The 3/12/2010 amendment provides for a response to the Agency's labeling comments conveyed in the IR letter dated March 4, 2010.
- <sup>16</sup>The 3/17/2010 amendment provides for a response to the Agency's questions conveyed in teleconferences dated March 5, 9 and 11, 2010 regarding product appearance/dosage form. The amendment includes the submission of six drug product samples as requested by the Agency in the teleconferences.
- <sup>17</sup>The 5/4/2010 and 5/5/10 amendments provide for a response to the information request letter dated April 23, 2010, and revised label/labeling.
- <sup>18</sup>The 5/24/2010 amendment provides for a response to the information request letter dated May 14, 2010 regarding turbidity method.
- <sup>19</sup>The 6/1/2010 amendment provides for a revised labeling.
- <sup>20</sup>The 6/15/2010 amendment provides for a revised labeling which contains all CMC-recommended changes.
- <sup>21</sup>Received via e-mail on 6/22/2010. It provides for the final version of carton/container labels. An official amendment submitted to CDER document room is said to follow by the applicant in the e-mail.

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Stiefel, a GSK Comapny  
Address: 20 TW Alexander Dr. Research Triangle Park, NC 27709  
Representative: Salisa Hauptmann, Vice President, Global Regulatory Affairs  
Telephone: 919-990-6133

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: VELTIN™ Gel  
b) Non-Proprietary Name (USAN): Clindamycin phosphate and tretinoin  
c) Code Name/# (ONDQA only): None  
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 4
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

10. PHARMACOL. CATEGORY: Skin agent  
Clindamycin Phosphate – Antibiotic  
Tretinoin - Retinoid

## Chemistry Review Data Sheet

11. DOSAGE FORM: Gel
12. STRENGTH/POTENCY: Clindamycin Phosphate 1.2%, Tretinoin 0.025%
13. ROUTE OF ADMINISTRATION: Topical
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
 SPOTS product – Form Completed  
 Not a SPOTS product

## Chemistry Review Data Sheet

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Clindamycin Phosphate

INN Name:

Compendial Name:

Chemical Name:

CAS Registry Number:

Molecular Formula:

Molecular weight:

Clindamycin phosphate

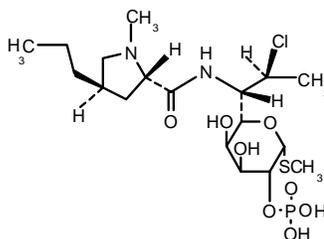
Clindamycin phosphate, USP

Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo- $\alpha$ -D-galacto-octopyranoside 2-(dihydrogen phosphate) or (7-(S)-chloro-7-deoxylincomycin-2-phosphate)

24729-96-2

 $C_{18}H_{34}ClN_2O_8PS$ 

504.97 g/mole



Tretinoin

INN Name:

Compendial Name:

Chemical Name:

CAS Registry Number:

Molecular Formula:

Molecular weight:

Tretinoin

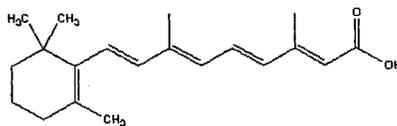
Tretinoin, USP

all-trans 3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

302-79-4

 $C_{20}H_{28}O_2$ 

300.44 g/mole



Chemistry Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	[REDACTED]	(b) (4)	3	Adequate	Oct. 9, 2009	Reviewed by Mahnaz Farahani on 10/07/2009, and deemed adequate to support ANDA 90-785 (Clindamycin phosphate foam 1%, Cobrek Pharmaceuticals). There have been no technical changes in the DMF since the review.
	II			1	Adequate	3/9/2010	Reviewed by Shulin Ding
	III			4	Adequate	5/8/2008	(b) (4) has been reviewed and deemed acceptable (see the DMF review by Bogdan Kurtyka dated 5/8/2008). No significant changes since the review.  Extractable studies were conducted (b) (4) meet the limits outlined in the USP <661> and 21CFR 175.300, indicating they are qualified for pharmaceutical uses and also safe to contact food.

