

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205583Orig1s000

OTHER REVIEW(S)

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title¹	DESVENLAFAXINE Extended-Release Tablets, for oral use
Applicant	Sun Pharma Global FZE
Application/Supplement Number	NDA 205583
Type of Application	Original
Indication(s)	Treatment of major depressive disorder
Office/Division	ODEI/DPP
Division Project Manager	ShinYe Chang
Date FDA Received Application	March 28, 2013
Goal Date	January 28, 2014
Date PI Received by SEALD	January 22, 2014
SEALD Review Date	January 23, 2014
SEALD Labeling Reviewer	Debra Beitzell
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

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Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment: *Waiver of 1/2 page HL limit to be granted by DPP in approval letter.*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *Correct horizontal lines on either sides of major headings to extend entire width of column.*

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *Insert one line of white space above the D&A and Dosage Forms and Strengths headings.*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format

Selected Requirements of Prescribing Information

is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: (b) (4) should not be in the HL Limitation Statement; the statement should include "DESVENLAFAXINE" only.

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

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Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

YES 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

NO 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: [REDACTED] ^{(b) (4)} should be removed from the I&U statement; only “Desvenlafaxine” should be included. The statement should read “Desvenlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of major depressive disorder (MDD) (1).”

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Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

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Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

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Comment: *Subsection 5.1: Remove additional text within cross reference to subsections 2.4 and 5.7; the cross reference should read "[see Dosage and Administration (2.4) and Warnings and Precautions (5.7)]". Subsection 8.4: In cross reference to Boxed Warning, change "Box" to "Boxed" (i.e., "[see Boxed Warning and Warnings and Precautions (5.1)]".*

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

Comment:

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Selected Requirements of Prescribing Information

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

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Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

DEBRA C BEITZELL
01/23/2014

ERIC R BRODSKY
01/23/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

505(b)(2) ASSESSMENT

Application Information		
NDA # 205583	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: desvenlafaxine fumarate Dosage Form: extended-release tablets Strengths: 50 mg and 100 mg		
Applicant: Sun Pharma Global FZE		
Date of Receipt: March 28, 2013		
PDUFA Goal Date: January 28, 2014		Action Goal Date (if different):
RPM: Shin-Ye Sandy Chang		
Proposed Indication(s): Major Depressive Disorder		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
YES NO

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



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

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

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
<i>NDA 21992 (Pristiq)</i>	<i>FDA's previous clinical and nonclinical finding of safety and effectiveness(all sections except for PK data that is relevant to desvenlafaxine fumarate)</i>

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

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

RELIANCE ON PUBLISHED LITERATURE

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

YES NO
If “NO,” proceed to question #5.

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

YES NO
*If “NO”, proceed to question #5.
 If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

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

YES NO

RELIANCE ON LISTED DRUG(S)

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

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

YES NO

If "NO," proceed to question #10.

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

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
<i>Pristiq (desvenlafaxine Succinate) tablets</i>	<i>21992</i>	<i>Yes</i>

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

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

N/A YES NO

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

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

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

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

YES NO

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

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

- b) Approved by the DESI process?

YES NO

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

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

- c) Described in a final OTC drug monograph?

YES NO

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

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

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

YES NO

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

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

This application provides for the use of desvenlafaxine fumurate (salt) as the active ingredient in the Sponsor's extended-release tablets, 50 mg and 100 mg formulation compared to the desvenlavaxine succinate (salt) in the innovator's (RLD) tablet formulation.

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

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

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

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

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

YES NO

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

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? N/A YES NO

If this application relies only on non product-specific published literature, answer “N/A”
If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

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

Pharmaceutical equivalent(s):

Teva Pharmaceuticals USA (desvenlafaxine fumurate), NDA 205208, was approved as a 505(b)(2) on October 11, 2013.

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

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

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

YES NO
If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? N/A YES NO

If this application relies only on non product-specific published literature, answer “N/A”
If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

NDA 204150: Alembic Pharmaceuticals LTD (desvenlafaxine), was approved (as a 505(b)(2) on March 4, 2013.

