

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-992**

**CHEMISTRY REVIEW(S)**

**ONDQA Division Director's CMC Memorandum No. 2 on NDA 21-992**

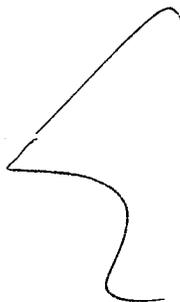
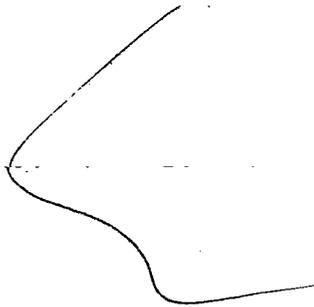
**Date:** February 22, 2008  
**From:** Chi-wan Chen, Ph.D., Deputy Director, Office of New Drug Quality Assessment  
**To:** NDA 21-992 File  
**Applicant:** Wyeth Pharmaceuticals, Inc.  
**Drug Name:** Pristiq (desvenlafaxine) extended tablets, 50 and 100 mg  
**Indication:** Major depressive disorder

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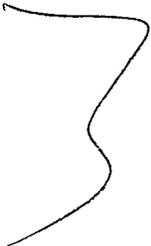
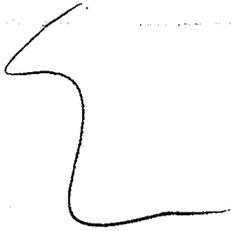
In the January 22, 2007, approvable letter for NDA 21-992, Wyeth's drug product manufacturing facility located in Guayama, PR, was found out of CGMP compliance, and additional information related to the comparability protocol (CP) was deemed necessary: (1) process analytical technology (PAT) and at-line measurement systems, including calibration, validation, and suitability, where applicable; (2) sampling plans, acceptance criteria, and tolerance limits for real-time release (RTR); and (3) procedure for releasing a batch in case of a PAT system failure. The PR facility was found acceptable in October, 2007. The applicant responded to the CMC approvability issues in a June 2007 amendment to this NDA and its companion NDA ~~XXXX~~ (vasomotor symptoms (VMS) associated with menopause). A pre-operational visit (POV) was conducted at the site in July 2007 at Wyeth's request to provide them with guidance on the implementation of their PAT/RTR proposal. Wyeth proposed to

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**Recommendation**

All CMC deficiencies have been adequately addressed and the CP has been satisfactorily revised to allow the implementation of PAT/RTR via a CBE-30 supplement at a later date. Therefore, it is recommended that NDA 21-992 be approved from the CMC standpoint.

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/s/

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Chi Wan Chen  
2/22/2008 07:18:42 PM  
CHEMIST

## ONDQA Division Director's CMC Memorandum on NDA 21-992

**Date:** January 12, 2007  
**From:** Chi-wan Chen, Acting Director, Division of Pre-Marketing Assessment I, Office of New Drug Quality Assessment  
**To:** DA 21-992 File

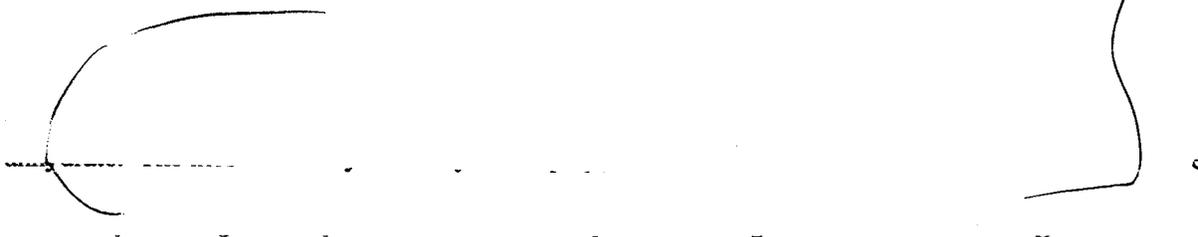
**Applicant:** Wyeth Pharmaceuticals, Inc.  
**Drug Name:** Pristiq (desvenlafaxine succinate) extended release tablets, 100 and 200 mg  
**Indication:** Major depressive disorder

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The CMC portion of this NDA was submitted on December 22, 2005, under the ONDQA Pilot Program to explore science- and risk-based approaches to assuring product quality. A comprehensive Quality Overall Summary (Module 2) and an expanded pharmaceutical development section (P.2 in Module 3) were submitted. Several quality-by-design (QbD) elements were presented with respect to product design and process understanding of the drug product.

### Drug Substance

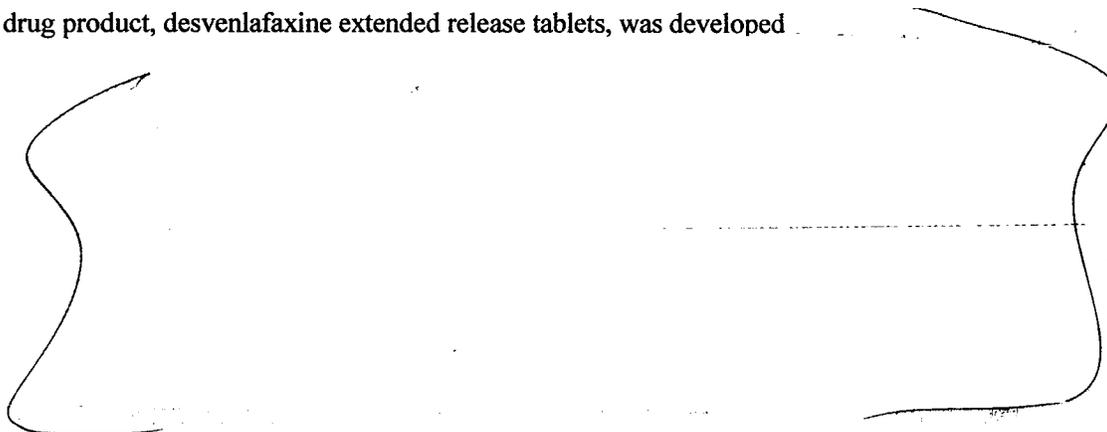
The drug substance, desvenlafaxine succinate (DVS),



DVS is manufactured and tested by \_\_\_\_\_ DMF [desvenlafaxine, \_\_\_\_\_] was found adequate in support of NDA 21-992 regarding the manufacturing and controls of the drug substance, after the initial deficiencies were satisfactorily addressed.

### Drug Product

The drug product, desvenlafaxine extended release tablets, was developed



manufacturers. The proposed design spaces for the CPPs were confirmed with the biobatches and registration batches. A 5-point dissolution method, which is sufficiently discriminatory between strengths, was developed and used to establish a level A in vivo-in vitro correlation (IVIVC-A) for 50 mg and 200 mg tablet strengths. OCP has accepted the proposed IVIVC-A for 50 mg, 100 mg, 150 mg and 200 mg tablet strengths\* and the proposed dissolution method as the bioequivalence standard for the drug product. \*(Only 100 and 200 mg strengths are proposed for the treatment of major depressive disorder in this NDA.)

Specifications are provided for batch release and for "design space exception" (i.e., when manufacturing occurs outside the established design space). The tests include appearance, identity (HPLC and UV spectrum), content uniformity, assay (HPLC), impurities (HPLC), and dissolution (UV spectrum or HPLC). Despite drug substance being less than

Four comparability protocols are included in the application. Two protocols for changes to the blister film and to the foil-based backing film, respectively, via an annual report are acceptable. The third protocol, i.e., optimization of the 100 mg tablet formulation, to be submitted as a CBE-30 supplement, is adequate.