<sup>1</sup>Action codes for DMF Table:

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

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,369	Original IND dated Oct. 23, 2002

**18. STATUS:**

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable	---	
EES	Acceptable	3/18/2010	E. Johnson
Pharm/Tox	Acceptable	2/16/2010 and 3/4/2010	Jill Merrill, Ph.D.
Biopharm	Not needed	1/21/10	Tapash Ghosh
DMEPA	Acceptable (proprietary name)	4/20/10	Zachary Oleszczuk
Methods Validation	Not planned	6/3/10	Shulin Ding, Ph.D.
Environment Assessment	Acceptable.	5/3/10	Shulin Ding, Ph.D.
Microbiology	Not applicable	5/3/10	Shulin Ding, Ph.D.

**19. ORDER OF REVIEW (OGD Only): N/A**

# The Chemistry Review for NDA 50-803

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP, and labels/labeling have adequate information required. Therefore, from a CMC perspective, this NDA is recommended for “Approval”.

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

None

### II. Summary of Chemistry Assessments

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

##### 1) Drug Product

This submission is a Class 2 resubmission of NDA 50803. NDA 50803 Velac gel received a “not approvable” action in the first cycle review due to a positive signal observed following exposure to Velac gel in both the vehicle and clindamycin arms of a carcinogenicity study in a Tg.AC mouse model. The applicant has reformulated since then, and resubmitted the NDA with the new formulation, Veltin gel. The new formulation, Veltin gel, is very similar to Velac gel in appearance and composition. The only formulation differences are that Veltin gel does not contain (b) (4) whereas Velac gel did (b) (4) and Veltin gel (b) (4) in Velac gel (b) (4).

The proposed product, Veltin gel, is a yellowish, opaque, aqueous gel containing two commercially available, USP grade active pharmaceutical ingredients: clindamycin phosphate (1.2% equivalent to 1% of clindamycin) and tretinoin (0.025%). Both clindamycin phosphate and tretinoin are fully solubilized in the formulation. The turbidity of the gel is (b) (4) an inherent property of the gel vehicle although it is unclear how the turbidity is produced.

Veltin gel is filled into (b) (4) aluminum tubes, sealed at the neck (b) (4) and capped with a white (b) (4) screw cap. At time of use, the aluminum seal is punctured to allow the formulation to be squeezed out. Veltin gel is proposed to be supplied in 30 g tubes. (b) (4)

The formulation of Veltin gel is consist of nine compendial excipients (butylated hydroxytoluene, Carbomer 940, citric acid anhydrous, edetate disodium, methylparaben, (b) (4), propylene glycol, tromethamine and purified water), and one non-compendial (b) (4) (POE-4) which is incorporated in the formulation (b) (4). POE-4 is listed in the FDA inactive

## Chemistry Assessment Section

ingredient database, and has been used in approved topical products with a maximum concentration of 5.22%.

The proposed to-be marketed formulation is the same formulation used in the Phase 3 clinical study. It is also the same formulation used in the bioavailability study, and the registration stability studies.

The real time long term stability data (12-30 months from four commercial scale batches) provided in the resubmission support the proposed 18 months expiration dating period for Veltin gel 30 g tubes stored at a controlled room temperature of 68-77°F (20-25°C). The proposed expiration dating period with storage condition is, therefore, acceptable.

## 2) Drug Substance

There are two drug substances involved in this NDA: clindamycin phosphate, USP, and tretinoin, USP. Their solid properties such as polymorph and particle size are not critical to the quality of the proposed drug product because the formulation and the manufacturing process of the proposed drug product are designed to ensure a complete solubilization of clindamycin phosphate and tretinoin.

### Clindamycin phosphate:

Clindamycin phosphate is very water soluble. (b) (4)

[REDACTED]

Clindamycin phosphate is a pro-drug of clindamycin. It is inactive *in vitro*. Topical application initiates hydrolysis to the formation of available or free clindamycin.

The applicant references DMF (b) (4) for clindamycin phosphate drug substance. DMF (b) (4) was most recently reviewed on Oct. 7, 2009, for ANDA 90-785 (Clindamycin phosphate foam 1%, Cobrek Pharmaceuticals, Inc.), and deemed adequate to support the ANDA. No technical changes in the DMF have been reported to the Agency since the last review. DMF (b) (4) is, therefore, concluded to be adequate to support NDA 50-803.