NDA 204683: Osmotica Pharmaceutical Corp (Khedezla [desvenlafaxine]) was approved as a 505(b)(2) on July 10, 2013.

RLD – NDA 021992: Wyeth (Pfizer) (Pristiq [desvenlafaxine succinate] was approved as 505(b)(1) on February 29, 2008

PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s): 6,673,838 AND 8,269,040

No patents listed proceed to question #14

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

YES NO

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

Listed drug/Patent number(s):

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

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

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

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

Patent number(s):

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

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be

infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

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

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

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

- (a) Patent number(s): 6,673,838 AND 8,269,040
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

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

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

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

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

Date(s): *July 9, 2013*

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

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

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

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

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/s/

SHIN-YE CHANG
01/23/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label Memorandum

Date: January 14, 2014

Reviewer: Loretta Holmes, BSN, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, MS, Pharm D
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Desvenlafaxine Extended-release Tablets
50 mg and 100 mg

Application Type/Number: NDA 205583

Applicant: Sun Pharma Global FZE

OSE RCM #: 2013-1293

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3	CONCLUSIONS AND RECOMMENDATIONS.....	3
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1 INTRODUCTION

This memorandum evaluates the revised container labels for Desvenlafaxine Extended-release Tablets submitted by the Applicant on January 3, 2014 (Appendix A) in response to recommendations provided via email on December 26, 2013 (Appendix B).

2 METHODS AND MATERIALS REVIEWED

DMEPA evaluated the revised container labels submitted on January 3, 2014. We compared the revised labels against our recommendations provided in OSE Review 2013-1293 dated September 16, 2013 and sent via email on December 26, 2013 to assess whether the revised labels address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

Our review of the revised container labels determined the Applicant has implemented all of our recommendations and we find the revisions acceptable. Therefore, we have no further recommendations at this time.

If you have further questions or need clarifications, please contact Louis Flowers, OSE Project Manager, at 301-796-3158.

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Appendix B: Recommendations sent to the Applicant on December 26, 2013

The Medication Guide (MG) statement reads: [REDACTED] (b) (4)
[REDACTED]. We recommend replacing the proposed statement with the following language “Dispense the accompanying Medication Guide to each patient” [see 21 CFR 208.24(d)]. Additionally, provide the Medication Guides in sufficient numbers to permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription for the product [21 CFR 208.24(b)(1)(2)].

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/s/

LORETTA HOLMES
01/14/2014

LUBNA A MERCHANT
01/15/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 6, 2014

TO: Mitchell Mathis, M.D.
Acting Director,
Division of Psychiatry Products
Office of New Drugs

FROM: Ruben C. Ayala, Pharm.D.
Pharmacologist
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Charles Bonapace, Pharm.D.
Chief, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: EIR covering NDA 205-583, Desvenlafaxine Fumarate
Extended Release Tablets, sponsored by SUN Pharma
Global FZE, United Arab Emirates

At the request of the Division of Psychiatry Products (DPP), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted an inspection of the clinical and analytical portions of the following bioequivalence studies:

PKD 12 170: "A randomized, open label, three treatment, three period, six sequence, single dose, crossover, bioequivalence study comparing SUN Pharmaceutical Industries Limited India's Desvenlafaxine 100 mg Extended Release Tablets when administered under fasting and fed condition and Pristiq® (Desvenlafaxine) 100 mg Extended Release Tablets of Wyeth Pharmaceuticals Inc. Philadelphia, PA 19101, when administered under fasting condition, in 36 healthy human adult subjects"

PKD 12 171: "A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence

study of Desvenlafaxine 50 mg Extended Release Tablets of SUN Pharmaceutical Industries Limited, India and Pristiq[®] (Desvenlafaxine) 50 mg Extended Release Tablets of Wyeth Pharmaceuticals Inc. Philadelphia, PA 19101 in 50 healthy human adult subjects under fasting conditions"

The inspection of the clinical and analytical portions of the studies at **SUN Pharmaceutical Industries Ltd., Vadodara, India (SUN Pharma)** were conducted by Kirtida Patel (ORA) and Ruben C. Ayala (OSI). Following the inspection (November 18-22, 2013), Form FDA 483 was issued (**Attachment 1**). The firm's response to Form FDA 483 was received on December 3, 2013 (**Attachment 2**).

