

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205583Orig1s000

CHEMISTRY REVIEW(S)

NDA 205583**Desvenlafaxine ER Tablets
50 and 100 mg****Sun Pharma Global FZE****Division of Psychiatry Products, HFD 130****Shastri Bhamidipati, Ph.D.
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment****Submission Date :28-Mar-2013
PDUFA Goal Date: 28-Jan-2014**

Table of Contents

The Executive Summary	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments	8
A. Description of the Drug Product(s) and Drug Substance(s).....	8
B. Description of How the Drug Product is intended to be used	9
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative	10

Chemistry Review Data Sheet

1. NDA 205583
2. REVIEW #: 2
3. REVIEW DATE: 20-Dec-2013
4. REVIEWER: Shastri Bhamidipati, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA 205583 Original Submission	28-MAR-2013
NDA 205583 SD# 6	31-JUL-2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
NDA 205583 SD# 9	27-NOV-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Sun Pharma Global, FZE
Office # 43, Block Y, SAIF Zone,
Address: P.O.Box # 122304, Sharjah, U.A.E

Telephone: 301-652-6110

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Desvenlafaxine
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: S

Executive Summary Section

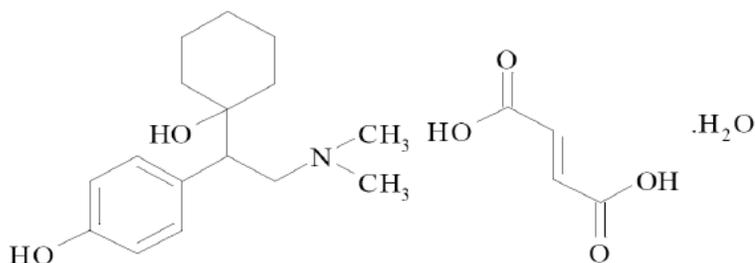
9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505(b)(2)
10. PHARMACOL. CATEGORY: Psychiatry, Major Depressive Disorder
11. DOSAGE FORM: Tablets, Extended Release
12. STRENGTH/POTENCY: 50 and 100 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product

Executive Summary Section

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

Chemical Name(s):

1. Chemical Name: (\pm) 4-[2-dimethylamino-1-(1-hydroxycyclohexyl)-ethyl]-phenol fumarate Monohydrate

Molecular Formula: $C_{16}H_{25}NO_2 \cdot C_4H_4O_4 \cdot H_2O$

Molecular weight: 397.45

CAS No: [313471-75-9] (fumarate monohydrate)

[93413-62-8] (free base)

[386750-22-7] RLD Desvenlafaxine succinate monohydrate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENC ED	CODE ¹	STATUS ₂	DATE REVIEW COMPLETED	COMMENTS
26615	II	Sun Pharma	Desvenlafaxi ne	1	Adequate	13-NOV-2013	S. Bhamidipati
(b) (4)	III		(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			

Executive Summary Section

			(b) (4)				
(b) (4)	III		(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
				4			
	IV			4			

¹ 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")

² 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	None	

Executive Summary Section

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics	N/A		
EES	Acceptable	Oct-04-2013	
Pharm/Tox	Recommends Approval	Dec-17-2013	Shiny Mathew, Ph.D.
Biopharmaceutics	Recommends approval with PMC for developing a more discriminatory dissolution method	Dec-13-2013	Elsbeth Chikhale, Ph.D
Methods Validation	Not requested. The methods are conventional and do not qualify for internal validation by FDA labs		
DMEPA	Recommends approval	Sept-16-2013	Loretta Holmes
EA	Categorical Exclusion granted		
Microbiology	Recommends approval	Aug-01-2013	Erika Pfeiler, Ph.D.

Chemistry Review for NDA 205583

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA 205583 for Desvenlafaxine ER Tablets (50 and 100 mg strengths) is recommended for approval from CMC perspective based on review of the information the applicant provided in response to CMC issues communicated in IR letter dated Nov.15th 2013. The Office of Compliance has provided an overall recommendation for all the manufacturing sites.

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

Refer to the biopharmaceutics review, which recommends a PMC to develop a more discriminating dissolution method.

II. Summary of Chemistry Assessments

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

Drug Product: Desvenlafaxine extended release tablets will be available in 50 mg and 100 mg tablet strengths. The 50 mg tablets are light-pink colored circular, biconvex, beveled edge film coated and imprinted with, "747" on one side and plain on the other side. The 100 mg tablets are brick-red colored circular, biconvex, beveled edge film coated and imprinted with, "804" on one side and plain on the other side. They are supplied in 40, 100 and 750 cc HDPE bottles of 30, 90 and 1000 count tablets. The formulation of Desvenlafaxine ER tablets was developed based on the ingredients listed in the approved reference product, Pristiq®. Inactive ingredients for the 50 mg and 100 mg tablets consist of microcrystalline cellulose, hypromellose, magnesium stearate, talc, colloidal silicon dioxide, ferric oxide red and film-coating which contains hypromellose, titanium dioxide, polyethylene glycol, talc, iron oxide red and iron oxide yellow. None of the excipients are of human or animal origin. The applicant provided detailed formulation, pharmaceutical and manufacturing process development studies.