### Tretinoin:

Tretinoin is sparingly soluble in water. It degrades upon exposure to oxygen and light (both visible and UV). (b) (4)

[REDACTED]

The applicant references DMF (b) (4) for tretinoin drug substance. DMF (b) (4) has been reviewed and deemed adequate to support this NDA (DMF Chemistry Review #7 by Shulin Ding on March 9, 2010).

## B. Description of How the Drug Product is Intended to be Used

The drug product is intended for topical treatment of acne vulgaris. It should be applied once daily in the evening, using a pea size amount to lightly cover the entire affected area. Avoid the eyes, lips, and mucous membranes.

## Chemistry Assessment Section

The drug product is supplied in 30 g aluminum tubes. [REDACTED] (b) (4)

**C. Basis for Approvability or Not-Approval Recommendation**

The NDA provided adequate information on the drug substances, formulation, the raw material controls, manufacturing process, specifications, and container/closures. It also provided sufficient stability data to assure the strength, purity, and quality of the drug product throughout its shelf-life. On March 18, 2010, the Office of Compliance has issued an “acceptable” overall recommendation for all the facilities involved (Attachment 1). The proposed proprietary name, Veltin™, has been accepted by DMEPA. Labels/labeling have required information.

**III. Administrative**

**A. Reviewer’s Signature:** in DARRTS

**B. Endorsement Block:** in DARRTS

**C. CC Block:** in DARRTS

51 Pages Have Been Withheld in Full  
Immediately Following this Page as B4  
(CCI/TS)

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

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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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SHULIN DING  
06/24/2010

MOO JHONG RHEE  
06/24/2010  
Chief, Branch IV

# **NDA 50-803**

**Velac® (Clindamycin 1% - Tretinoin 0.025%) Gel**

**Connetics Corporation**

**Shulin Ding, Ph.D.**

**Division of Metabolic and Endocrine Drug Products**

**HFD-510**

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# Chemistry Review Data Sheet

1. NDA 50-803
2. REVIEW #: 1
3. REVIEW DATE: June 1, 2005
4. REVIEWER: Shulin Ding, Ph.D.
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	Aug. 23, 2004
Amendment <sup>1</sup>	Oct. 8, 2004
Amendment <sup>2</sup>	Nov. 22, 2004
Amendment <sup>3</sup>	Dec. 6, 2004
Amendment <sup>4</sup>	Jan. 28, 2005
Amendment <sup>5</sup>	Feb. 17, 2005
Amendment <sup>6</sup>	March 2, 2005
Amendment <sup>7</sup>	March 8, 2005
Amendment <sup>8</sup>	March 22, 2005
Amendment <sup>9</sup>	April 5, 2005
Amendment <sup>10</sup>	April 22, 2005
Amendment <sup>11</sup>	May 12, 2005
Amendment <sup>12</sup>	May 16, 2005

<sup>1</sup>The 10/8/04 amendment provides for a response to clinical and CMC questions.

<sup>2</sup>The 11/22/04 amendment provides for a response to requests for information contained in the NDA filing Review Letter dated Nov. 5, 2004.

<sup>3</sup>The 12/6/04 amendment provides for a response to the chemist's request for samples contained in the NDA filing review letter dated Nov. 5, 2004.

<sup>4</sup>The 1/28/05 amendment provides for an additional comparability protocol.

<sup>5</sup>The 2/17/05 amendment provides for copies of foreign labels.

<sup>6</sup>The 3/2/05 amendment provides for two additional proposed proprietary trade names.

<sup>7</sup>The 3/8/05 amendment provides for supporting data for the proposed trade names.

<sup>8</sup>The 3/22/05 amendment provides for a response to CMC information request dated March 14, 2005.

<sup>9</sup>The 4/5/05 amendment provides for a response to CMC information request on comparability protocols dated March 29, 2005.

<sup>10</sup>The 4/22/05 amendment provides for a partial response to CMC information request dated April 15, 2005.

<sup>11</sup>The 5/12/05 amendment provides for a response to CMC information request dated April 15, 2005 (b) (4).

<sup>12</sup>The 5/16/05 amendment provides for a response to CMC information request dated April 15 and 28, 2005 regarding analytical methods and method validation.