The Form FDA 483 observations, SUN Pharma's response to Form FDA 483, and our evaluation follow.

- 1. Failure to document the corrective actions taken to resolve temperature excursions of long-term storage of study samples. Specifically, temperatures in the deep freezer (ID # PKD/653) exceeded +10°C for 14 hours during July 9-10, 2012. The temperature data logger contained a note of "temperature out of range" which was signed and dated on July 10, 2012.**

In their response to Form FDA 483, SUN Pharma acknowledged that the freezer's logging sheet did not document corrective actions taken to address the temperature excursion, the sample custodian's evaluation of the temperature excursion, or an explanation for this temperature excursion. SUN Pharma revised their SOP to include a freezer logging sheet, which documents actions taken to monitor and handle future temperature excursions (see **Attachment 3**).

In the opinion of this reviewer, this observation does not affect the study outcome, as the freezer did not contain study samples during the temperature excursion on July 9-10, 2012. In addition, SUN Pharma has taken adequate measures to monitor and document corrective actions taken for future and unexpected temperature excursions.

- 2. Re-integrations were applied to one study sample after the sample batch was already accepted. Specifically, the chromatogram labelled "Sub_01_P3_6.00 Hrs" for Subject 1 enrolled in Study PKD_12_170 was re-integrated resulting in a change of the concentration of desvenlafaxine from 290.01 to 273.33 ng/mL.**

SUN Pharma re-integrated chromatograms per their internal SOP. After evaluating chromatograms, the quality control team concluded that sample ID "Sub_01_P3_6.00 Hrs" had an unacceptable peak shape due to excessive tailing in comparison to other samples in the run. Therefore, the team ordered the analyst to re-integrate the chromatogram only for sample "Sub_01_P3_6.00 Hrs," and not for all the samples in the analytical run.

In their response to the FDA 483, SUN Pharma submitted results from an analysis evaluating the effect of the re-integration parameters from sample "Sub_01_P3_6.00 Hrs" when applied to all samples in that analytical run. The analysis also evaluated whether the change in the desvenlafaxine concentration resulting from the re-integration of sample "Sub_01_P3_6.00 Hrs" altered the original statistical BE results. SUN Pharma concluded that the statistical results were similar when only sample "Sub_01_P3_6.00 Hrs" was re-integrated and when all the chromatograms in the run were re-integrated (**Attachment 4**). In addition, SUN Pharma updated their SOP (PKD/S/015, Revision 5) to address future re-integrations.

In the opinion of this reviewer, this observation does not affect the study outcome.

Conclusion:

The clinical and analytical data from studies PKD_12_170 and PKD_12_171 were found to be reliable. Thus, this reviewer recommends that the data be accepted for Agency review.

Final Classification (Clinical and Analytical):

VAI - SUN Pharmaceutical Industries Ltd., Vadodara, India
FEI: 3004520113

Attachments

1. Form FDA 483
2. Firm's response to FDA 483
3. Updated freezer logging sheet
4. Statistical analysis with initial and re-integrated values for sample ID Sub_01_P3_6hr

Page 4 - NDA 205-583, Desvenlafaxine Fumarate Extended Release
Tablets, sponsored by SUN Pharma Global FZE, United Arab
Emirates

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Bonapace/Haidar/Mada/Ayala/Dejernet

CDER/OTS/OCP/DCPI/Mehta/Zhu/Kumi

CDER/OND/DPP/Mathis/Chang

HFR-PA250/Patel

Draft: RCA 12/23/2013; 01/06/2014

Edit: SRM 12/23/2013; CRB 01/06/2014

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Inspections/BE Program/Analytical
Sites/SUN Pharmaceuticals, Vadodara, India

