

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**203752Orig1s000**

**CHEMISTRY REVIEW(S)**



Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis  
St. Louis, MO 63101  
Tel. (314) 539-3874

Date: October 12, 2012  
To: Caroline Strasinger, Review Chemist, ONDQA  
Through: Benjamin Westenberger, Deputy Director, Division of Pharmaceutical Analysis  
From: Anna Wokovich, Chemist, Division of Pharmaceutical Analysis  
Subject: Crystal formation of (b) (4) Estradiol TDDS with elevated humidity

**Objective:**

To determine if crystals form when the (b) (4) estradiol transdermal drug delivery system is exposed to elevated humidity.

**Background:**

ONDQA Review Chemist, Dr. Caroline Strasinger, submitted a Methods Validation Request for NDA 203-752, Noven Pharmaceuticals's (b) (4) (Estradiol Transdermal System). The requested determinations were for Release Liner Peel Force, Shear Adhesion, Peel Adhesion, Probe Tack, and Cold Flow. Additionally, Dr. Strasinger requested that samples (opened and with adhesive matrix exposed) be placed in a humid environment for 2-5 days and examined for crystals using a microscope.

**Conclusions:**

No crystals were observed for the ambient Day 1- Day 4 samples with their release liners on and off. No crystals were observed for the chamber (32°C and 75% RH) Day 1- Day 4 samples with their release liners on and off. Also, no crystals were observed for the chamber Day 1 - Day 4 samples that were in their intact pouches before opening.

**Samples/Materials:**

NDA samples of 6.6 cm<sup>2</sup>, 3.3 cm<sup>2</sup>, 2.475 cm<sup>2</sup>, and (b) (4) (b) (4) estradiol transdermal systems. (See Attachment A.)

**Experimental/Methods:**

For each dosage, systems removed from their pouches with their release liners intact, systems removed from their pouches with their release liners removed, and systems in their intact (sealed) pouches were placed in an environmental test chamber at 32°C and 75% relative humidity for 4 days. Also, systems in their intact (sealed) pouches were placed on the lab bench at ambient conditions.

Each test day, the designated samples were removed from the chamber as well as the designated ambient samples and examined for crystals macroscopically and microscopically. (See Attachment A.) After examination, the samples were returned to their storage conditions.

**Results/Discussion:**

Ambient conditions ranged from 17°C-22°C and 42%-66% relative humidity (RH), and the environmental test chamber was set to 32°C and 75% RH. No crystals were observed for the ambient Time 0, Day 1, Day 2, Day 3, and Day 4 samples with their release liners on and off. No crystals were observed for the chamber Day 1, Day 2, Day 3, and Day 4 samples with their release liners on and off. No crystals were observed for the chamber Day 1, Day 2, Day 3, and Day 4 samples that were in their intact pouches before opening. For the samples that had their release liners off, some dirt/threads from the air adhered to the adhesive. (See Attachment B.)

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/s/  
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MICHAEL L TREHY  
10/11/2012

**NDA 203752**  
**ADDENDUM**

**Minivelle (estradiol transdermal system)**

**Noven Pharmaceuticals Inc.**

**Caroline Strasinger, Ph.D.**  
**Review Chemist**

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

**CMC Review of NDA 203752**  
**For the Division of Reproductive and Urological Products**

# Chemistry Review Data Sheet

1. NDA 203752
2. REVIEW #: #2
3. REVIEW DATE: 25-SEP-2012
4. REVIEWER: Caroline Strasinger, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Quality Review #1 30-AUG-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment 0010  
Amendment 0011

Document Date

17-SEP-2012  
19-SEP-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Noven Pharmaceuticals, Inc.  
Address: Empire State Building  
350 Fifth Avenue, 37<sup>th</sup> Floor  
New York, NY 10118  
Representative: Sean M. Russell, Associate Director, Regulatory  
Affairs  
Telephone: 212-299-4208

# The Chemistry Review for NDA 203752

## The Executive Summary

### I. Synopsis of Information

Several clarifications were required regarding the Applicant's commitment to qualify a more distinguishable ink ( (b) (4) ) provided to the NDA on 27-AUG-2012 and previously discussed in Review #1.

In summary, the Applicant will launch their commercial product utilizing (b) (4) ink and continue to utilize (b) (4) ink while completing their qualification and stability work of the more distinguishable ink. The Applicant confirmed they do not intend to switch between (b) (4) and (b) (4) based on the concern for potential patient confusion.

### II. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has issued an “*ACCEPTABLE*” overall recommendation on all the manufacturing facilities.

The labels/labeling have adequate information.

Therefore, from the ONDQA perspective, this NDA is recommended for approval.

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

None

## Chemistry Assessment

### **Background**

NDA 203752 which provides for the Minivelle (estradiol transdermal system) was originally submitted 29-DEC-2012.

This addendum to the Quality Review dated 30-AUG-2012 addresses the following:

- An assessment of the risk of using the ink (b) (4) versus (b) (4) including a summary of extractables and leachables testing as well as an up dated Letter of Authorization (LoA) to reference the (b) (4) ink.
- Clarifications regarding the use of (b) (4) versus (b) (4) at product launch and during the qualification period.

### **Assessment of Risk**

The Applicant provided information in amendments dated 17-SEP-2012 and 19-SEP-2012 demonstrating that the change in ink from (b) (4) to (b) (4) is not of significant risk to implement. The applicant provided and updated LoA to reference the appropriate inks in DMF (b) (4) and stated that (b) (4). Additionally, the applicant provided a summary of extractable and leachable testing of systems printed with (b) (4) and no peaks were detected above the LOQ of (b) (4) ppm.

**Reviewer Evaluation:** (b) (4) improves the readability of the identifying label. Based on the risk analysis provided by the Applicant, implementing (b) (4) in the manufacturing process does not present a safety risk nor is it considered a major amendment to Application. The Applicant has committed to conducting concurrent stability studies to qualify the (b) (4) as indicated in the amendment dated 27-AUG-2012.