Desvenlafaxine extended release oral tablets are manufactured (b) (4). The commercial drug product will be manufactured by Sun Pharmaceuticals, Halol, India and distributed by Caraco Pharmaceutical Laboratories, Detroit, MI.

The proposed regulatory specifications for desvenlafaxine ER tablets include appearance, active identification, assay and impurities, content uniformity, (b) (4), dissolution, residual solvents and microbial limits. The analytical methods employed are straight forward analytical procedures and validation reports are provided for the determination of assay, related substances, identification, content uniformity, blend homogeneity and

Executive Summary Section

dissolution. The applicant provided summary of the operational process parameters and in-process controls (testing/monitoring) recommended for manufacturing this product based on the process development and registration lots. Risk assessment data of unit manufacturing process has been provided for the (b) (4) manufacture of the drug product. Stability data for three pilot scale batches of 50 mg and 100 mg Desvenlafaxine Extended-Release Tablets packaged in HDPE bottles of 30, 90 and 1000 count packaging configurations stored at long term (25°C/65% RH) and accelerated (40°C/75% RH) conditions were provided up to 12 months and 6 months respectively. The applicant claimed that there were no observable trends in any of the quality attributes monitored on stability and proposed a (b) (4) month shelf life for the drug product. However, review of stability data showed (b) (4) increase on storage and a noticeable decrease in assay content for 50 mg strength tablets both of which were more pronounced in 30 count presentation relative to the 90 and 1000 count presentations. In response to the IR letter and the tele-conference, the applicant has agreed to (b) (4) the desiccant content (b) (4) to 2 g for 30 count packaging presentation. In addition, the applicant has submitted statistical analysis of stability data including 18 month interval to support the proposed (b) (4) month expiration dating for the drug product.

Drug Substance: Desvenlafaxine is a selective inhibitor of the human serotonin (5-HT) and norepinephrine (NE) monoamine transporters and is commonly referred to as a serotonin-norepinephrine reuptake inhibitor (SNRI) for oral administration. Desvenlafaxine fumarate monohydrate is a white off-white powder with one chiral center and synthesized as a (b) (4). The solubility of Desvenlafaxine base is pH dependent with maximum solubility of 31 mg/mL in 0.1N Hydrochloric acid. The sponsor referred to Type II DMF #26615 for all chemistry, manufacturing and controls information of Desvenlafaxine fumarate monohydrate through a letter of authorization from the DMF holder, Sun Pharmaceuticals. The DMF has been reviewed and deemed adequate to support this NDA. Desvenlafaxine fumarate monohydrate as (b) (4) and characterized by (b) (4). The drug substance has been analyzed at the drug product manufacturing site for identification, assay, related impurities, bulk and tapped densities, and particle size ascertaining its suitability for use. The stability of the drug substance was stated to have been adequately established by the DMF holder with a retest date of (b) (4) months from the time of manufacturing.

B. Description of How the Drug Product is intended to be used

Desvenlafaxine extended-release tablets are light pink (50 mg strength) or brick red (100 mg strength), circular, biconvex, beveled edge film-coated tablets, imprinted with '747' (50 mg strength) and '804' (100 mg strength) in black ink on one side and plain on the other side. Each tablet contains 72.035 mg or 144.07 mg of desvenlafaxine fumarate equivalent to 50 mg or 100 mg of desvenlafaxine. The tablets are supplied in HDPE bottles of 30 and 90 counts with Child Resistant Cap and bottles of 100c count with Non Child Resistant Cap. The drug product is stored at 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86°F) [USP Controlled Room Temperature]. The recommended dose is 50 mg once daily taken orally with or without

Executive Summary Section

food. The tablets should be taken intact without splitting, crushing, chewing or dissolving.

C. Basis for Approvability or Not-Approval Recommendation

This NDA for Desvenlafaxine Extended Release Tablets of 50 and 100 mg strength is recommended for approval based on Chemistry, Manufacturing and Controls information submitted in the application. The Office of Compliance has provided an overall acceptance recommendation for the manufacturing sites. A shelf-life of (b) (4) months is recommended for expiration dating of the drug product based on long term storage stability data submitted.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: Shastri Bhamidipati, Ph.D.
Chemistry Team Leader Name/Date: David Claffey
Project Manager Name/Date: Teshara Bouie

C. CC Block

Original NDA 205583
DNP (HFD-130)/NDA Division File
DNP(HFD-130)/CSO/S. Chang
ONDQA/DNDQAI/Chemist/S. Bhamidipati
ONDQA/DNDQAI RPM/T. Bouie
ONDQA/DNDQAI /Branch Chief/O. Stephens