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Inspections/BE Program/Clinical
Sites/SUN Pharmaceuticals, Vadodara, India

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/s/

RUBEN C AYALA
01/06/2014

CHARLES R BONAPACE
01/07/2014

WILLIAM H TAYLOR
01/14/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 205583
Product Name: Desvenlafaxine Extended Release Tablets, 50 mg/tablet and 100 mg/tablet

- PMR/PMC Description:
- The Applicant has agreed to develop an optimal discriminating dissolution method that can distinguish between batches of drug product that are bioequivalent to the listed drug and batches that are no bioequivalent to the listed drug for both the 50 mg and the 100 mg strengths.
 - Using the new discriminating dissolution method, the Applicant will set the acceptance criteria using the dissolution data from at least six batches (n=12) of 50 mg and 100 mg drug product. The selected dissolution acceptance criteria should reject those batches that are no bioequivalent to the reference listed drug.
 - Within one year of NDA approval date, the Applicant will submit a supplement to the NDA containing the dissolution method development report with all the necessary information/data supporting the selection of the new dissolution method; including raw data (n=12), tables, and figures, clearly stating the testing conditions used for each data set. The report will also include the Applicant's proposal for the new dissolution acceptance criteria based on the overall dissolution profile data collected with the more discriminating dissolution method.
-

PMR/PMC Schedule Milestones:	Final Protocol Submission:	NA
	Study/Trial Completion:	12/28/2014
	Final Report Submission:	01/28/2015
	Other:	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern

Other

The currently proposed dissolution method is NOT adequate, because it is not able of differentiate between batches of drug product that are bioequivalent to the listed drug and batches that are not bioequivalent to the listed drug. During a teleconference with the Applicant, they agreed to develop a more discriminating dissolution method and based on the data generated with the new dissolution method the Applicant will propose new dissolution acceptance criteria. For this PMC, the timeframe for collecting the additional dissolution data and submitting the final report (*under a supplement to the NDA*) is 12 months.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The currently proposed dissolution method is as follows:

Apparatus: USP 1 (basket)

Temperature: 37.0 °C

Speed: 100 rpm

Volume: 900 mL

Medium: 0.1 N HCl in water

This dissolution method is not adequate because it is NOT capable of discriminate between batches of drug product that are bioequivalent to the listed drug and batches that are not bioequivalent to the listed drug. Until the Applicant has developed a more discriminating dissolution method, the proposed method will be used for quality control testing for the drug product’s batch release and stability studies. The currently proposed dissolution acceptance criteria are based on the dissolution data generated using the currently proposed dissolution method.

Under this PMC, the development of a more discriminating dissolution method would result in a better/optimal dissolution methodology. At the end of this PMC, it is expected that the Applicant will implement a more appropriate dissolution method and acceptance criteria to better control the quality of the drug product and to have clinically relevance.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Applicant has agreed to develop a more discriminating dissolution method that can distinguish between batched of drug product that are bioequivalent to the listed drug and batches that are not bioequivalent to the listed drug for both the 50 mg and 100 mg strength. Within one year of NDA approval, the Applicant will submit a supplement to the NDA containing a dissolution method development report with all the necessary information used to select the new dissolution method; including raw data (n=12), tables, and figures, clearly stating the testing conditions used for each data set. Using the more discriminating dissolution method, the Applicant will set the acceptance criteria using the dissolution data from at least six batches of 50 mg and 100 mg drug product.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Dissolution studies
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(Signature line for BLAs)

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/s/

ELSBETH G CHIKHALE
12/23/2013

ANGELICA DORANTES
12/23/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: 12/17/2013

To: Sandy Chang, Pharm.D
Regulatory Project Manager
Division of Psychiatry Products (DPP)

Through Mathilda Fienkeng, PharmD
Team Leader
Office of Prescription Drug Promotion (OPDP)

From: Nazia Fatima, Pharm.D, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **OPDP Comments on desvenlafaxine fumarate extended-release tablets NDA 205583**

OPDP has reviewed the draft product labeling (PI), carton/container labelling and medication guide (MG) for desvenlafaxine fumarate extended-release tablets as requested in the consult from DPP dated May 14, 2013.