## Chemistry Review Data Sheet

**7. NAME & ADDRESS OF APPLICANT:**

Name: Connetics Corporation  
Address: 3290 West Bayshore Road, Palo Alto, CA 94303  
Representative: Sharon L. Hall, Senior Director, Regulatory Affairs  
Telephone: 650-843-2858

**8. DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: Velac<sup>®</sup> Gel  
b) Non-Proprietary Name (USAN): Clindamycin and tretinoin gel  
c) Code Name/# (ONDC only): None  
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 4
  - Submission Priority: S

**9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)**

**10. PHARMACOL. CATEGORY:** Skin agent  
Clindamycin – Anti-infective  
Tretinoin - Retinoid

**11. DOSAGE FORM:** Gel

**12. STRENGTH/POTENCY:** Clindamycin 1%, Tretinoin 0.025%

**13. ROUTE OF ADMINISTRATION:** Topical

**14. Rx/OTC DISPENSED:**  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product

## Chemistry Review Data Sheet

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Clindamycin Phosphate

INN Name:

Compendial Name:

Chemical Name:

CAS Registry Number:

Molecular Formula:

Molecular weight:

Clindamycin phosphate

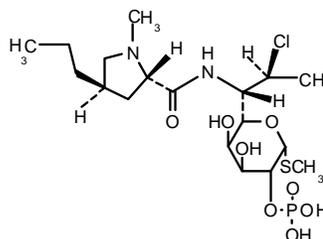
Clindamycin phosphate, USP

Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo- $\alpha$ -D-galacto-octopyranoside 2-(dihydrogen phosphate) or (7-(S)-chloro-7-deoxylincomycin-2-phosphate)

24729-96-2

 $C_{18}H_{34}ClN_2O_8PS$ 

504.97 g/mole



Tretinoin

INN Name:

Compendial Name:

Chemical Name:

CAS Registry Number:

Molecular Formula:

Molecular weight:

Tretinoin

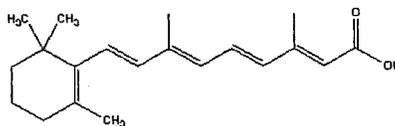
Tretinoin, USP

all-trans 3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid

302-79-4

 $C_{20}H_{28}O_2$ 

300.44 g/mole



Chemistry Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	Sep. 8, 2003	Reviewed by Bart Ho, Chemistry Review #5. No significant changes since the review.
	II			3	Adequate	April 8, 2004	Reviewed by Liang-Lii Huang, Chemistry Review #4
	III			4	Adequate	May 26, 2005	(b) (4) has been reviewed and deemed acceptable (see the DMF review by Ernest Pappas dated 5/6/2003).  Extractable studies were conducted (b) (4) meet the limits outlined in the USP <661> and 21CFR 175.300, indicating they are qualified for pharmaceutical uses and also safe to contact food.

<sup>1</sup>Action codes for DMF Table:

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

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,369	Original IND dated Oct. 23, 2002

**18. STATUS:**

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable	---	
EES	Pending	5/26/05	
Pharm/Tox	Not Approvable	5/16/05	Jill Merrill, Ph.D.
Biopharm	Acceptable	4/26/05	Chandra Chaurasia
DMETS	Unacceptable proprietary name	11/11/04	Jinhee Jahng
Methods Validation	Not planned	5/26/05	Shulin Ding, Ph.D.
Environment Assessment	Acceptable.	5/26/05	Shulin Ding, Ph.D.
Microbiology	Not applicable	5/26/05	Shulin Ding, Ph.D.

**19. ORDER OF REVIEW (OGD Only): N/A**

# The Chemistry Review for NDA 50-803

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 50-803 is recommended for **Approvable (AE)** action from the standpoint of chemistry, manufacturing and controls (CMC).

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

None

### II. Summary of Chemistry Assessments

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

##### 1) Drug Product

The proposed drug product is an aqueous-based gel containing two commercially available, USP grade active pharmaceutical ingredients: clindamycin phosphate (expressed as 1% clindamycin) and tretinoin (0.025%). The gel is yellowish, slightly viscous, and translucent to slightly turbid. It has a smooth consistency (b) (4). Both clindamycin phosphate and tretinoin are fully solubilized in the formulation of the proposed drug product.

The gel is filled into (b) (4) aluminum tubes, sealed at the neck with an (b) (4), and capped with a white (b) (4) screw cap. At time of use, the aluminum seal is punctured to allow the formulation to be squeezed out. The proposed drug product is end-crimped and supplied in (b) (4) 30 g (b) (4) tubes.