The fourth protocol, i.e., implementation of process analytical technology (PAT) for process control and real-time release of the drug product, is considerably more extensive and complex. It was significantly

However, the protocol as currently presented is not adequate to support the implementation of PAT and real-time release via a CBE-30 supplement post-approval. *Additional information has been requested regarding (1) PAT and at-line measurement systems, including calibration, validation, and suitability, where applicable; (2) sampling plans, acceptance criteria, and tolerance limits for real-time release; and (3) procedure for releasing a batch in case of a PAT system failure. The response from the applicant in their 12/8/06 amendment is still under review due to its complexity and appears inadequate. In addition, a pre-approval visit of the facility is necessary prior to the approval of the PAT CP protocol.*

#### Miscellaneous

The proposed retest period \_\_\_\_\_ for the drug substance and shelf life (24 months) for the drug product are acceptable based on the data submitted.

*The proposed established name does not correspond to the labeled strength.* The applicant has been advised of the FDA policy that the name and strength should match. Otherwise, the Description and How Supplied sections in the package insert are complete and acceptable from the CMC standpoint.

The applicant proposed a \_\_\_\_\_

\_\_\_\_\_ The agreement will not be approved at this time because FDA has not established a regulatory pathway to allow such an approval.

### **Recommendation**

The application is recommended for not approvable from a CMC standpoint for the following reasons:

1. Wyeth's drug product manufacturing facility located in Guayama, PR, was found unacceptable by the Office of Compliance due to an outstanding Warning Letter stemming from a recent CGMP inspection. A satisfactory inspection of this site is required before this application can be approved.
2. The applicant will need to adequately respond to a number of CMC approvability issues on drug substance control, design space for HPMC, PAT comparability protocol, and labeling, as outlined in *italic* above.

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/s/

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Chi Wan Chen  
1/12/2007 06:13:30 PM  
CHEMIST

**NDA 21-992**

**Pristiq™ (desvenlafaxine)**

**Wyeth Pharmaceuticals, Inc.**

**William M. Adams  
Terrance Ocheltree, Ph.D.  
Thomas Oliver, Ph.D.**

**DIVISION OF PSYCHIATRY PRODUCTS (HFD-130)**

**Review of Chemistry, Manufacturing, and Controls**

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# Chemistry Review Data Sheet

1. NDA 21-992
2. REVIEW #4
3. REVIEW DATE: February 16, 2007
4. REVIEWERS: William M. Adams  
Terrance Ocheltree, Ph.D.  
Thomas Oliver, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Submission</u>	<u>Document Date</u>
NDA 21-992 N-000	22 Dec 2005
Amendment N-005	16 Mar 2006
Amendment N-008	28 Apr 2006
Amendment N-013	03 Jul 2006
Amendment N-022	12 Oct 2006
Amendment N-024	01 Nov 2006
Amendment N-025	08 Dec 2006
CMC Review #1	01 Dec 2006
CMC Review #2	12 Jan 2007
CMC Review #3	04 Jun 2007

6. SUBMISSION(S) BEING REVIEWED:

<u>Submissions Reviewed</u>	<u>Document Date</u>
Amendment N-030	01 Jun 2007
Amendment N-031	27 Jun 2007
Amendment N-032	23 Aug 2007
Amendment N-033 (AZ)	29 Aug 2007
Amendment N-036	19 Dec 2007
Meeting Minutes	07 Feb 2008
Amendment N-043	20 Feb 2008
Amendment N-045	22 Feb 2008

7. NAME & ADDRESS OF APPLICANT:

Name: Wyeth Pharmaceuticals, Inc.  
Address: P.O. Box 8299  
Philadelphia, PA 19101



## CHEMISTRY REVIEW TEMPLATE



### Chemistry Assessment Section

Representative: Randall B. Brenner  
(Director II, Global Regulatory Affairs)  
Telephone: (484) 865-3792

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

- a) Proprietary Name: Pristiq™
- b) Non-Proprietary Name (USAN): desvenlafaxine succinate
- c) Code Name: DVS-233; DVS-233 monohydrate; O-desmethylvenlafaxine succinate monohydrate; ODV succinate monohydrate; WY-45233:succinate monohydrate; WY-45233-1; ODV succinate.H<sub>2</sub>O
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 1
  - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Major Depression Disorder (MDD)

11. DOSAGE FORM: Tablets (extended release)

12. STRENGTH/POTENCY: 50 and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  X  Rx   OTC

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

SPOTS product – Form Completed

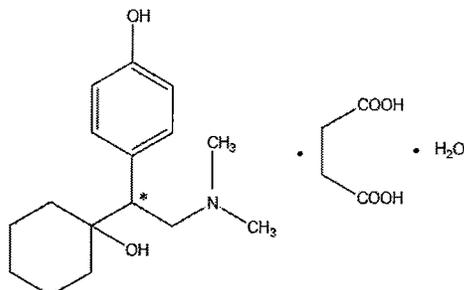
X  Not a SPOTS product

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

CA Name: 1-[(1*R,S*)-2-(Dimethylamino)-1-(4-hydroxyphenyl)ethyl] cyclohexanol hydrogen butanedioate monohydrate  
USAN Name: desvenlafaxine succinate  
Chemical Formula: C<sub>16</sub>H<sub>25</sub>NO<sub>2</sub>•C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>•H<sub>2</sub>O  
Molecular Weight: 399.48 (as the succinate, monohydrate)/ 263.38 (as the free base)  
CAS Registry #: 386750-22-7

## Chemistry Assessment Section

Molecular Structure:



\* Denotes chiral center, the compound is racemic.

17. RELATED/SUPPORTING DOCUMENTS: See Reviews #1-3

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Clinical	Approval	1/22/08	Robert Levin, MD
EES	Acceptable	10/10/07	Janine D'Ambrogio
Pharm/Tox	Approval	02/05/08	Linda Fossom, Ph.D.
OCP	Approval	1/28/08	Kofi Kumi, Ph.D.
Stat	Approval	01/08/08	Yeh-Fong Chen, Ph.D.
DMETS	Approval	01/15/08	Diane Smith, Pharm.D.
EA	Acceptable & FONSI	04/12/06	Bai Nguyen



# Chemistry Review for NDA 21-992

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 21-992 for Pristiq™ (desvenlafaxine) tablets, is recommended for **APPROVAL** with respect to the chemistry, manufacturing, and controls (CMC). A Comparability Protocol (CP) for the “implementation of process analytical technologies (PAT) and the implementation of real time release (RTR) via a CBE-30 supplement” has been found to be sufficient. The adequacy of the implementation of PAT and RTR will be determined once the appropriate supplement is submitted.

#### 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)

##### Drug Substance

Desvenlafaxine is a major metabolite of venlafaxine (Effexor® and Effexor® XR; as HCl salt). It selectively blocks the reuptake of serotonin and norepinephrine (sSNRI). Desvenlafaxine succinate was developed for extended release tablets. It is a white to off-white powder with a solubility that increases at lower pH. It is classified as a Class 3 (high solubility and low permeability) according to FDA’s Biopharmaceutics Classification System.

Desvenlafaxine succinate contains one chiral center, but is being developed as the racemate.