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/s/

SHASTRI P BHAMIDIPATI
12/20/2013

OLEN M STEPHENS
12/20/2013

NDA 205583**Desvenlafaxine ER Tablets
50 and 100 mg****Sun Pharma Global FZE****Division of Psychiatry Products, HFD 130****Shastri Bhamidipati, Ph.D.
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment****Submission Date :28-Mar-2013
PDUFA Goal Date: 28-Jan-2014**

Table of Contents

The Executive Summary	14
I. Recommendations.....	14
A. Recommendation and Conclusion on Approvability	14
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	14
II. Summary of Chemistry Assessments	14
A. Description of the Drug Product(s) and Drug Substance(s).....	14
B. Description of How the Drug Product is Intended to be Used	15
C. Basis for Approvability or Not-Approval Recommendation.....	15
III. Administrative	16
I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data	17
S DRUG SUBSTANCE [Desvenlafaxine fumarate, Sun Pharma].....	17
P DRUG PRODUCT [Desvenlafaxine ER tablets 50 and 100 mg]	23
P.1 Description and Composition of the Drug Product.....	23
P.2 Pharmaceutical Development [Desvenlafaxine Extended Release Tablets, 50 & 100mg]	24
P.3 Manufacture [Desvenlafaxine ER tablets, 50 and 100 mg]	89
P.4 Control of Excipients [Desvenlafaxine Extended Release Tablets]	94
P.5 Control of Drug Product [Desvenlafaxine Extended Release Tablets, 50 and 100 mg]	95
P.6 Reference Standards or Materials [Desvenlafaxine Extended Release Tablets 50 and 100 mg]	109
P.7 Container Closure System [Desvenlafaxine Extended Release Tablets, 50 and 100 mg]	109

Executive Summary Section

P.8	Stability [Desvenlafaxine Extended Release Tablets, 50 and 100 mg]	110
A	APPENDICES	123
A.1	Facilities and Equipment Establishment Evaluation Report	123
R	REGIONAL INFORMATION	125
II.	Review Of Common Technical Document-Quality (Ctd-Q) Module 1	126
A.	Labeling & Package Insert	126
B.	Environmental Assessment Or Claim Of Categorical Exclusion	129
III.	List Of Deficiencies To Be Communicated	129

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Chemistry Review Data Sheet

1. NDA 205583
2. REVIEW #: 1
3. REVIEW DATE: 27-Nov-2013
4. REVIEWER: Shastri Bhamidipati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

NDA 205583 Original Submission

28-MAR-2013

NDA 205583 SD# 6

31-JUL-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Sun Pharma Global, FZE

Office # 43, Block Y, SAIF Zone,

Address: P.O.Box # 122304, Sharjah, U.A.E

Karin A. Kook, PhD

C/O Salamandra LLC

Representative: 1 Bethesda Center 4800 Hampden Lane Suite 900
Bethesda, MD 208142998

Executive Summary Section

Telephone: 301-652-6110

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN): Desvenlafaxine
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505(b)(2)

10. PHARMACOL. CATEGORY: Psychiatry, Major Depressive Disorder

11. DOSAGE FORM: Tablets, Extended Release

12. STRENGTH/POTENCY: 50 and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

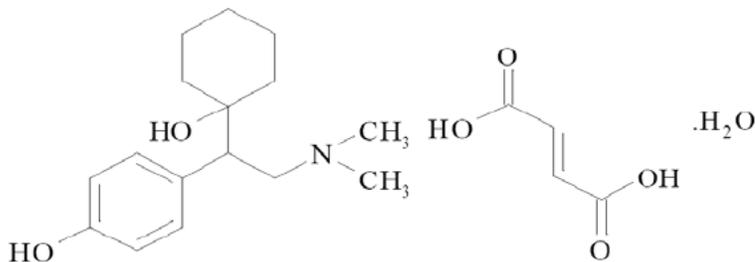
14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

Executive Summary Section

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

Chemical Name(s):

1. Chemical Name: (\pm) 4-[2-dimethylamino-1-(1-hydroxycyclohexyl)-ethyl]-phenol fumarate Monohydrate

Molecular Formula: $C_{16}H_{25}NO_2 \cdot C_4H_4O_4 \cdot H_2O$

Molecular weight: 397.45

CAS No: [313471-75-9] (fumarate monohydrate)

[93413-62-8] (free base)

[386750-22-7] RLD Desvenlafaxine succinate monohydrate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENC ED	CODE ¹	STATUS ₂	DATE REVIEW COMPLETED	COMMENTS
26615	II	Sun Pharma	Desvenlafaxi ne	1	Adequate	13-NOV-2013	S. Bhamidipati
(b) (4)	III	(b) (4)	(b) (4)	4			
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	III			4			
	III			4			

Executive Summary Section

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	III			4			
	III			4			
	III			4			
				4			
	IV			4			

¹ 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")

² 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	None	

Executive Summary Section

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics	N/A		
EES	Acceptable	Oct-04-2013	
Pharm/Tox	N/A		
Biopharmaceutics	Recommends approval with PMC for developing a more discriminatory dissolution method		Elsbeth Chikhale, Ph.D (Review not finalized in DARRRTS)
Methods Validation	Not requested. The methods are conventional and do not qualify for internal validation by FDA labs		
DMEPA	Recommends approval	Sept-16-2013	Loretta Holmes
EA	Categorical Exclusion granted		
Microbiology	Recommends approval	Aug-01-2013	Erika Pfeiler, Ph.D.