OPDP's review is based on the draft version of the PI sent via email on December 9, 2013, by Sandy Chang, Pharm.D. OPDP has reviewed the proposed PI and has no comments. OPDP has also reviewed the carton/container labeling submitted by the sponsor on March 28, 2013, accessed via EDR Location: <\\Cdsub1\evsprod\NDA205583\205583.enx>, and has no comments at this time. Combined OPDP and the Division of Medical Policy Programs (DMPP) comments on the proposed MG were provided under a separate cover by DMPP on December 17, 2013.

If you have any questions, please feel free to contact me, Nazia Fatima at 240-402-5041 or at Nazia.Fatima@fda.hhs.gov. Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

NAZIA FATIMA
12/17/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: December 17, 2013

To: Mitchell Mathis, MD
Acting Director
Division of Psychiatry Products (DPP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

Mathilda Fienkeng, Pharm.D
Team Leader, OPDP
Office of Prescription Drug Promotion (OPDP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Nazia Fatima, Pharm.D, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): Desvenlafaxine

Dosage Form and Route: Extended-Release Tablets

Application Type/Number: NDA 205583

Applicant: Sun Pharma Global FZE

1 INTRODUCTION

On March 25, 2013, Sun Pharma Global FZE submitted for the Agency's review an Original New Drug Application (NDA) for Desvenlafaxine Extended-Release Tablets indicated for the treatment of major depressive disorder (MDD).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on May 14, 2013, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for Desvenlafaxine Extended-Release Tablets.

2 MATERIAL REVIEWED

- Draft Desvenlafaxine MG received on March 25, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on December 9, 2013.
- Draft Desvenlafaxine MG received on March 25, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on December 9, 2013.
- Draft Desvenlafaxine Prescribing Information (PI) received on March 25, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on December 9, 2013.
- Draft Desvenlafaxine Prescribing Information (PI) received on March 25, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on December 9, 2013.
- Approved PRISTIQ (desvenlafaxine succinate) comparator labeling dated February 14, 2013.
- Approved desvenlafaxine fumarate comparator labeling dated October 11, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we have:

- ensured that the MG, is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
12/17/2013

NAZIA FATIMA
12/17/2013

MELISSA I HULETT
12/17/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: September 16, 2013

Reviewer: Loretta Holmes, BSN, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Desvenlafaxine Extended-release Tablets
50 mg and 100 mg

Application Type/Number: NDA 205583

Applicant: Sun Pharma Global, FZE

OSE RCM #: 2013-1293

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1 INTRODUCTION

This review evaluates the proposed container labels and insert labeling for Desvenlafaxine Extended-release Tablets, NDA 205583, for areas of vulnerability that can lead to medication errors.

1.1 REGULATORY HISTORY

NDA 205583 for Desvenlafaxine Extended-Release Tablets is a 505(b)(2) application relying on clinical and preclinical data for Pristiq Extended-Release Tablets (NDA 021992), which was approved on February 29, 2008.

1.2 PRODUCT INFORMATION

The following product information was provided in the March 28, 2013 submission.

Active Ingredient	Desvenlafaxine
Indication of Use	Treatment of major depressive disorder (MDD)
Route of Administration	Oral
Dosage Form	Extended-release Tablets
Strengths	50 mg and 100 mg
Dose and Frequency	The recommended dose is 50 mg orally once daily, with or without food. Tablets must be swallowed whole with fluid and not divided, crushed, chewed, or dissolved. <i>Moderate renal impairment:</i> 50 mg/day <i>Severe renal impairment or end-stage renal disease:</i> 50 mg every other day <i>Moderate to severe hepatic impairment:</i> 50 mg/day. Dose escalation above 100 mg/day is not recommended.
How Supplied	30-count, 90-count, and 1000-count bottles
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)
Container and Closure System	30-count and 90-count bottles have child resistant closures (CRC); 1000-count bottle has non-CRC closure