Desvenlafaxine succinate is manufactured and tested \_\_\_\_\_  
The applicant references DMF \_\_\_\_\_ [desvenlafaxine, \_\_\_\_\_] for all information in support of the drug substance. DMF \_\_\_\_\_ was found adequate in support of NDA 21-992. Wyeth has submitted Certificates of Analyses (CoAs) for three batches of desvenlafaxine succinate. Each batch is tested for: description, assay, identification, water, \_\_\_\_\_ impurities (venlafaxine, any unspecified, total), residual solvents, residual \_\_\_\_\_ and particle size. Total impurities were found to be \_\_\_\_\_ with venlafaxine, a previously approved drug (Effexor®), as the \_\_\_\_\_ impurity identified with a specification limit. Residual solvents were found to be well within the specification limits, which comply with the recommendations of ICH



# CHEMISTRY REVIEW TEMPLATE



## Chemistry Assessment Section

Q3C. The applicant provided 18 months of long term and 6 months of accelerated stability data for three batches of desvenlafaxine succinate. In addition, the sponsor provided supportive data for one additional batch. The sponsor has requested and will be granted a \_\_\_\_\_ retest date for desvenlafaxine succinate.

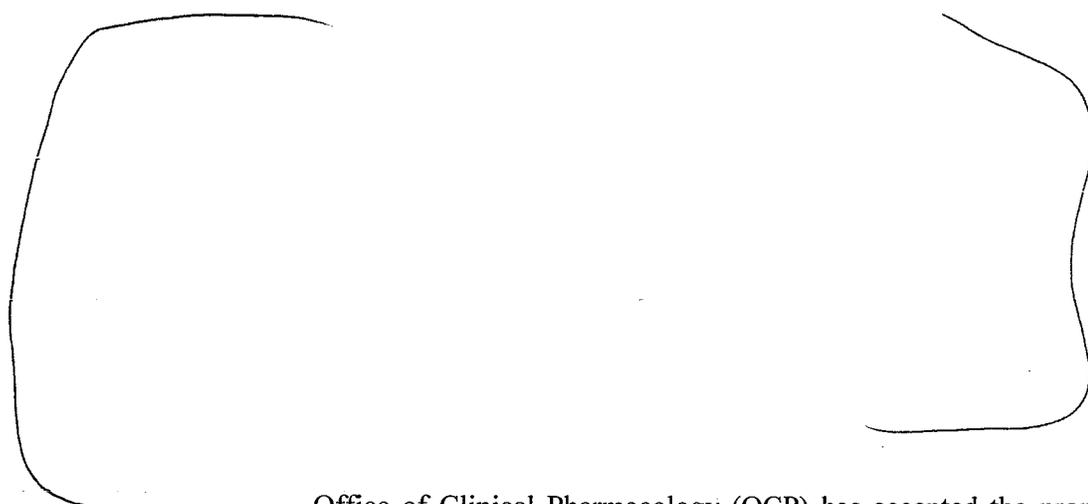
### Drug Product

Three tablet strengths (50 mg, 100 mg and 200 mg) have been proposed; however, the 200 mg strength tablet is not being approved by the clinical division. The proposed drug product is formulated as an extended-release (ER) tablet in 50 mg and 100 mg strengths (based on desvenlafaxine free base) using the succinate monohydrate salt. The tablets are packaged in multidose bottles and unit dose blister packs. Tablets are square with a pyramid shape on one side and flat on the other. The 50 mg tablet is light pink, debossed with "W" over "50". The 100 mg tablet is reddish orange, debossed with "W" over "100".

The product was developed using \_\_\_\_\_

The proposed ER tablet consists of a hypromellose (HPMC) \_\_\_\_\_

Tablet manufacture occurs in \_\_\_\_\_



Office of Clinical Pharmacology (OCP) has accepted the proposed IVIVC-A and the proposed five point dissolution method as the bioequivalence standard for the drug product (refer to OCP reviews for NDAs 21-992 : \_\_\_\_\_). Tablets are manufactured, tested and packaged by Wyeth (Guayama, PR); release and stability tested at Wyeth (Pearl River, NY); and packaged by three contractors. All sites have been found to meet cGMP standards.

Unit and batch formulations are provided. Tablet formulations : \_\_\_\_\_

\_\_\_\_\_ No excipient is novel or of human or animal origin. Design and control spaces are provided for HPMC. A specification is provided for each of the \_\_\_\_\_ of microcrystalline cellulose and the film coating material. All other excipients meet USP, NF or EP monograph requirements. The non-monograph methods for these materials are described in sufficient detail.



## CHEMISTRY REVIEW TEMPLATE



### Chemistry Assessment Section

Specifications are provided for batch release (operating space) and for "design space exception" (when manufacture occurs outside the manufacturing design space). The tests address tablet appearance, drug identity (HPLC and UV spectrum), content uniformity, drug strength (HPLC), purity (HPLC) and dissolution (UV spectrum or HPLC).

Criterion for strength is accepted as  $\frac{1}{2}$  of label claim at release and  $\frac{1}{2}$  for the stability studies. Criterion for dissolution is accepted as a 5-point (2, 4, 8, 12, 24 hour) dissolution profile.

The proposed packaging presentations are 14, 30, 90-count commercial packages composed of an opaque, white bottle with aluminum foil innerseal, cotton wadding and a child resistant closure; and a non-child resistant 2x5 unit dose card composed of a clear blisters with push-thru aluminum foil backing intended as a physician sample or hospital-use package. The count bottle is a physician sample package. Packaging component descriptions and acceptance specifications are acceptable. The container/closure systems are qualified through the stability studies.

The Post Approval Stability Protocol is to place the first three production lots of each strength in each market package on stability at ICH long term condition with testing at 0,3,6,9,12,18 months and annually to expiration; then NLT lot annually in each packaging configuration on stability at ICH long term with testing at 0,6,12,18 months and annually to expiration. The results are to be submitted in the annual reports. Deviations are to be addressed per 21 CFR 314.81(b)(1)(ii). These lots will be tested for appearance, strength, purity and 5-point dissolution.

Primary stability studies were performed on the 3 registration lots of 50 mg, 100 mg and 200 mg tablets in 14, 30, 90-count bottles and both blister packages. Stability results are presented for 50 mg tablets stored 12 months under ICH intermediate and long term conditions, and 100 mg tablets and 200 mg tablets stored 24 months under ICH intermediate and long term conditions. Stability results are presented for all three strengths of tablets stored 6 months at ICH accelerated conditions. One lot of each strength in one blister package was evaluated for photostability under ICH option 2 conditions. The protocol for the long term and intermediate condition studies includes bracketing of the 14-count bottle, a reduction matrix for each bottle each blister lot at for long term and intermediate conditions, and 6 months accelerated conditions for each package. Testing was for appearance, potency, purity, 5-point dissolution profile,

The study data showed no trends over time across strengths, lots, packages or conditions, except for an blister stored at





Chemistry Assessment Section

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

Pristiq™ (desvenlafaxine succinate) extended release tablets will be marketed in 50 mg and 100 mg strengths for the once-a-day treatment of major depressive disorder (MDD). The recommended dose is 50 mg once daily, with or without food.

no additional benefit was demonstrated at doses greater than 50 mg per day. Pristiq™ extended release tablets should be taken at approximately the same time each day. Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

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

N/A

**III. Administrative**

Chemists: William M. Adams, Terrance Ocheltree, Ph.D., Thomas Oliver, Ph.D. (lead)

Deputy Office Director: Chi-wan Chen, Ph.D. (secondary review)

Project Managers: Amy Bertha and Rebecca McKnight

**Chemistry Assessment**

The following CMC issues were sent to the applicant as part of an AE letter dated January 22, 2007. The issues have been addressed and are evaluated as part of this review.