### **Clarification**

In a teleconference on 20-SEP-2012 it was confirmed that (b) (4) ink would be used to print the identifying label on the transdermal system at product launch, once the product is branded (b) (4) and during the on-going qualification and stability assessment of (b) (4). The Applicant confirmed they do not intend to switch between (b) (4) and (b) (4) based on the concern for potential patient confusion despite both inks being approved for use.

**Reviewer Evaluation:** The information is adequate.

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/s/  
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CAROLINE STRASINGER  
09/25/2012

TERRANCE W OCHELTREE  
09/28/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION REPORT SUMMARY**

**TO:** Caroline Strassinger, CMC Reviewer  
Office of New Drug Quality Assessment (ONDQA)  
E-mail Address: caroline.strassinger@fda.hhs.gov  
Phone: (301)-796-3776  
Fax: (301)-796-9877

**FROM:** FDA  
Division of Pharmaceutical Analysis  
Michael Trehy, MVP Coordinator  
Suite 1002  
1114 Market Street  
St. Louis, MO 63101  
Phone: (314) 539-3815

**Through:** Benjamin J. Westenberger, Deputy Director  
Phone: (314) 539-3869

**SUBJECT:** Methods Validation Report Summary

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Application Number: 203-752

Name of Product: (b) (4) (Estradiol transdermal System); (b) (4), 0.0375, 0.05, 0.075, 0.1 mg/day

Applicant: Noven Pharmaceuticals, Inc.

Applicant's Contact Person: Sean M. Russell

Address: 350 Fifth Avenue, 37<sup>th</sup> Floor, New York, NY 10118

Telephone: (212) 229-4208 Fax: NA

---

Date Methods Validation Consult Request Form Received by DPA: 5/7/2012

Date Methods Validation Package Received by DPA: 5/7/2012

Date Samples Received by DPA: 7/3/2012

Date Analytical Completed by DPA: 9/19/2012

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Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.   
2. Methods are acceptable with modifications (as stated in accompanying report).   
3. Methods are unacceptable for regulatory purposes.

Comments:

See attached memo for analyst's comments.



Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis  
St. Louis, MO 63101  
Tel. (314) 539-3874

Date: September 20, 2012  
To: Dr. Caroline Strasinger, Reviewer, Office of New Drug Quality Assessment  
Through: Benjamin Westenberger, Deputy Director, Division of Pharmaceutical Analysis  
From: Anna Wokovich, Chemist, Division of Pharmaceutical Analysis  
Subject: Method Validation for NDA 203-752  
NDA 203-752, (b) (4) transdermal drug delivery system  
Probe Tack, Peel Adhesion, Release Liner Peel Force, Cold Flow, and Shear Adhesion

The following methods were evaluated:

Probe-Tack Test for Transdermal Systems (DOCUMENT NO STP-QC-0516 REVISION 1 EFFECTIVE DATE 16 MAR 2012)

Peel Adhesion Test for Transdermal Systems (DOCUMENT NO STP-QC-0514 REVISION 2 EFFECTIVE DATE 29 MAR 2012)

Determination of the Peel Force from Release Liner for Transdermal Systems with small Area- Peel from Liner Test (DOCUMENT NO STP 412 REVISION 2 EFFECTIVE DATE 29 MAR 2012)

Cold Flow Test (DOCUMENT NO STP-QC-0515 REVISION 1 EFFECTIVE DATE 16 MAR 2012; Cold Flow test for Transdermal Systems)

Shear Adhesion of Transdermal Systems with Small Area- Shear Test (DOCUMENT NO STP 411 REVISION 3 EFFECTIVE DATE 14 MAR 2012)

The following methods are acceptable for quality control and regulatory purposes:

Probe-Tack Test for Transdermal Systems (DOCUMENT NO STP-QC-0516 REVISION 1 EFFECTIVE DATE 16 MAR 2012)

The following method was evaluated and is acceptable for quality control and regulatory purposes with modification:

Peel Adhesion Test for Transdermal Systems (DOCUMENT NO STP-QC-0514 REVISION 2 EFFECTIVE DATE 29 MAR 2012)

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/s/  
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MICHAEL L TREHY  
09/20/2012

BENJAMIN J WESTENBERGER  
09/21/2012

# **NDA 203-752**

## **Minivelle (estradiol) Transdermal System**

**Noven Pharmaceuticals, Inc.**

**Caroline Strasinger, Ph.D.**  
Review Chemist

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

**CMC Review of NDA 203-752  
For the Division of Reproductive and Urological Products**

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# Chemistry Review Data Sheet

1. NDA 203-752
2. REVIEW #: #1
3. REVIEW DATE: August 20, 2012
4. REVIEWER: Caroline Strasinger, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

29-DEC-2011

Amendment 0002

27-APR-2012

Amendment 0005

15-JUN-2012

Amendment 0006

02-JUL-2012

Amendment 0007

31-JUL-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Noven Pharmaceuticals, Inc.  
Address: Empire State Building  
350 Fifth Avenue, 37<sup>th</sup> Floor  
New York, NY 10118  
Representative: Sean M. Russell, Associate Director  
Telephone: 212-299-4208

## Chemistry Review Data Sheet

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

- a) Proprietary Name: Minivelle  
b) Non-Proprietary Name (USAN): estradiol transdermal system  
c) Code Name/#: N/A  
d) Chem. Type/Submission Priority:  
• Chem. Type: 3  
• Submission Priority: Standard

## 9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

## 10. PHARMACOL. CATEGORY: Steroid hormones

## 11. DOSAGE FORM: Transdermal System

## 12. STRENGTH/POTENCY: (b) (4), 0.0375, 0.05, 0.075, 0.1 mg/day;

## 13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

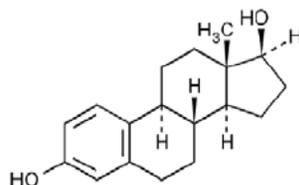
**Estradiol:**

Estra-1,3,5(10)-triene-3,17-diol, (17 $\beta$ )