2 METHODS AND MATERIALS REVIEWED

NDA 205583 for Desvenlafaxine was filed as a 505(b)(2) application. The referenced drug is Pristiq, a currently marketed product. Thus, DMEPA searched the FDA Adverse Events Reporting System (FAERS) database for Pristiq medication errors that may inform this review. We also reviewed the proposed labels and labeling submitted by the Applicant. Furthermore, the Desvenlafaxine labels and labeling were compared to the currently marketed Pristiq labels and labeling to determine if there were any areas of vulnerability that could lead to medication errors.

2.1 SELECTION OF MEDICATION ERROR CASES

We previously conducted a search of the FDA Adverse Event Reporting System (FAERS) for Pristiq medication errors in a previous review¹. The previous search covered the time period 08/09/12 to 02/07/13 and identified 44 medication errors found in 39 cases. Thus, for this review, we searched the FAERS database for cases received since 02/08/13 using the strategy listed in Table 1.

Date range	02/08/13 through 08/09/13
Drug Names	<u>Active Ingredient:</u> Desvenlafaxine; Desvenlafaxine Succinate <u>Trade Name:</u> Pristiq Extended Release (this was the term found in the database, “Pristiq” was not a selection option)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues (HLT) Product Label Issues (HLT) Product Quality Issues NEC (HLT)

The FAERS database search identified 47 new cases. Each case was reviewed for relevancy and duplication. After individual review, 19 cases were not included in the final analysis for the following reasons:

- Adverse event(s) not related to a medication error
- Dose omission
- Product complaint not related to the labels or labeling
- Pristiq was concomitant medication only
- Intentional overdose
- Patient non-compliance leading to wrong dose

¹ Holmes, Loretta, Khedezla Label and Labeling Review, OSE Review 2013-307, dated June 24, 2013.

² See Appendix A for a description of the FAERS database.

2.2 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,³ along with postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted on March, 28, 2013 (Appendix B)
- Insert Labeling submitted March 28, 2013 (no image)
- Medication Guide submitted on March 28, 2013 (no image)

Additionally, we compared the Desvenlafaxine proposed labels and labeling against the currently marketed Pristiq labels (Appendix C) and labeling to identify any potential safety issues.

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA recently reviewed the labels and labeling for the following Desvenlafaxine products so we looked at those reviews to determine if there were any recommendations that would also be applicable to this review and should be included in our recommendations:

- OSE Review 2012-1546 dated November 2, 2012
- OSE Review 2013-307 dated June 24, 2013
- OSE Review 2013-200 dated August 2, 2013

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Desvenlafaxine Extended-release Tablets labels and labeling.

3.1 MEDICATION ERROR CASES

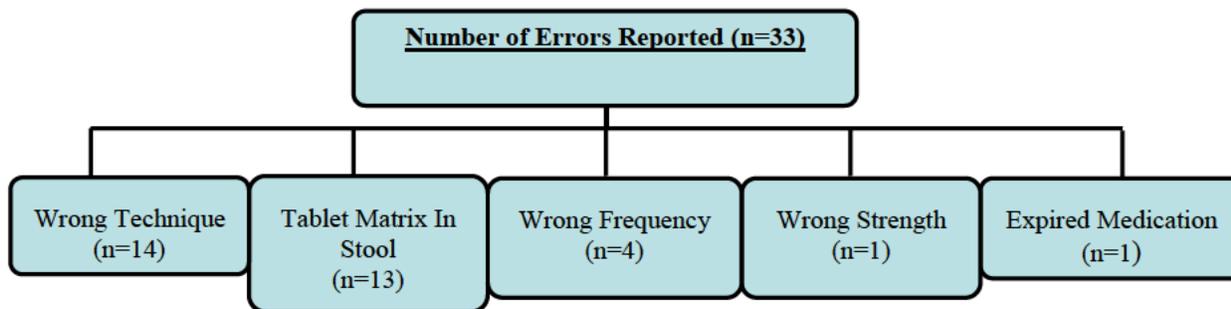
Following exclusions as described in Section 2.1, twenty-eight Pristiq medication error cases remained for our detailed analysis (see Appendix D for the FAERS case numbers). The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter.⁴ Figure 1 provides a stratification of the number of errors (by type of error) identified in the 28 cases reviewed. The number of errors (n=33) exceeds the number of cases analyzed because some cases reported more than one type of error.