Chemistry Review for NDA 205583

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA 205583 for Desvenlafaxine ER Tablets (50 and 100 mg strengths) is recommended for approval from CMC perspective. However, a Post Marketing Commitment as listed below will be discussed with the applicant and finalized prior to approval of this NDA. The Office of Compliance has provided an overall recommendation for all the manufacturing sites.

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

The applicant has been communicated to consider changing desiccant content for 30-Count packaging configuration due to observed stability trends (b) (4).

II. Summary of Chemistry Assessments

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

Drug Product: Desvenlafaxine extended release tablets will be available in 50 mg and 100 mg tablet strengths. The 50 mg tablets are light-pink colored circular, biconvex, beveled edge film coated and imprinted with, "747" on one side and plain on the other side. The 100 mg tablets are brick-red colored circular, biconvex, beveled edge film coated and imprinted with, "804" on one side and plain on the other side. They are supplied in 40, 100 and 750 cc HDPE bottles of 30, 90 and 1000 count tablets. The formulation of Desvenlafaxine ER tablets was developed based on the ingredients listed in the approved reference product, Pristiq®. Inactive ingredients for the 50 mg and 100 mg tablets consist of microcrystalline cellulose, hypromellose, magnesium stearate, talc, colloidal silicon dioxide, ferric oxide red and film-coating which contains hypromellose, titanium dioxide, polyethylene glycol, talc, iron oxide red and iron oxide yellow. None of the excipients are of human or animal origin. The applicant provided detailed formulation, pharmaceutical, and manufacturing process development studies. Desvenlafaxine extended release oral tablets are manufactured (b) (4). The commercial drug product will be manufactured by Sun Pharmaceuticals, Halol, India and distributed by Caraco Pharmaceutical Laboratories, Detroit, MI.

The proposed regulatory specifications for desvenlafaxine ER tablets include appearance, active identification, assay and impurities, content uniformity, (b) (4), dissolution, residual solvents and microbial limits. The analytical methods employed are straight forward analytical procedures and validation reports are provided for the determination of assay, related substances, identification, content uniformity, blend homogeneity and dissolution. The applicant provided

Executive Summary Section

summary of the operational process parameters and in-process controls (testing/monitoring) recommended for manufacturing this product based on the process development and registration lots. Risk assessment data of unit manufacturing process has been provided for the robust manufacture of the drug product. Stability data for three pilot scale batches of 50 mg and 100 mg Desvenlafaxine Extended-Release Tablets packaged in HDPE bottles of 30, 90 and 1000 count packaging configurations stored at long term (25°C/65% RH) and accelerated (40°C/75% RH) conditions were provided up to 12 months and 6 months respectively. The applicant claimed that there were no observable trends in any of the quality attributes monitored on stability and proposed a ^(b)₍₄₎ month shelf life for the drug product. However, review of stability data showed ^(b)₍₄₎ increase on storage and a noticeable decrease in assay content for 50 mg strength tablets both of which were more pronounced in 30 count presentation relative to the 90 and 1000 count presentations (see the CMC issues communicated to the applicant).

Drug Substance: Desvenlafaxine is a selective inhibitor of the human serotonin (5-HT) and norepinephrine (NE) monoamine transporters and is commonly referred to as a serotonin-norepinephrine reuptake inhibitor (SNRI) for oral administration. Desvenlafaxine fumarate monohydrate is a white off-white powder with one chiral center and synthesized as a ^(b)₍₄₎. The solubility of Desvenlafaxine base is pH dependent with maximum solubility of 31 mg/mL in 0.1N Hydrochloric acid. The sponsor referred to Type II DMF #26615 for all chemistry, manufacturing and controls information of Desvenlafaxine fumarate monohydrate through a letter of authorization from the DMF holder, Sun Pharmaceuticals. The DMF has been reviewed and deemed adequate to support this NDA. Desvenlafaxine fumarate monohydrate ^(b)₍₄₎ and characterized by ^(b)₍₄₎. The drug substance has been analyzed at the drug product manufacturing site for identification, assay, related impurities, bulk and tapped densities, and particle size ascertaining its suitability for use. The stability of the drug substance was stated to have been adequately established by the DMF holder with a retest date of ^(b)₍₄₎ months from the time of manufacturing.