The formulation of Velac gel consists of nine (9) compendial excipients (butylated hydroxytoluene, Carbomer 940, citric acid anhydrous, edetate disodium, methylparaben, (b) (4) (b) propylene glycol, tromethamine and purified water), and (b) (4) non-compendial (b) (4) (POE-4 (b) (4)). (b) (4) (b) (4).

POE-4 is listed in the FDA inactive ingredient database, and has been used in approved topical products with a maximum concentration of 5.22%. (b) (4)

The proposed to-be marketed formulation is identical to the one used in the Phase 3 clinical studies.

Long term stability data (12 months, three batches) are provided for (b) (4) 30 g (b) (4) tube size (b) (4). The batches meet the proposed product specification (b) (4) when stored at

## Chemistry Assessment Section

25°C/60%RH. A significant degradation was noticed in all of the samples stored under the accelerated condition, and the samples failed some of the proposed related substance criteria at the end of the accelerated studies (6 months). The 30°C samples also showed an upward trend in related substances.

The batch release and the primary stability data on clindamycin phosphate, its related substances, and (b) (4) were generated using an HPLC method (Method 73.5556) which was different from the proposed regulatory method (R0252). The batch release and the primary stability data on (b) (4) and (b) (4) have been accepted to support drug product expiry period and specification after bridging data were provided in the amendment dated May 16, 2005, showing that these two methods yield comparable results for these two tests. The batch release and the primary stability data provided in the original submission on (b) (4) and unspecified related substances are, however, concluded to be irrelevant because the two methods are not comparable for these tests.

As a result of the irrelevant data, the proposed acceptance criteria for clindamycin related substances are recommended as tentative. The criteria should be reviewed again when adequate relevant data become available.

The expiry period of the proposed drug product is recommended to be set based on real time data due to (1) the lack of release and stability data generated by the proposed regulatory method R0252, and (2) the significant drug degradation noticed in the accelerated stability studies. Submitted stability data support (b) (4) of expiry period for (b) (4) 30g (b) (4) of Velac Gel stored at a controlled room temperature of 68-77°F (20-25°C).

## 2) Drug Substance

There are two drug substances involved in this NDA: clindamycin phosphate, USP, and tretinoin, USP. Their solid properties such as polymorph and particle size are not critical to the quality of the proposed drug product because the formulation and the manufacturing process of the proposed drug product are designed to ensure a complete solubilization of clindamycin phosphate and tretinoin.

### Clindamycin phosphate:

Clindamycin phosphate is very water soluble (b) (4)

Clindamycin phosphate is a pro-drug of clindamycin. It is inactive *in vitro*. Topical application initiates hydrolysis to the formation of available or free clindamycin.

The applicant references DMF (b) (4) for clindamycin phosphate drug substance. DMF (b) (4) was most recently reviewed on Sep. 8, 2003, for NDA 50756/S-011 (BenzaClin topical Gel), and deemed adequate to support the NDA. No significant technical changes have been reported to the agency since the last review. DMF (b) (4) is concluded to be adequate to support NDA 50-803.

## Chemistry Assessment Section

Tretinoin:

Tretinoin is sparingly soluble in water. It degrades upon exposure to oxygen and light (both visible and UV) [REDACTED] (b) (4)

The applicant references DMF [REDACTED] (b) (4) for tretinoin drug substance. DMF [REDACTED] (b) (4) was most recently reviewed on June. 8, 2004, for ANDA 76-498 (Tretinoin topical cream), and deemed adequate to support the ANDA. No changes have been reported to the agency since the last review. DMF [REDACTED] (b) (4) is concluded to be adequate to support NDA 50-803.

**B. Description of How the Drug Product is Intended to be Used**

The drug product is intended for topical treatment of acne vulgaris. It should be applied once daily in the evening, using enough to lightly cover the entire affected area.

The drug product is supplied in 30 g aluminum tubes. [REDACTED] (b) (4)

**C. Basis for Approvability or Not-Approval Recommendation**

NDA 21-688 is approvable from the stand point of CMC pending an acceptable overall recommendation from Office of Compliance, and a satisfactory response for pending deficiencies listed on the last page of this review document.