Molecular Formula: C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>

Molecular Weight: 272.38

Chemistry Review Data Sheet



**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	5/24/2011	Dr. S. Dhanesar for ANDA (b) (4)
	III		3	Adequate	4/25/2011	Dr. R. Shaltmaz for ANDA (b) (4)	
	IV		4	N/A			
	III		1	Adequate	04/04/2012	Dr. C. Strasinger for NDA 203-752	
	IV		3	Adequate	06/14/2005	Dr. D. Klien for NDA (b) (4)	
	III		1	Adequate	08/12/2012	Dr. C. Strasinger for NDA 203-752	
	III		1	Adequate	04/04/2012	Dr. C. Strasinger for NDA 203-752	
	III		3	Adequate	11/30/2011	Dr. X. Li for ANDA (b) (4)	

<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")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-323	Vivelle®



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

NDA	20-538	Vivelle-Dot®
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### 18. STATUS:

#### ONDQA:

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	N/A		
EES	Acceptable	15-AUG-2012	Office of Compliance
Pharm/Tox	N/A		
Biopharm	Acceptable	20-AUG-2012	Tapash Ghosh, Ph.D.
LNC	N/A		
Methods Validation	To be done per ONDQA's policy Submitted 7-MAY-2012		Pending
DMEPA	N/A		
EA	Claim for categorical exclusion is granted	15-FEB-2012	Caroline Strasinger, Ph.D.
Microbiology	N/A		

# The Chemistry Review for NDA 203-752

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The Applicant of this NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has issued an overall "Acceptable" recommendation for the facilities involved in the NDA. The labels have adequate information as required.

Therefore, from the ONDQA perspective, this NDA is recommended for approval.

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

No CMC related Phase 4 are proposed at this time.

### II. Summary of Chemistry Assessments

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

##### Drug Substance:

The drug substance, estradiol, is a white to practically white crystal or powder with a melting point of 173-179°C. It has an empirical formula of C<sub>18</sub>H<sub>24</sub>O<sub>2</sub> and a molecular weight of 272.38. The drug substance will be manufactured and packaged at (b) (4)

The drug substance contains (b) (4)

In 30 years of manufacturing experience at (b) (4) no changes affecting (b) (4) have arisen. Estradiol is used in several currently approved FDA products including the referenced NDA 20-538 for Vivelle-Dot. The applicant references DMF (b) (4) for all relevant information pertaining to the manufacture, control and release of the drug substance. DMF (b) (4) was most recently reviewed and deemed adequate on 24-MAY-2011; no changes to the DMF have been made since this review, therefore DMF (b) (4) is deemed adequate to support NDA 203-752.

##### Drug Product:

Minivelle is a transdermal drug delivery system (TDDS) designed to continuously release 17β-estradiol when applied to intact skin. (b) (4) systems are proposed for market in this application ranging in strength from (b) (4) mg/day to 0.1 mg/day containing (b) (4)

## Executive Summary Section

mg to 1.65 mg estradiol. Minivelle has the same multipolymeric adhesive platform as the currently marketed Vivelle-Dot and has been designed to deliver the same therapeutic levels of estradiol as Vivelle and Vivelle-Dot, but from a smaller active surface area. The TDDS are circular in shape and translucent to slightly opaque white. The TDDS is manufactured at **Noven Pharmaceuticals in Miami, FL**. Two additional facilities have been listed for raw material and finished product microbial testing all of which are domestic. It was noted during review, that the maximum storage time for the raw material (b) (4) is (b) (4) from the date of manufacture. Use within (b) (4) prevents the impurity (b) (4) from rising above USP acceptance criterion of (b) (4).

The quality of the drug product is controlled by tests for appearance, assay, content uniformity, identification, adhesion, drug release, impurities, cold flow, pouch seal integrity and microbial limits. Each carton will contain eight TDDS of one strength. A 24 month expiration date has been granted based on 12 months of provided stability data and supporting Vivelle-Dot data.

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

Minivelle (estradiol) (b) (4) 0.0375, 0.05, 0.075, 0.1 mg/day is a multipolymeric adhesive system that releases estradiol continuously upon application to intact skin for the treatment of severe vasomotor symptoms associated with menopause. The adhesive side of Minivelle should be placed on a clean, dry area of the trunk of the body (including the abdomen or buttocks). Minivelle should not be applied to the breast. The transdermal delivery system is designed for continuous wear with application of a new system twice weekly to a different site with each application. The product should be stored at room temperature.

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

From the ONDQA perspective, this NDA is recommended for Approval.

The Applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. Also sufficient stability information is provided on the drug product in the NDA to assure strength, purity, and quality of the drug product during the expiration dating period (24 months).

Office of Compliance has issued an "Acceptable" overall recommendation for all facilities involved.

Labels/labeling have the required information.

**III. Administrative****A. Reviewer's Signature**

## Executive Summary Section

**B. Endorsement Block**

Chemist Name/Date: Caroline Strasinger, PhD 27-AUG-2012

ChemistryTeamLeaderName/Date: Donna Christner, PhD; 27-AUG-2012

ProjectManagerName/Date: Rebecca McKnight; 27-AUG-2012

**C. CC Block**

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/s/  
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CAROLINE STRASINGER  
08/30/2012

TERRANCE W OCHELTREE  
08/30/2012

Initial Quality Assessment  
Branch IV  
Division of New Drug Quality Assessment II

**OND Division:** Division of Reproductive and Urologic Products  
**NDA:** 203752  
**Applicant:** Noven Pharmaceuticals  
**Stamp Date:** 29-Dec-2011  
**PDUFA Date:** 29-Oct-2012  
**Trademark:** (b) (4)  
**Established Name:** Estradiol  
**Dosage Form:** Transdermal system  
**Route of Administration:** Transdermal  
**Indication:** Treatment of VMS  
  
**CMC Lead:** Donna F. Christner, Ph.D.

	YES	NO
<b>ONDQA Fileability:</b>	X	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	X	<input type="checkbox"/>

**Summary and Critical Issues:**

**A. Summary**

The drug product is a translucent, round, estradiol transdermal system available in (b) (4) sizes as follows, with the following estradiol concentrations. The patch is applied twice weekly.