1. Your drug product manufacturing facility located in Guayama, PR (CFN #1819470) was found unacceptable during a recent cGMP inspection. A satisfactory inspection of this site will be required before this application may be approved.
2. The Comparability Protocol (CP) for "implementation of PAT and real time release via a CBE-30 supplement" is inadequate. We acknowledge the receipt on December 12, 2006, of your December 8, 2006, amendment intended to address this deficiency. The information concerning the CP in this amendment was not reviewed for this action. You may refer to the portion of the amendment regarding the CP in your response to this deficiency.
3. \_\_\_\_\_
4. The design space for HPMC should be revised to include a particle size specification.
5. The established name does not match the labeled strength. Revise all labeling using either of the following example formats:
  - a) Pristiq  
desvenlafaxine \_\_\_\_\_  
Extended Release Tablets
  - b) Pristiq  
desvenlafaxine  
Extended Release Tablets

36 Page(s) Withheld

X Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

Withheld Track Number: Chemistry- 1

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/s/  
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Thomas Oliver  
2/22/2008 06:51:56 PM  
CHEMIST

We would like to acknowledge M. Adams contributions on  
this review as he was unable to sign  
off due to technical difficulties.

Terrance Ocheltree  
2/22/2008 07:06:20 PM  
CHEMIST

Chi Wan Chen  
2/22/2008 07:11:00 PM  
CHEMIST

**NDA 21-992**

**Pristiq™ (desvenlafaxine succinate)**

**Wyeth Pharmaceuticals, Inc.**

**William M. Adams  
Terrance Ocheltree, Ph.D.  
Thomas Oliver, Ph.D.**

**DIVISION OF PSYCHIATRY PRODUCTS (HFD-130)**

**Review of Chemistry, Manufacturing, and Controls**

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# Chemistry Review Data Sheet

1. NDA 21-992
2. REVIEW #3
3. REVIEW DATE: June 4, 2007
4. REVIEWERS: William M. Adams  
Terrance Ocheltree, Ph.D.  
Thomas Oliver, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Submission</u>	<u>Document Date</u>
Amendment N-005	16 Mar 2006
Amendment N-013	03 Jul 2006
Amendment N-022	12 Oct 2006
Amendment N-024	01 Nov 2006
CMC Review #1	01 Dec 2006
CMC Review #2	12 Jan 2007

6. SUBMISSION(S) BEING REVIEWED:

<u>Submissions Reviewed</u>	<u>Document Date</u>
NDA 21-992 N-000	22 Dec 2005
Amendment N-008	28 Apr 2006
Amendment N-025	08 Dec 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Wyeth Pharmaceuticals, Inc.  
Address: P.O. Box 8299  
Philadelphia, PA 19101  
Representative: Randall B. Brenner  
(Director II, Global Regulatory Affairs)



## CHEMISTRY REVIEW



### Executive Summary Section

Telephone: (484) 865-3792

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

- a) Proprietary Name: Pristiq™
- b) Non-Proprietary Name (USAN): desvenlafaxine succinate
- c) Code Name: DVS-233; DVS-233 monohydrate; O-desmethylvenlafaxine succinate monohydrate; ODV succinate monohydrate; WY-45233:succinate monohydrate; WY-45233-1; ODV succinate.H<sub>2</sub>O
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 1
  - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Major Depression Disorder (MDD)

11. DOSAGE FORM: Tablets (extended release)

12. STRENGTH/POTENCY: 100 mg and 200 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

CA Name: 1-[(1R,S)-2-(Dimethylamino)-1-(4-hydroxyphenyl)ethyl] cyclohexanol hydrogen butanedioate monohydrate –

USAN Name: desvenlafaxine succinate

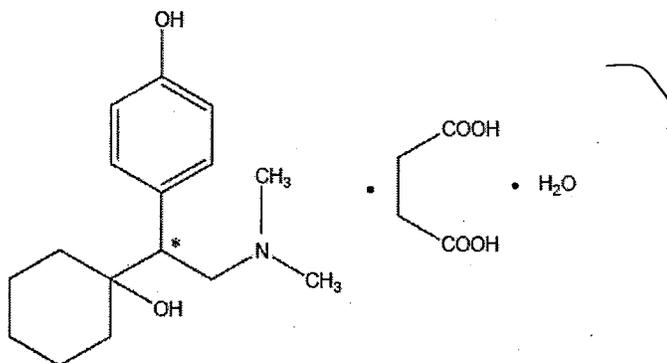
Chemical Formula: C<sub>16</sub>H<sub>25</sub>NO<sub>2</sub>•C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>•H<sub>2</sub>O

Molecular Weight: 399.48 (as the succinate, monohydrate)/ 263.38 (as the free base)

CAS Registry #: 386750-22-7

## Executive Summary Section

Molecular Structure:



\* Denotes chiral center, the compound is racemic.

17. RELATED/SUPPORTING DOCUMENTS: See Review #1

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Clinical	Approvable	10/24/06	Robert Levin
EES	Acceptable	05/02/07	Janine D'Ambrogio
Pharm/Tox	Acceptable	01/22/07	Linda Fossom
OCP	Approval for 5-point bioeqv standard Pending for 1-point release criterion	10/26/06	Kofi Kumi
Stat	Safe, but not Efficacious	08/03/06	Fanhui Kong
DMETS	Comments	04/14/06	Tina Tesky
EA	Acceptable & FONSI	04/12/06	Bai Nguyen



# The Chemistry Review for NDA 21-966

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 21-992 for Pristiq™ (desvenlafaxine succinate) tablets is recommended APPROVABLE from the CMC standpoint. The Comparability Protocol (CP) for "implementation of PAT and real time release via a CBE-30 supplement" is inadequate.

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

None

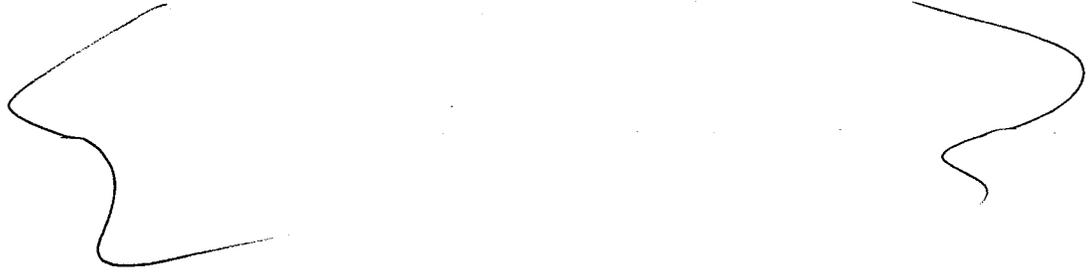
### II. Summary of Chemistry Assessments

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

##### Drug Substance

Desvenlafaxine is a major metabolite of venlafaxine (Effexor® and Effexor® XR; as HCl salt). It selectively blocks the reuptake of serotonin and norepinephrine (sSNRI). Desvenlafaxine succinate was developed for extended release tablets. It is a white to off-white powder with a solubility that increases at lower pH. It is classified as a Class 3 (high solubility and low permeability) according to FDA's Biopharmaceutics Classification System.