B. Description of How the Drug Product is intended to be used

Desvenlafaxine extended-release tablets are light pink (50 mg strength) or brick red(100 mg strength), circular, biconvex, beveled edge film-coated tablets, imprinted with '747' (50 mg strength) and '804'(100 mg strength) in black ink on one side and plain on the other side. Each tablet contains 72.035 mg or 144.07 mg of desvenlafaxine fumarate equivalent to 50 mg or 100 mg of desvenlafaxine. The tablets are supplied in HDPE bottles of 30 and 90 counts with Child Resistant Cap and bottles of 1000 count with Non Child Resistant Cap. The drug product is stored at 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° and 86°F) [USP Controlled Room Temperature]. The recommended dose is 50 mg once daily taken orally with or without food. The tablets should be taken intact without splitting, crushing, chewing or dissolving.

C. Basis for Approvability or Not-Approval Recommendation

This NDA for Desvenlafaxine Extended Release Tablets of 50 and 100 mg strength is recommended for approval based on Chemistry, Manufacturing and Controls information submitted in the application. The Office of Compliance has provided an overall acceptance

Executive Summary Section

recommendation for the manufacturing sites. A shelf-life of 12 months is recommended for expiration dating of the drug product based on long term storage stability data submitted and may extended pending verification of the applicant's response regarding observed stability trends for the 50 mg 30-count presentation

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: Shastri Bhamidipati, Ph.D.

Chemistry Team Leader Name/Date:

Project Manager Name/Date:

C. CC Block

Original NDA 205583

DNP (HFD-130)/NDA Division File

DNP(HFD-130)/CSO/

ONDQA/DNDQAI/Chemist/S. Bhamidipati

ONDQA/DNDQAI RPM/T. Bouie

ONDQA/DNDQAI /Branch Chief/O. Stephens

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/s/

SHASTRI P BHAMIDIPATI
11/27/2013

OLEN M STEPHENS
11/27/2013

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I (Branch I)**

Initial Quality Assessment

NDA: 205583

OND Division:	Division of Psychiatry Products
Applicant:	Sun Pharma Global FZE, United Arab Emirates
NDA Filing Category:	505(b)(2)
Letter Date:	28-MAR-13
Stamp Date:	28-MAR-13
PDUFA Date:	28-JAN-14
Proposed Trade Name:	Tradename has not been proposed
Established Name:	Desvenlafaxine Fumarate Extended-Release Tablets
Dosage Form:	Tablet (Extended-Release)
Strengths:	Equivalent to 50 mg and 100 mg Desvenlafaxine
Route of Administration:	Oral
Indication:	Treatment of major depressive disorder [MDD]
Assessor:	Chhagan G. Tele, Ph.D.
CMC Reviewer:	Shastri Bhamidipati, Ph.D.
ONDQA Biopharm Reviewer:	Elsbeth Chikhale, Ph.D.
Clinical PM:	Sandy Chang
ONDQA PM:	Teshara Bouie
ONDQA Fileability:	Yes

Background

Desvenlafaxine (O-desmethylvenlafaxine), a serotonin and norepinephrine reuptake inhibitor (SNRI), is the major active metabolite of the antidepressant, venlafaxine. Desvenlafaxine succinate monohydrate was originally approved by FDA in February 2008 as Pristiq® (NDA 021992) for the treatment of major depressive disorder (MDD). Pristiq® is available in 50 mg and 100 mg strength tablets. The recommended dose is 50 mg once daily, with or without food, although higher doses are also used (up to 400 mg/day in clinical trials). The route of administration, dosage form, and strengths of Desvenlafaxine Fumarate ER Tablets 50 mg and 100 mg of Sun Pharma are same as that of the Reference Listed Drug (RLD), Pristiq® (desvenlafaxine succinate) ER Tablets 50 mg and 100 mg. Sun has developed Desvenlafaxine Extended Release Tablets in strengths equivalent to 50 mg and 100 mg of desvenlafaxine (as the free base). As this represents a new salt of the active moiety, this New Drug Application (NDA) is submitted under Section 505(b)(2) of the Food, Drug and Cosmetic Act, identifying Pristiq® as the reference product. Both the 50-mg and 100-mg tablets are similar in size and shape, but differ in color for identification purposes. Desvenlafaxine Extended Release Tablets are intended for the treatment of adults with MDD, the same indication as Pristiq® with the same dosage and administration instructions as the RLD. Electronic submission is provided for the CMC information for the review. The applicant provided Quality Overall Summary in the submission. The applicant had Pre-IND meeting (IND 113361, Type B, 12-SEP-2011) with the clinical division to discuss biopharmaceutics, pharmtox, and clinical biopharmaceutics issues. Minutes of these meetings can be found in DARRTS and should be read by the respective reviewers. No CMC specific meetings have been held with the sponsor; however the reviewers need to bridge any changes and agreements evolved from this meeting, amendments, and annual reports submitted during the drug development. The labeling proposed for the Sun Pharma Global FZE, United Arab Emirates is the same as the labeling for the listed drug except for changes required because (1) the drugs are produced and distributed by different manufacturers, (2) differences in package configurations, (3) differences in the salt form of the active ingredient, including differences in the molecular weight and equivalency statements, (4) inactive ingredients are not identical, and (5) differences in the tablet descriptions. No toxicological testing has been performed related to impurities and excipients. Sun's proposed drug product Desvenlafaxine Extended-Release Tablets, 100 mg has undergone, a randomized, open label, three treatments, three periods, six sequence, single dose, crossover, bioequivalence study in healthy human adult subjects under fasting conditions, to demonstrate its bioequivalence to the listed drug, Pristiq® (desvenlafaxine) Extended-Release Tablets, 100 mg strength of Wyeth Pharmaceuticals Inc. and to evaluate effect of food on pharmacokinetic parameters of Sun's proposed drug product when administered under fasting and fed condition. Sun's proposed drug product Desvenlafaxine Extended-Release Tablets, 50 mg has undergone, a randomized, open label, two treatment, two periods, two sequence, single dose, crossover, bioequivalence study in healthy human adult subjects under fasting conditions to demonstrate its bioequivalence to the listed drug, Pristiq® (desvenlafaxine) Extended-Release Tablets, 50 mg strength of Wyeth Pharmaceuticals.