**Table 2: Strengths of Estradiol Transdermal System**

Strength	Patch Size	Estradiol Concentration in Adhesive Blend	Estradiol Content per Unit
0.0375 mg/day	2.48 cm <sup>2</sup>	(b) (4)	0.62 mg
0.05 mg/day	3.30 cm <sup>2</sup>	(b) (4)	0.83 mg
0.075 mg/day	4.95 cm <sup>2</sup>	(b) (4)	1.24 mg
0.1 mg/day	6.60 cm <sup>2</sup>	(b) (4)	1.65 mg

Each transdermal system is composed of three layers as follows:

Proceeding from the visible surface toward the surface attached to the skin, these layers are:

- Layer 1: (b) (4)  
(b) (4) printed backing film.
- Layer 2: The active layer consisting of an acrylic adhesive, silicone adhesive, oleyl alcohol, povidone, dipropylene glycol and estradiol, with a (b) (4) mg/cm<sup>2</sup> coat weight.
- Layer 3: (b) (4) polyester (b) (4) release liner. (b) (4)  
(b) (4)

Each estradiol transdermal system is sealed in one pouch. There are two different pouch sized to accommodate different patch sizes. Patches are provided in “Calendar Packs” of 8 systems and in cartons containing 3 “Calendar Packs.”

## B. Critical issues for review

The applicant has performed a pivotal bioequivalence study, N28-004, which evaluated the highest dosage strength of (b) (4) of 1.65 mg estradiol/6.6 cm<sup>2</sup> (0.1 mg/day). They have also provided a supportive dose-proportionality study, N28-005, on three dosed of (b) (4) (b) (4) 0.827 mg estradiol/3.3 cm<sup>2</sup>, and 1.65 mg estradiol/6.6 cm<sup>2</sup> patches. They are requesting a biowaiver of the lower dosage strengths. Tapash Ghosh, Ph.D. has been assigned to address all BioPharmaceutic issues.

The applicant has used a bracketing design for their stability studies, since the different strengths are the same formulation and differ only by the size of the patch cut from the roll. This will require careful review.

## C. Comments for 74-Day Letter

See ATTACHMENT 1 for comments to be conveyed to the sponsor.

## D. Recommendation:

This NDA is fileable from a CMC perspective. Caroline Strasinger, Ph.D. is the primary CMC reviewer. Tapash Ghosh, Ph.D. is the assigned BioPharm reviewer.

REGULATORY BRIEFING RECOMMENDATION: Branch-level, since the formulation is highly similar to the approved Vivelle-Dot patch.

\_\_\_\_\_  
Donna F. Christner, Ph.D.

NDA Number: 203752    Type: 5

Established/Proper Name:  
estradiol transdermal system

Applicant: Noven  
Pharmaceuticals

Letter Date: 29-Dec-2011

Stamp Date: 29-Dec-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?		X	Drug substance information is provided in Module 3 Drug product information is provided as attachment to 356h and in Module 3
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>		X	N/A

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		Information provided in Module 3
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		Information provided on attachment to 356h

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		Information provided on 356h
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion requested as per 21 CFR 25.31(b) and 25.15(a)

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-reference to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross-reference to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Cross-reference to DMF (b) (4)
15.	Does the section contain controls for the DS?	X		Cross-reference to DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?	X		Cross-reference to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	Not a filing issue

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		Executed batch records are provided. Proposed MBR will be requested.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?	X		Pivotal BE study performed using highest dosage strength of 1.65 mg estradiol/6.6 cm <sup>2</sup> (0.1 mg/day). Requests biowaiver of lower dosage strengths: <div style="background-color: #cccccc; display: inline-block; padding: 2px;">(b)</div> <div style="background-color: #cccccc; display: inline-block; padding: 2px;">(4)</div> <ul style="list-style-type: none"> <li>• 0.62 mg/2.48 cm<sup>2</sup> (0.375 mg/day)</li> <li>• 0.83 mg/3.30 cm<sup>2</sup> (0.05 mg/day)</li> <li>• 1.24 mg/4.95 cm<sup>2</sup> (0.075 mg/day)</li> </ul>
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		Applicant has used a bracketing design since the formulation and packaging of each patch are the same and differ only by the punch size. 24 month expiry requested based on 9 months data on three batches and reference to Vivelle-Dot drug product
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	N/A

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	LOA DATE	COMMENTS
	III			25-Oct-2011	ADEQUATE on 29-Oct-2010 by S. Read. No new information since that time.
	III			18-Oct-2011	No review found.
	III			19-Oct-2011	ADEQUATE on 08-Jul-1999 by A. Mitra. Updated information provided. <b>May require review.</b>
	IV			01-Nov-2011	No review found.
	III			03-Feb-2011	No review found.
	III			30-Nov-2011	No review found.
	IV			13-Oct-2011	No review found.
	II			13-Oct-2011	ADEQUATE on 16-May-2011 by S. Dhaneasar. Updated information provided Sept 2011. <b>May require review.</b>

*\*Policy on the Review of Container Closure Systems for Solid Oral Drug Products (Bottles), 26-Apr-2001  
Policy on the Review of Blister Container Closure Systems for Oral Tablets and Hard Gelatin Capsules, 29-May-2002*

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		NDC numbers will need to be updated.
33.	Have the immediate container and carton labels been provided?	X		Applicant has not included the proposed tradename on the packaging. NDC numbers will need to be updated. Updated labels should be provided to allow review.