Desvenlafaxine succinate contains one chiral center, but is being developed as the racemate.



Desvenlafaxine succinate is manufactured and tested by \_\_\_\_\_  
The applicant references DMF \_\_\_\_\_ [desvenlafaxine, \_\_\_\_\_] for all information in support of the drug substance. DMF \_\_\_\_\_ was found adequate in support of NDA 21-992. Wyeth has submitted Certificates of Analyses (CoAs) for three batches (#0505H044, #0505H045, and #0507H 001) of desvenlafaxine succinate. Each batch is tested for: description, assay, identification, water, \_\_\_\_\_ impurities (venlafaxine, any unspecified, total), residual solvents, \_\_\_\_\_ and particle size. Total impurities were found to be \_\_\_\_\_, with venlafaxine, a previously approved drug (Effexor®), as the only impurity identified with a specification limit. Residual solvents were



# CHEMISTRY REVIEW



## Executive Summary Section

found to be well within the specification limits, which comply with the recommendations of ICH Q3C. The applicant provided 18 months of long term and 6 months of accelerated stability data for three batches (0341H028, 0341H029, and 0341H 030) of desvenlafaxine succinate. In addition, the sponsor provided supportive data (0418H034) for one additional batch. The sponsor has requested and will be granted a \_\_\_\_\_ retest date for desvenlafaxine succinate.

### Drug Product

The proposed drug product is formulated as an extended-release (ER) tablet in 100 mg and 200 mg strengths (based on desvenlafaxine free base) using the succinate monohydrate salt. The tablets are packaged in multidose bottles and unit dose blister packs. Tablets are square with a pyramid shape on one side and flat on the other. The 100 mg tablet is reddish orange, debossed with "W" over "100".

The product was developed \_\_\_\_\_

The proposed ER tablet consists of a Hypromellose (HPMC) \_\_\_\_\_



A 5-point dissolution method which is sufficient to discriminate between strengths was developed and used to establish a level A *in vivo-in vitro* correlation (IVIVC-A) for 50 mg and 200 mg tablet formulations. Office of Clinical Pharmacology (OCP) has accepted the proposed IVIVC-A and the proposed five point dissolution method as the bioequivalence standard for the drug product (refer to OCP reviews for NDAs 21-992 and \_\_\_\_\_). A \_\_\_\_\_ dissolution method proposed for batch release is still under consideration by OCP.

Tablets are manufactured, tested and packaged by Wyeth (Guayama, PR); release and stability tested at Wyeth (Pearl River, NY); and packaged by three contractors. All sites have been found to meet cGMP standards.

Unit and batch formulations are provided. Tablet formulations \_\_\_\_\_

No excipient is novel or of human or animal origin. Design and control spaces are provided for HPMC. A specification is provided for each of the \_\_\_\_\_ of microcrystalline cellulose and the film coating material. All other excipients

## Executive Summary Section

meet USP, NF or EP monograph requirements. The non-monograph methods for these materials are described in sufficient detail.

Tablet manufacture occurs in

Specifications are provided for batch release (operating space) and for "design space exception (when manufacture occurs outside the manufacturing design space). The tests address tablet appearance, drug identity (HPLC and UV spectrum), content uniformity, drug strength (HPLC), purity (HPLC) and dissolution (UV spectrum or HPLC).

Criterion for strength is accepted as  $\frac{1}{2}$  of label claim at release and  $\frac{1}{2}$  for the stability studies. Criterion for dissolution is accepted as a 5-point (2, 4, 8, 12, 24 hour) dissolution profile. Conclusion on a proposed  $\frac{1}{2}$  criterion for batch release is pending further discussion between ONDQA and OCP.

The proposed packaging presentations are 14, 30, 90-count commercial packages composed of an opaque, white bottle with aluminum foil, cotton wadding and a child resistant closure; and a non-child resistant 2x5 unit dose card composed of a clear blisters with push-thru aluminum foil backing intended as a physician sample or hospital-use package. Packaging component descriptions and acceptance specifications are acceptable. The container/closure systems are qualified through the stability studies.

The Post Approval Stability Protocol is to place the first three production lots of each strength in each market package on stability at ICH long term condition with testing at 0,3,6,9,12,18 months and annually to expiration; then NLT lot annually in each packaging configuration on stability at ICH long term with testing at 0,6,12,18 months and annually to expiration. The results are to be submitted in the annual reports. Deviations are to be addressed per 21 CFR 314.81(b)(1)(ii). These lots will be tested for appearance, strength, purity and dissolution.

Primary stability studies were performed on the 3 registration lots of 100 mg and 200 mg tablets in 14, 30, 90-count bottles and both blister packages. Stability results are presented for tablets 100 mg and 200 mg tablets stored 24 months ICH intermediate and long term conditions; and 6 months at ICH accelerated conditions. One lot of each strength in one blister package was



## CHEMISTRY REVIEW



### Executive Summary Section

evaluated for photostability under ICH option 2 conditions. The protocol for the long term and intermediate condition studies includes bracketing of the 14-count bottle, a reduction matrix for each bottle each blister lot at for long term and intermediate conditions, and 6 months accelerated conditions for each package. Testing was for appearance, potency, purity, 5-point dissolution profile, . The study data showed no trends over time across strengths, lots, packages or conditions, except for an

blister stored at accelerated conditions. to product degradation or dissolution profile changes. Intermittent failures were observed without trend over time for strength, lot, package or condition. Statistical analysis of the long term and intermediate stability data is included. The applicant commits to

The submitted studies support the applicant's proposal for an initial 24 month expiry period in each market package with a label storage statement of USP controlled room temperature. The blister packages are marketed in a carton, thus a light protection statement is not mandated. The content does not affect product stability, thus a is not mandated. The results of these studies support the absence of testing for r at batch release.

Four comparability protocols are included in the application. Protocols for changes to the blister film and the foil-based backing film with submission of changes and supporting data in an annual report are acceptable. A third protocol for optimization of the 100 mg tablet formulation with submission of the change and supporting data as a CBE-30 supplement is acceptable. The fourth protocol for implementation of process analytical technology (PAT) for process control and real time release of drug product has been significantly revised since initially submitted and comments requesting extensive further development are being sent to the applicant. This protocol proposes

Draft labels and labeling indicate the

An environmental assessment statement is provided and has been found acceptable. A FONSI has been prepared.

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

Pristiq™ (desvenlafaxine succinate) extended release tablets will be marketed in 100 mg and 200 mg strengths for the once-a-day treatment of major depressive disorder (MDD). The recommended dose is 100 mg once daily, with or without food.

Pristiq™ extended release tablets should be taken at approximately the same time each day. Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

**Executive Summary Section****C. Basis for Approvable Recommendation**

NDA 21-992 for Pristiq™ (desvenlafaxine succinate) is recommended Approvable (AE) from a CMC standpoint in that the sponsor will need to adequately respond to CMC approvability issues (PAT with real time release comparability protocol, labeling) as outlined in this review. These deficiencies, issued in an information request letter dated 03 May 2007, are detailed at the end of this review.