Drug Substance

The drug substance, Desvenlafaxine Fumarate Monohydrate will be manufactured commercially by Sun Pharmaceutical Industries Limited, in Ahmednagar (Maharashtra, India). Desvenlafaxine Fumarate information is cross-referenced to DMF #26615 regarding chemistry, manufacture, control, reference standards, stability, and packaging. The applicant provided a LoA dated 19-DEC-12 to refer DMF #26615 for the drug substance CMC information. DMF #26615 will need to be found adequate to support NDA. In NDA submission, the applicant provided Desvenlafaxine Fumarate Monohydrate release specification, release data of the drug substance batches used in manufacture of drug product batches for NDA submission batches, and summary of the analytical method verification reports. Desvenlafaxine Fumarate is a white to off-white powder. The melting point of the Desvenlafaxine Fumarate is 141°C-145°C (b) (4). Desvenlafaxine fumarate monohydrate exhibits polymorphism. (b) (4) of Desvenlafaxine fumarate monohydrate has been confirmed by (b) (4) and FT-IR analysis on in-house Working standard and three production batches of Desvenlafaxine fumarate monohydrate. The reviewer need to evaluate this information to be sure that there is no change in polymorphic form during stability studies.

Drug Product

It is noted that Desvenlafaxine Extended Release Tablets and the RLD both are having similar release mechanism. The Desvenlafaxine is present as a extended release (b) (4) tablet. In Both the products, Desvenlafaxine releases through diffusion. (b) (4). The components of the both the products are similar with respect to the design except change in the grades of excipients and its quantity.

The excipients used in Desvenlafaxine Fumarate ER tablets were selected based on what was used in the RLD including excipient compatibility studies, physico-chemical properties, dosage form requirements, pharmaceutical functionalities, safety, and Inactive Ingredient Guide (IIG) limits for the (b) (4). Inactive ingredients for the 50 mg tablet consist of microcrystalline cellulose NF, hypromellose USP, magnesium stearate NF, talc, colloidal silicon dioxide, ferric oxide, NF red and film-coating which contains hypromellose USP, titanium dioxide, polyethylene glycol, talc USP, iron oxide red and iron oxide yellow. Inactive ingredients for the 100 mg tablet consist of microcrystalline cellulose NF, hypromellose USP, magnesium stearate NF, talc USP, colloidal silicon dioxide NF, and film-coating which contain hypromellose USP, titanium dioxide, polyethylene glycol, iron oxide red and iron oxide yellow. The imprinting ink contains shellac, black iron oxide, n-butyl alcohol, propylene glycol and ammonium hydroxide. All excipients are commonly used in the solid dosage forms (no novel excipients). It is noted that all excipients in the unit dose are below the IIG limits for oral route of administration. None of the excipients are of human or animal origin.

The applicant provided calculations for maximum daily dose of elemental iron from inactive ingredient (iron oxide red and iron oxide yellow used in the formulation) that will be getting to the patients (2 doses/day of 50 mg desvenlafaxine tablets: (b) (4) and one dose/day of 100 mg desvenlafaxine tablet (b) (4)). This amount is well within the FDA limit for elemental Iron of 5 mg/day [CFR 73.1200(c)]. The reviewer need to evaluate the calculations for maximum daily dose of elemental iron that will be getting to the patients.

Desvenlafaxine Fumarate extended release oral tablets will be available in 50 mg and 100 mg (equivalent to desvenlafaxine) tablet strengths (a generic version of Pristiq® Tablets 50 mg and 100 mg, listed as the RLD). 50 mg, light pink, circular, biconvex, beveled edge film-coated tablets, imprinted with '747' in black ink on one side and plain on the other side. 100 mg, brick red, circular biconvex, beveled edge, film-coated tablets, imprinted with '804' in black ink on one side and plain on the other side. The drug product will be packaged in 30, 90, and 1000 counts in 40cc, 100cc, and 750cc white round HDPE bottles containing (b) (4) in each bottle, respectively. Each tablet contains 72.035 mg or 144.07 mg of desvenlafaxine fumarate equivalent to 50 mg or 100 mg of desvenlafaxine, respectively.