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.		X	N/A
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	X		See Attachment 1 for comments to send to the Applicant.  (b) (4)

*{See appended electronic signature page}*

Donna F. Christner, Ph.D.  
 CMC Lead  
 Division of New Drug Quality Assessment II  
 Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

Terrance Ocheltree, Ph.D.  
 Division Director  
 Division of New Drug Quality Assessment II  
 Office of New Drug Quality Assessment

Date

Attachment A: Nanotechnology product evaluating questions:

1, This review contains new information added to the table below: _____ Yes; <input checked="" type="checkbox"/> No Review date: <u>21-Jan-2012</u>
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes _____; No <input checked="" type="checkbox"/> ; Maybe (please specify) _____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____
3 b) What is the source of the nanomaterial? _____
4) Is the nanomaterial a reformulation of a previously approved product? Yes _____ No _____
5) What is the nanomaterial functionality? Carrier _____; Excipient _____; Packaging _____ API _____; Other _____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment? Soluble _____; Insoluble _____
7) Was particle size or size range of the nanomaterial included in the application? Yes _____ (Complete 8); No _____ (go to 9).
8) What is the reported particle size? Mean particle size _____; Size range distribution _____; Other _____
9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____
11) List all methods used to characterize the nanomaterial? _____ _____

## REVIEW NOTES

Clinical studies in support of this NDA have been performed under IND 76647. The sponsor also provides a cross reference to NDAs 20-323 (Vivelle) and 20-538 (Vivelle-Dot). The sponsor states that [REDACTED] (b) (4)

The applicant states that the objective of the [REDACTED] (b) (4) development program was to demonstrate bioequivalence to Vivelle and show dose proportionality between all strengths of [REDACTED] (b) (4). The applicant states that clinical efficacy and safety data were provided from previously conducted clinical trials with Vivelle.

The following CMC-related activities occurred during the development of the IND. DARRTS should be referred for more complete information on the development pathway of this product.

### **PIND meeting held 11-Sep-2007:**

The sponsor requested that the printing on the backing film contain an [REDACTED] (b) (4) in lieu of the strength. The sponsor was advised that the ETS should have the name and strength printed on the backing film. The sponsor also asked if a [REDACTED] (b) (4) font would be acceptable and was advised that any size font should be readable.

Discussions continued on the BE study and what formulations would be acceptable.

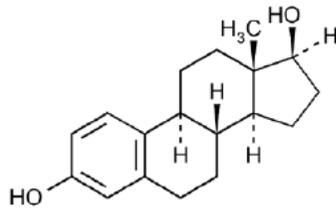
### **IND opened 17-Oct-2007:**

Jane Chang, Ph.D. was the assigned reviewer. The IND was opened using two different formulations that differed by [REDACTED] (b) (4). There were minor comments to be held until the EOP2 meeting. No comments were sent to the sponsor.

During development, Dr. Chang has noted changes in formulation and submission of stability data. No additional CMC comments have been conveyed to the sponsor.

## DRUG SUBSTANCE

Drug substance information is provided in the cross-referenced DMF (b) (4). The following information is provided in the NDA.



**Table 1: Name and Addresses of Manufacturer**

Facility	Responsibility
(b) (4)	

*Comment:* EES was submitted on (b) (4) by (b) (4). The Office of Compliance has made a recommendation of **ACCEPTABLE** based on profile on (b) (4) for this site, with a EER re-evaluation date of (b) (4). The overall recommendation is still pending.

The applicant has provided the following flow chart for the synthesis of estradiol:



**Table 1: Specification for Estradiol**

Test	Acceptance Criteria	Analytical Method
Appearance	(b) (4)	Visual
Potency, Estradiol	(b) (4)	HPLC
Identification A) IR B) UV	(b) (4)	USP
Melting Range	(b) (4)	USP
Specific Rotation	(b) (4)	USP
Moisture	(b) (4)	USP
Particle Size <sup>a</sup>	(b) (4)	Microscopic
Chromatographic Impurities	(b) (4)	USP

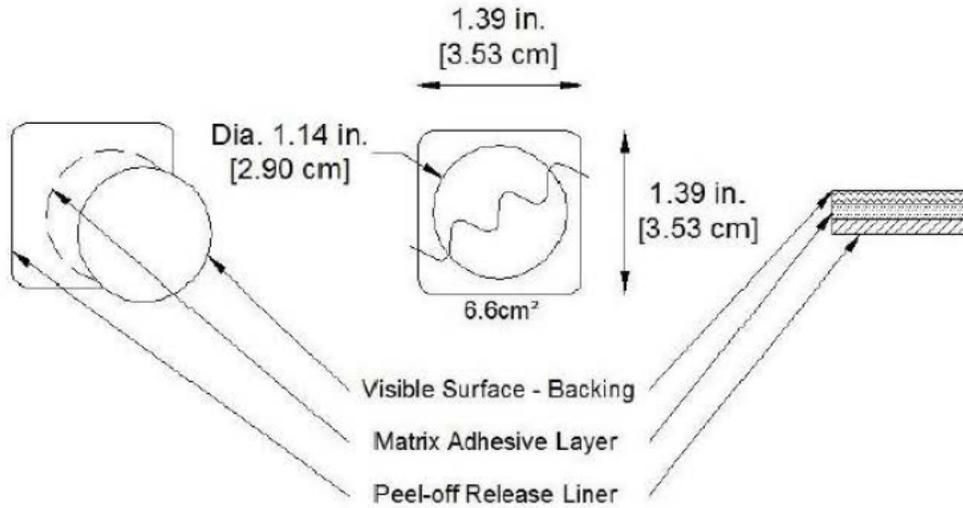
<sup>a</sup> Data supplied from manufacturer's Certificate of Analysis

**Comment:** Information is adequate to allow review. The DMF should be requested to see if the information submitted in September 2011 requires review.

**DRUG PRODUCT**

The applicant has provided the following information on the drug product:

The drug product is a translucent, round estradiol transdermal patch available in (b)(4) sizes (b)(4) (b)(4), 2.48 cm<sup>2</sup>, 3.30 cm<sup>2</sup>, 4.95 cm<sup>2</sup>, and 6.60 cm<sup>2</sup>. Each patch consists of three layers (Figure 1).