**III. Administrative**

Chemists: William M. Adams, Terrance Ocheltree, Ph.D., Thomas Oliver, Ph.D (lead)  
Deputy Office Director: Chi-wan Chen, Ph.D. (secondary review)  
Project Manager: Amy Bertha

47 Page(s) Withheld

X Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

Withheld Track Number: Chemistry-2

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this page is the manifestation of the electronic signature.**  
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/s/

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Mike Adams  
6/6/2007 11:53:44 AM  
CHEMIST

Terrance Ocheltree  
6/6/2007 10:12:35 PM  
CHEMIST

Thomas Oliver  
6/7/2007 07:46:40 AM  
CHEMIST

Chi Wan Chen  
6/8/2007 11:31:21 AM  
CHEMIST

**NDA 21-992**  
**Desvenlafaxine Succinate Extended Release Tablets**  
**CMC REVIEW #2**

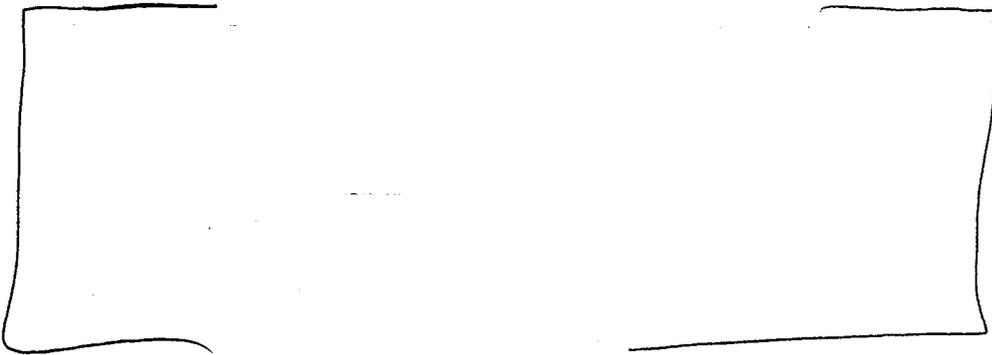
**Applicant:** Wyeth Pharmaceuticals, Inc.  
P.O. Box 8299  
Philadelphia, PA 19101

**Indication:** Major Depressive Disorder

**Dosage Form:** 100 mg and 200 mg Extended Release Tablets

**Background:** In a CMC IR letter, dated November 6, 2006, Wyeth was asked to respond to six issues. In a submission dated, December 8, 2006, Wyeth responded to each of the CMC issues. This review covers our evaluation to date of Wyeth's responses to these six issues.

1)



2) *Provide further justification for the proposed design space for HPMC as it relates to particle size and*



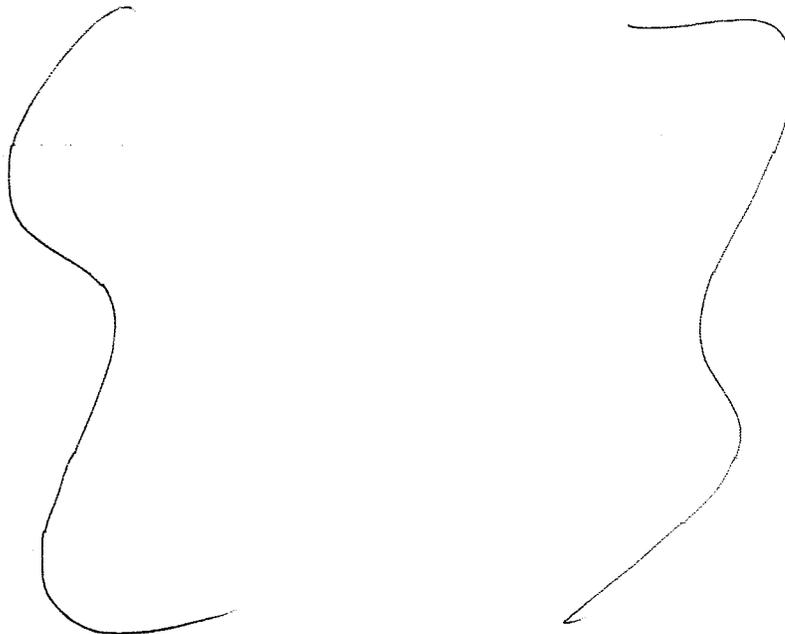
-----  
**Comment for Letter:** The design space for HPMC should be revised to include a particle size specification.

3) *With respect to the Comparability Protocol for the Optimization of Desvenlafaxine Succinate Extended Release Tablet Composition (100 mg formulation):*

b) *Include a 5-point dissolution profile with similarity factors for each sampling time point in the supporting data package. **Evaluation: Adequate.***

4) *Specify whether the proposed blister packages are intended to be child resistant and/or geriatric friendly. **Evaluation: Adequate.** The applicant stated that the blister packages are intended for hospital use or as physician samples, therefore child resistant or geriatric friendly is not mandated.*

5) *For the proposed labeling, it is FDA policy that the established name and labeled strength be in agreement with each other. Therefore, adopt one of the following two options: (a) change the name to desvenlafaxine and retain 100 mg or 200 mg as the strength, or (b) retain the name as desvenlafaxine succinate and change the strength to 151 mg or 303 mg, respectively. In addition, the statement, "each tablet contains 100 mg desvenlafaxine," should be revised accordingly. For example, if Option (a) is adopted, this statement should be modified to read, "each tablet contains 151 mg desvenlafaxine succinate equivalent to 100 mg desvenlafaxine." If Option (b) is adopted, this statement will become unnecessary and can thus be deleted. **Evaluation: Inadequate.** The name/strength in the modified container label dated 12/4/06, shown below, is still a mismatch.*



**Printer to insert DATA MATRIX CODE  
XXXXXXXXX  
at size and position shown on drawing.**

**Comment for Letter:** The name/strength in the modified container label dated 12/4/06, is still a mismatch (refer to the CMC IR letter dated November 6, 2006). Please adopt one of the two formats from below:

a) Pristiq  
(desvenlafaxine \_\_\_\_\_)  
Extended Release Tablets

b) Pristiq  
(desvenlafaxine)  
Extended Release Tablets

6) *The Comparability Protocol for Implementation of PAT and the Implementation of Real Time Release of Desvenlafaxine Succinate Extended Release Tablets is inadequate as currently presented (refer to CMC IR letter dated November 6, 2006 for comments a-g).* **Evaluation:** The CMC information submitted in response to this comment is still

under evaluation. We will provide a written response when the evaluation has been completed. **Comment for Letter:** The Comparability Protocol (CP) for "implementation of PAT and real time release via a CBE-30 supplement" is inadequate. We acknowledge the receipt on December 12, 2006, of your December 8, 2006, amendment intended to address this comment. Evaluation of this information was not completed in time for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter. In addition, a pre-operational visit of the Guayama facility to be used for the implementation of PAT and real time release is necessary before the CP can be approved.

**Recommendation:**

The NDA is approvable until the deficiencies identified above are addressed. Additionally, the drug product manufacturing facility located in Guayama, PR (CFN #1819470) remains unacceptable after a recent cGMP inspection.

**CMC Comments to be Included in Action Letter**

1) Your drug product manufacturing facility located in Guayama, PR (CFN #1819470) was found unacceptable by the Office of Compliance during a recent cGMP inspection. A satisfactory inspection of this site will be required before this application may be approved.

2)  

3) The design space for HPMC should be revised to include a particle size specification.