The applicant used Quality by Design (QbD) approach to develop Desvenlafaxine Extended Release tablets that are (b) (4). Initially, the quality target product profile (QTPP) was defined based on the properties of the drug substance, characterization of the RLD product, and consideration of the RLD label and intended patient population. The reviewer need to review the provided data for the consistent manufacturing of the product.

The applicant defined the quality target product profile (QTPP) based on the properties of the drug substance, characterization of the RLD product, and consideration of the RLD label and intended patient population. The investigation during pharmaceutical development is focused on those Critical Quality Attributes (CQAs) that could be impacted by a realistic change to the drug product formulation or manufacturing process. For proposed Desvenlafaxine extended release tablets, these Critical Quality Attributes (CQAs) includes assay, content uniformity, dissolution and degradation products. The reviewer needs to evaluate the risk assessment data for the drug product CQAs.

(b) (4)
The assigned reviewer will need to review in detail about these studies for the (b) (4) manufacturability of the drug product. The reviewer need to check (b) (4) desvenlafaxine is used in the commercial formulation.

A risk assessment of formulation was conducted by the applicant by identifying and evaluating drug product CQAs. Formulation variables used for determining drug product CQA (assay, impurities, content uniformity, and dissolution) are provided. The reviewer needs to evaluate the risk assessment data for the drug product CQAs.

A risk assessment of manufacturing process was conducted by the applicant by identifying and evaluating drug product CQAs. Manufacturing process used for determining drug product CQA (assay, impurities, content uniformity, and dissolution) (b) (4). The reviewer needs to evaluate the risk assessment data of manufacturing process for the drug product CQAs.

Manufacturing, processing, packaging, labeling and handling of Desvenlafaxine Fumarate ER Tablets will take place at the manufacturing facility, Sun Pharmaceutical Industries Ltd., Halol, Gujarat, India. (b) (4)

The proposed regulatory specifications for desvenlafaxine ER tablets involve description, identification (HPLC and UV), (b) (4) average weight, dissolution (HPLC), content uniformity (HPLC), assay (HPLC), related substances (HPLC), microbial limit test (USP), and residual solvents (GC). Validated analytical methods are provided for the determination of assay, related substances, content uniformity, residual solvents, and dissolution. The reviewer needs to evaluate the adequacy of the validation parameters. The batch analyses of the NDA exhibit batches of drug product (50 mg and 100 mg strengths) are provided. The dissolution test method (HPLC) is performed in accordance with USP <711> using the USP Apparatus 1 (Basket) at 100 rpm to determine the amount of drug substance released. The adequacy of the dissolution method and specification limits will need to be determined in conjunction with the ONDQA Biopharmaceutics reviewer.

Exhibit batches of Desvenlafaxine Fumarate Extended-Release Tablets 50 mg and 100 mg are packed in HDPE bottles of 30, 90, and 1000 counts. 6 months accelerated and 12 months long term stability data for 50 mg strength and 12 months long term stability data for 100 mg strength of Desvenlafaxine Fumarate Extended-Release Tablets are provided. In accordance with our policy, the assigned expiration dating period will be based on the extent and quality of the primary stability data provided. The applicant proposed a tentative (b) (4) month expiry for the product based on the stability data.

Critical Issues for Review

Drug Substance

- The NDA applicant references DMF #26615 [Sun Pharmaceutical Industries Limited, in Ahmednagar (Maharashtra, India)] for information on Desvenlafaxine Fumarate Monohydrate. DMF #26615 will need to be evaluated and found acceptable to support this NDA.
- It is noted in the submission that the polymorphic form is retained with the drug substance during stability (b) (4). The reviewer need to evaluate this information to be sure that there is no change in polymorphic form during stability studies.

Drug Product

- The compatibility of the excipients used in the drug product will need to be evaluated.
- The applicant provided calculations for maximum daily dose of elemental iron from inactive ingredient (iron oxide red and iron oxide yellow used in the formulation) that will be getting to the patients (2 doses/day of 50 mg desvenlafaxine tablets (b) (4) and one dose/day of 100 mg desvenlafaxine tablet: (b) (4)). This amount is well within the FDA limit for elemental Iron of 5 mg per day [CFR 73.1200(c)]. The reviewer needs to evaluate the calculations for maximum daily dose of elemental iron that will be getting to the patients.
- A risk assessment of formulation was conducted by the applicant by identifying and evaluating drug product CQAs. Formulation variables used for determining drug product CQA (assay, impurities, content uniformity, and dissolution) are (b) (4) talc amount, and magnesium stearate amount. The reviewer needs to evaluate the risk assessment data for the drug product CQAs.
- A risk assessment of manufacturing process was conducted by the applicant by identifying and evaluating drug product CQAs. Manufacturing process used for determining drug product CQA (assay, impurities, content uniformity, and dissolution) are (b) (4). The reviewer needs to evaluate the risk assessment data of manufacturing process for the drug product CQAs.
- The effect of (b) (4) tablet strength need to be examined closely.
- Need to confirm the adequacy of the critical parameters for the tablets like thickness, length, width, Tablet Hardness and Friability. Tablet hardness and friability needed to be evaluated.
- Justification of the exclusion of tests and acceptance criteria for tablet hardness, friability, and microbial limits needs to be requested to evaluate whether the level of process understanding and process controls is adequate.
- The adequacy of the dissolution method and specification limits will need to be determined in conjunction with the ONDQA biopharm reviewer.
- Stability data (6 months accelerated and 12 months long-term) of 50 mg and 100 mg ER tablets strengths is provided in the NDA submission packaged in commercial configuration at commercial packaging site. The reviewer needs to confirm the expiry date on the quality of the data.
- NDA submission contains (b) (4). However, the reviewer should indicate that (b) (4) (see MAPP 5015.9 entitled, "Reporting Format for Nanotechnology—Related Information in CMC Review.")
- The reviewer need to confirm consistency in chemical structure, chemical name, molecular formula, and molecular weight of the drug substance with the current USP dictionary and USAN in the Description section of the labeling. Additionally reviewer need to confirm that all the excipients used in the drug product formulation are included.