**Figure 1: Diagram of the Estradiol Transdermal System (6.6 cm<sup>2</sup>)**

Proceeding from the visible surface toward the surface attached to the skin, these layers are:

- Layer 1: (b)(4) printed backing film.
- Layer 2: The active layer consisting of an acrylic adhesive, silicone adhesive, oleyl alcohol, povidone, dipropylene glycol and estradiol, with a (b)(4) mg/cm<sup>2</sup> coat weight.
- Layer 3: (b)(4) polyester (b)(4) release liner. (b)(4).

**Table 1: Estradiol Transdermal System Dimensions**

Size (cm <sup>2</sup> )	Release Liner Dimensions	Patch Diameter
(b)(4)	(b)(4)	(b)(4)
2.48	24.1 x 24.1 mm	17.8 mm
3.30	26.8 x 26.8 mm	20.5 mm
4.95	31.5 x 31.5 mm	25.1 mm
6.60	35.3 x 35.3 mm	29.0 mm

The drug product is available in the following strengths. The unit composition of each transdermal system is also provided:

**Table 2: Strengths of Estradiol Transdermal System**

Strength	Patch Size	Estradiol Concentration in Adhesive Blend	Estradiol Content per Unit
0.0375 mg/day	2.48 cm <sup>2</sup>	(b) (4)	0.62 mg
0.05 mg/day	3.30 cm <sup>2</sup>	(b) (4)	0.83 mg
0.075 mg/day	4.95 cm <sup>2</sup>	(b) (4)	1.24 mg
0.1 mg/day	6.60 cm <sup>2</sup>	(b) (4)	1.65 mg

**Table 3: Unit Composition of Estradiol Transdermal Systems**

Ingredient	Reference to Quality Standard	Function	Theoretical Weight (mg) per Patch			
			2.48 cm <sup>2</sup>	3.30 cm <sup>2</sup>	4.95 cm <sup>2</sup>	6.6 cm <sup>2</sup>
Estradiol	USP	Active	0.62	0.83	1.24	1.65
Silicone Adhesive (b) (4)	In-house standard	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Acrylic Adhesive (b) (4)	In-house standard	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Povidone (b) (4)	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Oleyl Alcohol	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Dipropylene Glycol (b) (4)	In-house standard	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Ingredient	Reference to Quality Standard	Function	Theoretical Weight (mg) per Patch			
			2.48 cm <sup>2</sup>	3.30 cm <sup>2</sup>	4.95 cm <sup>2</sup>	6.6 cm <sup>2</sup>
(b) (4) Polyester Release Liner	In-house standard	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Polyester Laminate (b) (4)	In-house standard	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	N/A	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

The patch is to be applied twice weekly.

**Comment:** Information is adequate to allow review.

## BIOWAIVER REQUEST

The applicant has performed a pivotal bioequivalence study, N28-004, which evaluated the highest dosage strength of (b) (4) of 1.65 mg estradiol/6.6 cm<sup>2</sup> (0.1 mg/day). They have also provided a supportive dose-proportionality study, N28-005, on three doses of (b) (4) (b) (4) (b) (4), 0.827 mg estradiol/3.3 cm<sup>2</sup>, and 1.65 mg estradiol/6.6 cm<sup>2</sup> patches. Therefore, they are requesting a biowaiver of the lower dosage strengths based on the following rationale:

- Bioequivalence was established for (b) (4) (1.65 mg estradiol/6.6 cm<sup>2</sup> patch) to the Vivelle ETS (8.66 mg estradiol/29 cm<sup>2</sup> patch).
- The patches are different strengths of the same formulation and are from the same sheet of the formulation. The only difference is the surface area of the patches.
- Comparative dissolution testing was performed between the three equivalent strengths of (b) (4) and Vivelle, bracketing the (b) (4) strengths available (see table below). All strengths exhibited similar dissolution profiles in multiple dissolution media.
- Different strengths of the (b) (4) were compared (6.6 cm<sup>2</sup> vs. (b) (4), 6.6 cm<sup>2</sup> vs. 3.3 cm<sup>2</sup> and 3.3 cm<sup>2</sup> vs. (b) (4) and met the criteria for similarity, supporting dose proportionality of the (b) (4) product. The f<sub>1</sub> and f<sub>2</sub> factors were within the guidelines and the dissolution curves matched.
- Dose proportionality of (b) (4) strengths was established in clinical study N28-005 of three doses of (b) (4) (b) (4) 0.827 mg estradiol/3.3 cm<sup>2</sup> patch, and 1.65 mg estradiol/6.6 cm<sup>2</sup> patch.

**Comment:** A BioPharm consult was requested on 23-Jan-2012. Dr. Tapash Ghosh was assigned on 25-Jan-2012.

## MANUFACTURING

The following facilities have responsibilities for manufacture of the drug product:

Table 1: Firm's Responsibilities

Name and Address	Responsibility/Function
Noven Pharmaceuticals, Inc. 11960 SW 144 <sup>th</sup> Street Miami, FL 33186 Establishment Number: 1058171	Release testing of drug substance, excipients, packaging components, and finished product Manufacturing Primary and secondary packaging and labeling Secondary packaging and labeling Stability testing of finished product
(b) (4)	

**Comment:** EES was submitted on (b) (4) by (b) (4). The Office of Compliance has made a recommendation of ACCEPTABLE based on profile on (b) (4) for the three sites, with EER re-evaluation dates of in 2013 and 2014 for the testing sites and 06-May-2012 for the drug product manufacturing site. The overall recommendation is still pending.