4) The name/strength in the modified container label dated 12/4/06, is still a mismatch (refer to the CMC IR letter dated November 6, 2006). Please adopt one of the two formats shown below:

a) Pristiq  
(desvenlafaxine)   
Extended Release Tablets  


b) Pristiq  
(desvenlafaxine)  
Extended Release Tablets

5) The Comparability Protocol (CP) for "implementation of PAT and real time release via a CBE-30 supplement" is inadequate. We acknowledge the receipt on December 12, 2006, of your December 8, 2006, amendment intended to address this comment.

Evaluation of this information was not completed in time for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter. In addition, a pre-operational visit of the Guayama facility to be used for the implementation of PAT and real time release is necessary before the CP can be approved.

**CMC Review Team**

William M. Adams

Terrence Ocheltree, Ph.D.

Thomas Oliver, Ph.D. (Lead)

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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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Thomas Oliver  
1/12/2007 11:58:46 AM  
CHEMIST

Mike Adams  
1/12/2007 12:04:32 PM  
CHEMIST

Terrance Ocheltree  
1/12/2007 12:07:55 PM  
CHEMIST

Chi Wan Chen  
1/12/2007 12:14:05 PM  
CHEMIST

**NDA 21-992**

**Pristiq™ (desvenlafaxine succinate)**

**Wyeth Pharmaceuticals, Inc.**

**William M. Adams  
Terrence Ocheltree, Ph.D.  
Thomas Oliver, Ph.D.**

***DIVISION OF PSYCHIATRY PRODUCTS***

**Review of Chemistry, Manufacturing, and Controls**

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# Chemistry Review Data Sheet

1. NDA 21-992
2. REVIEW #1
3. REVIEW DATE: December 1, 2006
4. REVIEWERS: William M. Adams  
Terrance Ocheltree, Ph.D.  
Thomas Oliver, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 64,552	April 2, 2002

6. SUBMISSION(S) BEING REVIEWED:

<u>Submissions Reviewed</u>	<u>Document Date</u>
NDA 21-992 000	22 Dec 20/05
Amendment 005 (BZ)	16 Mar 2006
Amendment 008 (BC)	28 Apr 2006
Amendment 013 (BC)	03 Jul 2006
Amendment 022 (BL)	12 Oct 2006
Amendment 024 (C)	01 Nov 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Wyeth Pharmaceuticals, Inc.  
Address: P.O. Box 8299  
Philadelphia, PA 19101  
Representative: Kenneth R. Bonk  
(Director II, Worldwide Regulatory Affairs)  
Telephone: (484) 865-3103

8. DRUG PRODUCT NAME/CODE/TYPE:

## Executive Summary Section

- a) Proprietary Name: **Pristiq™**  
 b) Non-Proprietary Name (USAN): desvenlafaxine succinate  
 c) Code Name: DVS-233; DVS-233 monohydrate; O-desmethylvenlafaxine succinate monohydrate; ODV succinate monohydrate; WY-45233:succinate monohydrate; WY-45233-1; ODV succinate.H<sub>2</sub>O  
 d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
  - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Major Depressive Disorder

11. DOSAGE FORM: Tablets (extended release)

12. STRENGTH/POTENCY: 100 mg and 200 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

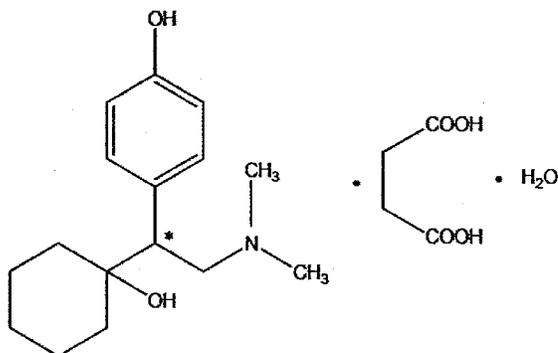
Not a SPOTS product

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

CA Name: 1-[(1R,S)-2-(Dimethylamino)-1-(4-hydroxyphenyl)ethyl] cyclohexanol hydrogen butanedioate monohydrate  
 USAN Name: desvenlafaxine succinate  
 Chemical Formula: C<sub>16</sub>H<sub>25</sub>NO<sub>2</sub>•C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>•H<sub>2</sub>O  
 Molecular Weight: 399.48 (as the succinate, monohydrate)/ 263.38 (as the free base)  
 CAS Registry #: 386750-22-7

Executive Summary Section

Molecular Structure:



\* Denotes chiral center, the compound is racemic.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	II		Desvenlafaxine succinate	1	Adequate	mm/dd/2006	
	IV			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

<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

**Executive Summary Section**

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
IND (Wyeth)	64,552	Desvenlafaxine succinate XR Tablets, MDD
NDA (Wyeth)	20-699	Effexor® XR Capsules, MDD
NDA (Wyeth)	20-151	Effexor® Tablets, MDD
NDA (Wyeth)		Desvenlafaxine succinate XR-Tablets, vasomotor symptoms from menopause
IND (Wyeth)		Desvenlafaxine succinate XR-Tablets, vasomotor symptoms from menopause

**18. STATUS:**

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Clinical	Pending		Robert Levin, MD
EES	<b>Withhold</b>	8/31/06	Janine D'Ambrogio
Pharm/Tox	Pending		Linda Fossom, Ph.D.
Biopharm	1 item Pending	10/26/06	Kofi Kumi, Ph.D.
DMETS	Pending		Tina Tesky, Pharm.D.
EA	Approval (FONSI)	4/21/06	Bai Nguyen

# The Chemistry Review for NDA 21-992

## The Executive Summary

### I. Recommendations

A. Recommendation and Conclusion on Approvability  
NDA 21-992 for Pristiq™ (desvenlafaxine succinate) tablets is recommended NOT APPROVABLE from the CMC standpoint. Wyeth's drug product manufacturing facility located in Guayama, PR (CFN #1819470) was found unacceptable by the Office of Compliance. A satisfactory inspection of this site will be required before this application may be approved. In addition, the applicant will need to adequately respond to a number of CMC issues as outlined in this review.

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)

##### Drug Substance

Desvenlafaxine is a major metabolite of venlafaxine (Effexor® and Effexor® XR; as HCl salt). It selectively blocks the reuptake of serotonin and norepinephrine (sSNRI). Desvenlafaxine succinate was developed for extended release tablets. It is a white to off-white powder with a solubility that increases at lower pH. It is classified as a Class 3 (high solubility and low permeability) according to FDA's Biopharmaceutics Classification System.

Desvenlafaxine succinate contains one chiral center, but is being developed as the racemate.

Desvenlafaxine succinate is manufactured and tested by: \_\_\_\_\_  
The applicant references DMF \_\_\_\_\_ [desvenlafaxine, \_\_\_\_\_] for all information in support of the drug substance. DMF \_\_\_\_\_ was found adequate in support of NDA 21-992. Wyeth has submitted Certificates of Analyses (CoAs) for three batches (#0505H044, #0505H045, and #0507H 001) of desvenlafaxine succinate. Each batch is tested for: description, assay, identification, water, \_\_\_\_\_ impurities (venlafaxine, any

Executive Summary Section

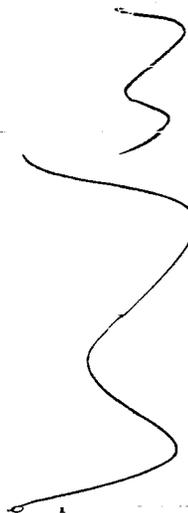
unspecified, total), residual solvents, \_\_\_\_\_ and particle size. Total impurities were found to be \_\_\_\_\_ with venlafaxine, a previously approved drug (Effexor®), as the \_\_\_\_\_ impurity identified with a specification limit. Residual solvents were found to be well within the specification limits, which comply with the recommendations of ICH Q3C. The applicant provided 18 months of long term and 6 months of accelerated stability data for three batches (0341H028, 0341H029, and 0341H 030) of desvenlafaxine succinate. In addition, the sponsor provided supportive data (0418H034) for one additional batch. The sponsor has requested and will be granted a \_\_\_\_\_ retest date for desvenlafaxine succinate.