**III. Administrative**

**A. Reviewer's Signature:** [REDACTED] in DFS

**B. Endorsement Block:** in DFS

**C. CC Block:** in DFS

41 Pages Have Been Withheld in Full Immediately  
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Shulin Ding  
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CHEMIST

Mamta Gautam-Basak  
6/2/05 10:01:59 AM  
CHEMIST  
Concur, Approvable

## NDA FILEABILITY CHECKLIST

**NDA Number:** (b) (4)

**Drug Name:** Velac<sup>®</sup> Gel (Clindamycin 1% - Tretinoin 0.025%)

**Applicant:** Connetics Corporation, 3290 West Bayshore Rd., Palo Alto, CA 94303

**IS THE CMC SECTION OF THIS APPLICATION FILEABLE? (Yes or No)** Yes

**Table 1 Fileability Checklist**

The following parameters are necessary for initiating a full review, e.g. complete enough for review but may have deficiencies.

	PARAMETER	YES	NO	COMMENT
1	Is the NDA organized adequately for its CMC content?	x		
2	Are the CMC sections adequately indexed & paginated?	x		
3	Is the CMC sections legible?	x		
4	Are all facilities identified with full street addresses, contact names & CFN#s?	x		No CFN#. Only registration # provided.
5	Is there a statement that all facilities are prepared for GMP inspections?	x		CTD Module 3 3.2.P.3.1 The only site in question is DP stability testing site, which is scheduled to be moved in January, 2005.
6	Has an environmental assessment or categorical exclusion been provided?	x		CTD Module 1 1.3.5
7	Does the drug substance section contain controls?	x		CTD Module 3 3.2.S.4
8	Does the drug product section contain controls?	x		CTD Module 3 3.2.P.5
9	Has stability data been submitted to justify the requested expiry date?	x		CTD Module 3 3.2.P.8
10	Has the applicant provided all requested data by the division during the IND & pre-NDA phases?		x	All requested are provided except method validation for potential interference from the other API and its degradants/impurities.
11	Have draft container labels been provided?	x		CTD Module 1 1.3.2.2
12	Has a draft package insert been provided?	x		CTD Module 1 1.3.2.1
13	Has an Investigational Formulations section been included?	x		CTD Module 3 3.2.P.2.2
14	Are there three Methods Validation documents?	x		
15	Is a statistical consult required?		x	
16	Is there a separate microbiological section? Is a micro consult required?		x	There is one page information in pharmaceutical development report (CTD Module 3 3.2.P.2.5) regarding selection of preservative concentration.

**Table 2 STABILITY DATA REQUIRED FOR FILEABILITY**

	<b>STABILITY DATA REQUESTED</b>	<b>YES</b>	<b>NO</b>
1	Does the NDA include 12 or more months of stability data?	<b>x</b>	
2	Does the stability data cover the expiry date?		<b>x</b>
3	Does the stability data include only the largest & smallest container sizes?	<b>x</b>	
4	Does the stability data include all packages sizes?		<b>x</b>
5	Are there tabular data for each size and batch?	<b>x</b>	
6	Are there graphical data for each size and batch?	<b>x</b>	
7	Is a statistical consult required?		<b>x</b>
8	Is a stability protocol included?	<b>x</b>	
9	Are the stability-indicating assays described?	<b>x</b>	
10	Is there the three-point stability commitment?	<b>x</b>	

**Table 3 DMF INFORMATION**

<b>DMF #</b>	<b>DMF HOLDER</b>	<b>TYPE</b>	<b>LOA DATE</b>	<b>DATE OF LAST REVIEW</b>
(b) (4)	(b) (4)	Type II	8/13/04	9/14/03
		Type II	8/11/04	6/6/04
		Type III	1/20/04	5/6/04

COMPLETION DATE: Oct. 13, 2004

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Shulin Ding, Ph.D.  
Review Chemist, HFD 510

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Mamta Gautam-Basak, Ph.D.  
Chemistry Team Leader, HFD 510

Attachment

Cc: Original NDA  
HFD-540/Division File  
HFD-510/Chm/SDing  
HFD-510/ChmTL/MGautam-Basak  
HFD-540/ProjMgr/MCwens  
HFD-830/DivDir/DLin

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Mamta Gautam-Basak  
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