The applicant has provided the following flow diagram for manufacture of the drug product. A narrative is also provided:

**3.3.1. Process Flow Diagram**

Provided below is the manufacturing flow diagram for Estradiol Transdermal System:



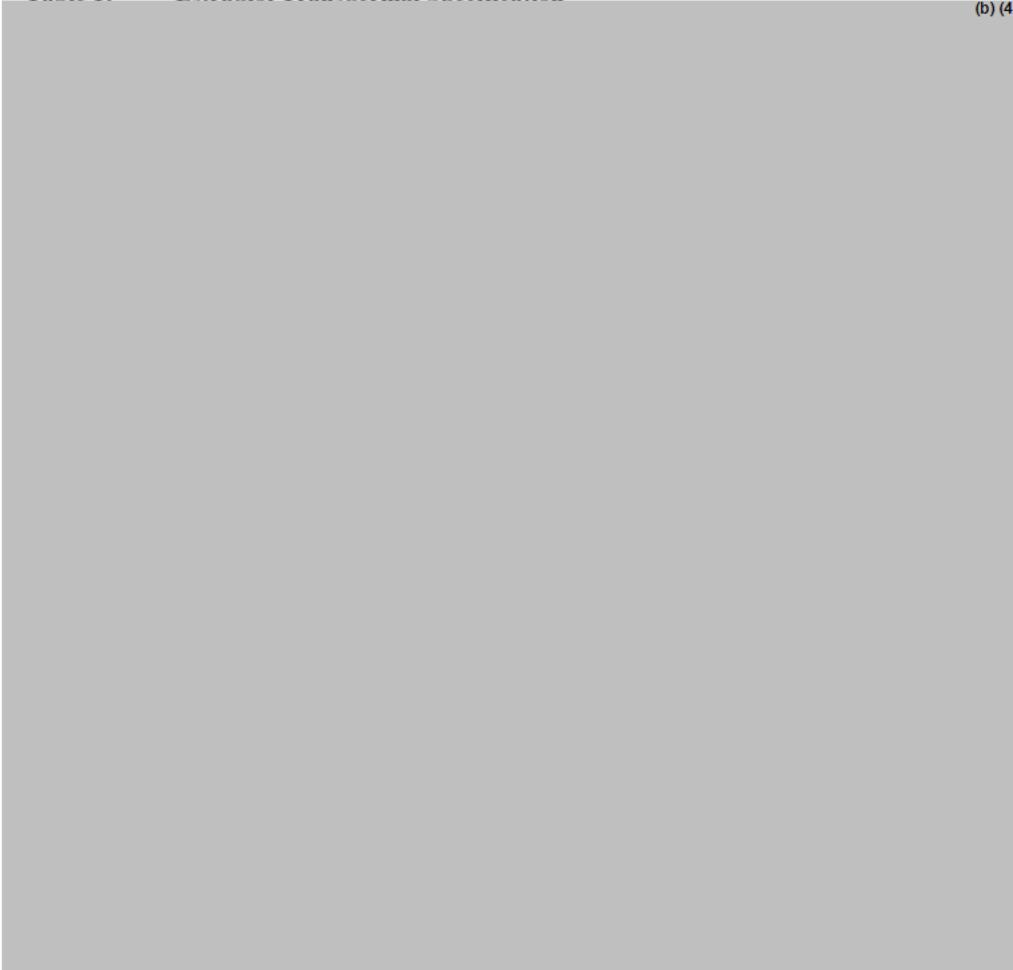
*Comment: Information is adequate to allow review.*

SPECIFICATION

The applicant has provided the following specification table:

**Table 1: Estradiol Transdermal Specification**

(b) (4)

A large rectangular area is completely redacted with a solid grey fill, obscuring the content of Table 1.

**Table 1: Estradiol Transdermal Specification (Continued)**

(b) (4)

A large rectangular area is completely redacted with a solid grey fill, obscuring the content of Table 1 (Continued).

Noven will perform annual testing on one lot of material

***Comment:*** *Information is adequate to allow review.*

STABILITY

The applicant has used a bracketing design for their stability studies, since the different strengths are the same formulation and differ only by the size of the patch cut from the roll.

**Table 1: Estradiol Transdermal Stability Bracket Design**

	Batch Size	(b) (4)	2.48 cm <sup>2</sup>	3.30 cm <sup>2</sup>	4.95 cm <sup>2</sup>	6.60 cm <sup>2</sup>
Batch 1	(b) (4)	(b) (4)				X
Batch 2	(b) (4)	(b) (4)				X
Batch 3	(b) (4)	(b) (4)		X		X

The applicant has requested an expiry of 2 years based on the following information:

- 9 months of long term and 6 months of accelerated stability data on 3 lots (1 pilot and 2 commercial scale batches) of drug product. Variations include lots with unprinted and printed backing and unprinted and printed pouch stock to assess the potential impact of the inks used in the process.
- Photostability data
- (b) (4)

**Table 2: Estradiol Transdermal Stability Batches and Printing Configurations**

Blend Lot	Size (cm <sup>2</sup> )	Packaging Lot	Blend Size	Pouchstock	Backing
51377	(b) (4)	50852	(b) (4)	Unprinted	Unprinted
	6.6	50847		Unprinted	Unprinted
51375	(b) (4)	51557		Unprinted	Unprinted
		50854		Printed	Unprinted
	6.6	51555		Unprinted	Unprinted
50843		50849		Printed	Unprinted
	(b) (4)	50856	Printed	Printed	
	3.3	50858	Printed	Printed	
	6.6	50851	Printed	Printed	
	(b) (4)	50855	Unprinted	Printed	
	3.3	50857	Unprinted	Printed	
	6.6	50850	Unprinted	Printed	

**Comment:** Information is adequate to allow review. Although only 9 months of real time stability data are available for this formulation, the supporting data on the similar formulations may provide enough data to support the proposed expiry. Therefore, the Applicant will be requested to submit additional stability data by Month 4 of the review cycle to provide additional support for their proposed expiry.

## CONTAINER CLOSURE

Each estradiol transdermal system is sealed in one pouch. There are two different pouch sized to accommodate different patch sizes. Patches are provided in “Calendar Packs” of 8 systems and in cartons containing 3 “Calendar Packs.”



Figure 1: Diagram of Estradiol Transdermal System Pouch

Individual pouches are packaged into a carton with the package insert and/or patient package insert.

*Comment: Information is adequate to allow review.*

## LABELING

Carton/container labeling, and the Physician Insert are provided and is based on labeling for the approved Vivelle-Dot patches. Placement for NDC numbers are provided, but the actual numbers should be updated both on the carton/container labels and the PI.