Drug Product

The proposed drug product is 100 mg and 200 mg desvenlafaxine free base formulated with the succinate monohydrate salt as an extended-release (ER) tablet packaged in multidose bottles and unit dose blister packs. Tablets are square with a pyramid shape on one side and flat on the other. The 100 mg tablet is reddish orange and debossed "W" over "100". \_\_\_\_\_

The product was developed \_\_\_\_\_

The proposed ER tablet consists of a Hypromellose (HPMC) \_\_\_\_\_



A 5-point dissolution method which is sufficient to discriminate between strengths was developed and used to establish a level A *in vivo-in vitro* correlation (IVIVC-A) for 50 mg and 200 mg tablet formulations. OCP has accepted the proposed IVIVC-A for 50 mg, 100 mg, 150 mg and 200 mg tablet strengths, and the proposed dissolution method as the bioequivalence standard for the drug product.

Tablets are manufactured, tested and packaged by Wyeth (Guayama, PR); release and stability tested at Wyeth (Pearl River, NY); and packaged by three contractors. With the exception of the tablet manufacturing site, which has an unresolved Warning Letter, all sites meet cGMP standards.

Unit and batch formulations are provided. Tablet formulations \_\_\_\_\_ No excipient is novel or of human or animal origin. Design and control spaces are provided for HPMC. A specification is provided for each

## Executive Summary Section

of the \_\_\_\_\_ of microcrystalline cellulose and for \_\_\_\_\_ film coatings. All other excipients meet USP, NF or EP monograph requirements. Non-monograph methods for these materials are described in sufficient detail.

Tablet manufacture occurs in \_\_\_\_\_

Specifications are provided for batch release and for "design space exception" (when manufacture occurs outside the manufacturing design space). The tests address tablet appearance, drug identity (HPLC and UV spectrum), content uniformity, drug strength (HPLC), purity (HPLC) and dissolution (UV spectrum or HPLC).

Criterion for strength is accepted as \_\_\_\_\_ of label claim at release and \_\_\_\_\_ for the stability studies. A 5-point dissolution profile (testing at 2H, 4H, 8H, 12H, 24H) is proposed for the "design space exception" and \_\_\_\_\_. Sampling times and criteria for the 5-point specification have been accepted by OCP. The \_\_\_\_\_ dissolution is still under evaluation. The registration stability studies show that \_\_\_\_\_ over 18 months under various ICH conditions, however, degradant formation is not observed, the 5-point dissolution profile is not affected and all release criteria are met. Therefore, \_\_\_\_\_ is proposed. In addition, stability testing for \_\_\_\_\_ show no changes after 12 months, therefore these tests are also not proposed for release testing.

The proposed packaging presentations are 14, 30, 90-count multi-dose packages composed of an opaque, white \_\_\_\_\_ bottle with aluminum foil \_\_\_\_\_ innerseal, cotton wadding and a \_\_\_\_\_ child resistant closure; and a 2x5 unit dose card composed of a clear \_\_\_\_\_ blisters with push-thru aluminum foil backing. Packaging component descriptions and acceptance specifications are acceptable. The container/closure systems are qualified through the stability studies.

The Post Approval Stability Protocol is to place the first three production lots of each strength in each market package on stability at ICH long term condition with testing at 0,3,6,9,12,18 months and expiration; then NLT - lot annually in each packaging configuration on stability at ICH long term with testing at 0,6,12,18 months and expiration. The results are to be submitted in the annual reports. Deviations are to be addressed per 21 CFR 314.81(b)(1)(ii). These lots will be tested for appearance, strength, purity and \_\_\_\_\_ dissolution \_\_\_\_\_

## Executive Summary Section

Primary stability studies were performed on the 3 registration lots of 100 mg and 200 mg tablets in 30, 90-count bottles and both blister packages. Samples were stored up to 18 months long term, up to 18 months intermediate, and up to 6 months accelerated ICH stability conditions. The applicant also evaluated the photostability under ICH option 2. The study protocol which was not submitted for comment before filing includes bracketing of the 14-count bottle; a reduction matrix for each blister lot at long term and intermediate conditions; a reduction matrix for each bottle lot at long term and intermediate conditions; 6 months at accelerated conditions for each package; and photostability on the blister package only. Testing was for Appearance, Potency, Purity, 5-point Dissolution Profile, Content (only). The study data shows no trends over time across strengths, lots, packages or conditions, except for an

blister stored at accelerated conditions. The steady to product degradation or dissolution profile changes. Statistical analysis of the long term stability data is included. The applicant commits to complete the primary stability studies and submit the results in the annual reports. The submitted studies support the applicant's proposal for an initial 24 month expiry period in each market package with a label storage statement of USP controlled room temperature. Since the blister packages are marketed in a carton, a light protection statement is not mandated. Since the content does not affect product stability, a is not mandated.

Four comparability protocols are included in the application. Protocols for changes to the blister film and the foil-based backing film with submission of changes and supporting data in an annual report are acceptable. Further refinement of a protocol for optimization of the 100 mg tablet formulation with submission of the change and supporting data as a CBE-30 supplement has been requested of the applicant. The fourth protocol for implementation of process analytical technology (PAT) for process control and real time release of drug product was significantly revised half way through the review cycle and comments requesting extensive further development have been sent to the applicant. The protocol proposes for the addition of

Supporting feasibility studies were provided for each of the PAT systems.

Draft labels and labeling indicate the Except for a comment regarding the statement of established name and table strength the CMC information is complete and acceptable.

An environmental assessment statement is provided and has been found acceptable. A FONSI has been prepared.

## Executive Summary Section

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

Pristiq™ (desvenlafaxine succinate) extended release tablets will be marketed in 100 mg and 200 mg strengths for the once-a-day treatment of major depressive disorder. The recommended dose is 100 mg once daily, with or without food.

Pristiq™ extended release tablets should be taken at approximately the same time each day. Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved.

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

NDA 21-992 for Pristiq™ (desvenlafaxine succinate) is recommended Not Approvable from a CMC standpoint based on the following:

- Wyeth's drug product manufacturing facility located in Guayama, PR (CFN #1819470) was found unacceptable by the Office of Compliance during a recent cGMP inspection. A satisfactory inspection of this site will be required before this application may be approved.

In addition, the sponsor will need to adequately respond to a number of CMC approvability issues (drug substance control, PAT comparability protocol, labeling) as outlined in this review. These deficiencies are detailed in the draft deficiency letter at the end of this review and they have been forwarded to the NDA applicant. The applicant has not yet responded to these issues, as of December 1, 2006.

**III. Administrative**

Chemists: William M. Adams, Terrence Ocheltree, Ph.D., Thomas Oliver, Ph.D (lead)  
Deputy Office Director: Chi-wan Chen, Ph.D.  
Project Manager: Amy Bertha

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