We also considered the previously identified errors from OSE Review 2013-307 in the following risk assessment.

³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

⁴ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

Figure 1: Pristiq medication error (n = 33) categorized by type of error



Our search of the FAERS database did not identify any new signals. We previously evaluated cases of tablet matrix appearing in stool (medication residue in stool), wrong technique errors, wrong strength, and use of expired medication in OSE Review 2012-1546. Additionally, the cases involving wrong technique and tablet matrix appearing in stool were further reviewed in OSE Review 2013-307. Therefore, we will not expound further on the similar errors retrieved in this search.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Our review of the Desvenlafaxine Extended-release Tablets labels and labeling identified areas of concern that can be improved for clarity to promote the safe use of the product. These areas of concern include the presentation of the Medication Guide (MG) statement on the container labels and the lack of units of measure in the insert labeling. We provide recommendations for the labels and labeling in Section 4, below.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes the proposed container labels and insert labeling can be improved for clarity to promote the safe use of the product or to mitigate any confusion that can lead to medication errors. We provide recommendations below in Sections 4.1 and 4.2.

If you have further questions or need clarifications, please contact Louis Flowers, OSE Project Manager, at 301-796-3158.

4.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for consideration by the review division prior to the approval of this NDA:

A. Insert Labeling

In the Highlights of Prescribing Information, *Dosage Forms and Strengths* and Full Prescribing Information, 2.3 *Discontinuing Desvenlafaxine Extended-Release Tablets* sections of the insert labeling, there are instances where the numerical strength is not followed by its unit of measure (i.e., "...50 and 100 mg tablets" and "50 to 400 mg", respectively). We recommend revising such that the numerical strength is followed by its unit of measure (e.g., 50 mg and 100 mg tablets and 50 mg to 400 mg).

4.2 COMMENTS TO THE APPLICANT

DMEPA advises the recommendations below be implemented prior to approval of this NDA:

A. General Comment for container labels (50 mg, 100 mg)

The Medication Guide (MG) statement reads: [REDACTED] (b) (4)
[REDACTED]. We recommend replacing the proposed statement with the following language “Dispense the accompanying Medication Guide to each patient” [see 21 CFR 208.24(d)]. Additionally, provide the Medication Guides in sufficient numbers to permit the authorized dispenser to provide a Medication Guide to each patient receiving a prescription for the product [21 CFR 208.24(b)(1)(2)].

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

3 Page(s) of Draft Labeling have been Withheld in Full as b4
(CCI/TS) immediately following this page

Appendix D: FAERS case numbers discussed in this review

FAERS Case Numbers		
9096750	9192540	9242403
9130211	9192587	9252045
9131441	9196520	9263571
9132601	9202720	9280812
9135038	9213054	9290874
9152184	9216737	9311136
9154216	9222005	9322108
9157474	9223797	9441284
9170891	9226702	
9190781	9232139	

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

/s/

LORETTA HOLMES
09/16/2013

IRENE Z CHAN
09/16/2013

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: May 15, 2013

TO: Chief,
Medical Products and Tobacco Trip Planning Branch
Division of Medical Products and Tobacco Inspections
Office of Medical Products and Tobacco Operations

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: **FY 2013, CDER High Priority User Fee NDA, Pre-Approval
Data Validation Inspection**, Bioresearch Monitoring,
Human Drugs, CP 7348.001