Comments and Recommendation:

The NDA is fileable from a CMC perspective. The NDA does not appear to incorporate elements of QbD. NDA submission contains (b) (4). The drug substance is manufactured under DMF #26615. DMF should be reviewed to support this NDA. Assignment of the NDA to a

single reviewer is recommended. The dissolution part of the submission should be consulted to the ONDQA biopharm group. Biopharmaceutics reviewer has been assigned yet.

A claim for categorical exclusion under 21 CFR §25.31(b) is provided in Module 1. In accordance with 21 CFR §25.31, Sun Pharma Global FZE requested a categorical exclusion [25.31(a)] from the requirement for an Environmental Assessment or Environmental Impact Statement based upon two facts indicating that the approval of the drug product will not increase the use of the active moiety and not toxic to organisms in the environment. In addition, it is noted that Desvenlafaxine Extended-Release Tablets, 50 mg and 100 mg will be administered at the same dosage level, for the same indications as the "listed" drug, Pristiq® (desvenlafaxine) Extended-Release Tablets, 50 mg and 100 mg. In addition, Sun Pharma indicated that they are unaware of any other data that would establish that its Dcsvcnlafaxine Extended-Release Tablets, 50 mg and 100 mg might be toxic to organisms in the environment at expected levels of exposure. Sun Pharma Global FZE also ceertifies that, it is in compliance with all federal. state and local environmental protection requirements. On the basis of the foregoing, Sun Pharma Global FZE submits that an Environmental Assessment statement is not required with this application and therefore requests that it be categorically excluded from the requirement to submit an Environmental Assessment statement.

The list of manufacturing, testing, and packaging sites for drug substance and drug product is provided to enter into EES. The ONDQA PM submitted all testing, packaging, and manufacturing sites into EES. The reviewer will need to confirm that these sites are correct and that there are no additional sites that need to be entered.

**PRODUCT QUALITY: CMC AND BIOPHARMACEUTICS
FILING REVIEW FOR NDA**

NDA Number: 205583	Applicant: Sun Pharma Global FZE, United Arab Emirates	Stamp Date: 28-MAR-13
Drug Name: Desvenlafexine Fumarate ER Tablets	NDA Type: Standard	Filing:

CMC Reviewer: Shastri Bhamidipati, Ph.D.
Biopharmaceuticals Reviewer: Elsbeth Chikhale, Ph. D.

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		
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? This question is not applicable for synthesized API.			NA

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"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing 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"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

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"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
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

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

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		
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?			Biopharmaceutics reviewer's input needed
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		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

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	

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		

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
34.	Does the application contain dissolution data?	X		
35.	Is the dissolution test part of the DP specifications?	X		
36.	Does the application contain the dissolution method development report?	X		
37.	Is there a validation package for the analytical method and dissolution methodology?	X		
38.	Does the application include a biowaiver request?			Biopharmaceutics reviewer need to review the information if provided in the application
39.	Does the application include a IVIVC model?			Biopharmaceutics reviewer need to review the information if provided in the application
40.	Is information such as BCS classification mentioned, and supportive data provided?		X	
41.	Is there any <i>in vivo</i> BA or BE information in the submission?			Biopharmaceutics reviewer's input needed

K. FILING CONCLUSION				
	Parameter	Yes	No	Comment
42.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
43.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
44.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			Biopharmaceutics reviewer's input needed
45.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	

Chhagan Tele

18-APR-13

Name of Pharmaceutical Assessment Lead or CMC Lead/CMC Reviewer
 Division of Pre-Marketing Assessment #
 Office of New Drug Quality Assessment

Date

Ramesh Sood

Name of Branch Chief
 Division of Pre-Marketing Assessment #
 Office of New Drug Quality Assessment

Date

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

/s/

CHHAGAN G TELE
04/18/2013

RAMESH K SOOD
04/19/2013