On the Physician Insert in the DESCRIPTION section, the following comment is made:

(b) (4)

Vivelle-Dot does not include this promotional statement, and it should be stricken from this label.

*Comment: The following comments should be conveyed to the sponsor:*

- Update the NDC numbers on all carton/containers and the PI
- Delete the phrase (b) (4) from the DESCRIPTION section.

ATTACHMENT 1

The following comments should be communicated to the Applicant:

General Comments:

1. **Update the NDC numbers on all carton/containers and the PI**
2. **Delete the phrase “ [REDACTED] (b) (4) ” from the DESCRIPTION section.**
3. **Provide a copy of your proposed Master Batch Record to the application.**

Drug Product:

In-Process Controls:

4. **Provide a sampling plan for in process testing of the laminate. The plan should assure consistency throughout the laminate from a quality perspective. Samples should be taken across the width and length of each laminate.**

Drug Product Specification:

5. **Include in Appearance acceptance criterion an observation for crystals and/or visible particulates.**
6. **Establish a test for cold flow.**
7. **Establish a target (in addition to a range) for potency for the product specification.**
8. **Establish acceptance criteria for Content Uniformity. USP <905> does not identify acceptance criteria for transdermal systems.**
9. **Provide a sampling plan for Content Uniformity testing that assures consistency throughout the final laminate web (before cutting into individual patches). Samples should be taken across the width and length of the uncut web.**
10. **Establish a specification and acceptance criteria, both upper and lower limits, for adhesion to steel (or other substrate) and tack.**
11. **Establish acceptance criteria, both upper and lower limits, for shear adhesion and release liner peel force for all sizes of the transdermal system.**
12. **Provide the methods for all adhesion tests for all sizes of the transdermal system.**
13. **Establish package integrity or burst test and acceptance criteria for the product specification.**

Stability

14. **Establish acceptance criteria for all stability tests.**

15. Establish a test for cold flow.
16. Add release liner adhesion test to the stability protocol.
17. Establish a test for adhesion to steel and tack in addition to release liner peel force and shear adhesion for all transdermal system sizes.
18. Perform stability challenging studies such as temperature excursions, freeze/thaw, and/or crystal seeding studies to assess the potential for drug substance crystallization.
19. Acknowledge that you agree that expiry begins when [REDACTED] (b) (4)
20. To support the proposed shelf-life of the drug product, provide additional stability data no later than month 4 of the review cycle.

Container Closure

21. Provide extractable and leachable information for the container closure.

Biopharmaceutics

22. Provide the *in vitro* drug release method report supporting the selection of the proposed test. The report should include the following information; 1) detailed description of the *in vitro* drug release method proposed for your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro drug release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select/identify the proposed drug release method as the most appropriate. The testing conditions used for each test should be clearly specified, 2) the complete drug release profile data (*individual, mean, SD, profiles*) for your product. The drug release data should be reported as the cumulative percentage of drug being released with time (*the percentage is based on the product's label claim*), and 3) include the testing conducted to demonstrate the discriminating capability of the selected drug release test as well as the validation data for the drug release method (*i.e., method robustness, etc.*) and analytical method (*precision, accuracy, linearity, stability, etc.*).
23. We found the comparative *in vitro* drug release profiles of your proposed 6.6 cm<sup>2</sup> size product vs. the reference Vivelle 29.0 cm<sup>2</sup> patch. However, we could not locate the comparative dissolution profiles for the other sizes of your proposed product. Provide those comparative drug release profiles along with the raw data and f2 values associated with these calculations.

Additional CMC Considerations:

Adhesives

- 24. It is recommended to qualify adhesives both prior to and post drug formulation. This insures both optimum product quality attributes in transdermal and topical formulations, and a seamless post-approval change process, in case the raw materials, manufacturing process, or manufacturer of the adhesive(s) is changed. The following tests are not required for release of the drug product but rather to qualify the adhesive component. Proper qualification of the adhesives used to formulate the drug product may include the following when applicable:**
- Readily available polymer - molecular weight distribution, polydispersity, spectroscopic analysis (IR), thermal analysis, intrinsic viscosity, and measurement of residual monomers, dimers, solvents, heavy metals, catalysts and initiators.
  - Adhesive as a Lamina (without drug substance or other adhesive matrix excipients) - residual solvents, extractable and leachables, and an evaluation for peel, tack, shear, and adhesion.
  - Adhesive in the final Drug Product - residual monomers, dimers and solvents, viscosity, IR identification, loss on drying, impurities, and content uniformity. Functionality parameters to be assessed include but are not limited to peel, shear, adhesion, tack, *in vitro* drug release, and *in vitro* drug permeation.

Pharmaceutical Development:

- 25. It is recommended that sufficient scientific justification to support the amount of residual drug in a TDDS be included in the 3.2.P.2 section of the common technical document (CTD) format discussion of the product and process development and justification for the final formulation and system design. The level of information in the submission should be sufficient enough to demonstrate product and process understanding and assure that a science and risk based approach has been taken to minimize the amount of residual drug in a system after use. The justification for the percent of residual drug and the overall amount of remaining drug will be assessed during review. Refer to the Guidance for Industry – Residual Drug in Transdermal and Related Drug Delivery Systems for additional information. (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220796.pdf>).**
- 26. As migration of the drug substances and excipients within the individual drug product throughout shelf life is of potential concern, a complete understanding of the drug product matrix, specifically where the active drug substances are within the adhesive matrix (e.g., emulsion system, suspension, completely dissolved in the adhesive, etc) and what changes the matrix may undergo from the time of manufacture to product expiry is suggested. Useful tools to support your explanation for the above may include SEM imaging and Elemental Mapping (via SEM-EDX) of the cross section and surface of the Transdermal Drug Delivery System (TDDS) at release and through the end of stability. Information should be included in the 3.2.P.2 section of the common technical document (CTD) format discussion of the product and process development.**

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/s/  
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DONNA F CHRISTNER  
02/27/2012

TERRANCE W OCHELTREE  
03/02/2012