RE: NDA 205583
DRUG: Desvenlafaxine Fumarate Extended-Release 50 mg
and 100 mg Tablets
SPONSOR: SUN Pharma Global FZE,
United Arab Emirates

This memo requests that you arrange for inspections of clinical and analytical portions of the following bioequivalence studies. **Once an ORA investigator is identified, please contact the DBGLPC point of contact (POC) listed at the end of this memo for background materials. A DBGLPC scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact DBGLPC POC upon receipt of this assignment to arrange scheduling of the analytical inspection. Please complete the inspections prior to November 8, 2013.**

Do not notify the sites of the application number, the studies to be inspected, drug name, or the study investigators prior to the start of the inspection. The information will be provided to the site(s) at the inspection opening meeting. Please note that this inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to Dr. Sam Haidar and the DBGLPC POC.

1. Study Number: PKD_12_170

Study Title: "A randomized, open label, three treatment, three period, six sequence, single dose, crossover, bioequivalence study comparing SUN Pharmaceutical Industries Limited India's Desvenlafaxine 100 mg Extended Release tablets when administered under fasting and fed condition and Pristiq® (Desvenlafaxine) 100 mg Extended Release tablets of Wyeth Pharmaceuticals Inc. Philadelphia, PA 19101, when administered under fasting condition, in 36 healthy human adult subjects"

Clinical Site: SUN Pharmaceutical Industries Ltd.
Clinical Pharmacology Unit
Near R.C. Patel Estate
Akota Road, Akota
Vadodara - 390 020, India
TEL: 91-265-2339103, 91-265-2330815

Investigator: Dr. Aman Khanna, MD

Contact Person: Vipul Doshi, M.Sc
Executive Vice President - Quality
Tel: 91-265-2350756
Fax: 91-265-2354897

2. Study Number: PKD_12_171

Study Title: "A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Desvenlafaxine 50 mg Extended Release tablets of SUN Pharmaceutical Industries Limited, India and Pristiq® (Desvenlafaxine) 50 mg Extended Release tablets of Wyeth Pharmaceuticals Inc. Philadelphia, Pa 19101 in 50 healthy human adult subjects under fasting conditions"

Clinical Site: SUN Pharmaceutical Industries Ltd.
Tandalja,
Vadodara - 390 020, India
TEL: 91-265-2350789, 91-265-6615500

Investigator: Dr. Aman Khanna, MD

Contact Person: Vipul Doshi, M.Sc
Executive Vice President - Quality
Tel: 91-265-2350756
Fax: 91-265-2354897

SECTION A

RESERVE SAMPLES: Because these are bioequivalence studies subject to 21 CFR 320.38 and 320.63, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the sponsor for subject dosing.

Please note that the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies

(<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples

(<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

Please follow the instructions below:

- Verify if reserve samples were retained according to regulations.
- If the reserve samples were stored at a third party site, please verify and collect an affidavit to confirm that the third party is independent from the sponsor, manufacturer, and packager, and that the sponsor was notified in writing of the location. In an event the reserve samples were not retained or are not adequate in quantity, please notify the POC immediately.
- Please obtain a written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a, Affidavit.
- Samples of the test and reference products in their

**original containers should be collected and shipped to the
Division of Pharmaceutical Analysis, St. Louis, MO, for
screening, at the following address:**

Benjamin Westenberger, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Customhouse Bldg.
1114 Market Street, Room 1002
St. Louis, MO 63101
TEL: (314) 539-2135

SECTION B

**Please confirm the informed consent and records for 100% of
subjects enrolled at the sites. The study records in the NDA
submission should be compared to the original documents at the
sites. Include a description of your findings in the EIR.**

Data Audit Checklist:

- Evidence of under-reporting of AEs identified? _____
- Evidence of inaccuracy in electronic data capture? _____
- Presence of 100% of signed and dated informed consent forms: _____
- Reports for the subjects audited: _____
- Number of subject records reviewed during the inspection: _____
- Number of subjects screened at the site: _____
- Number of subjects enrolled at the site: _____
- Number of subjects completing the study: _____
- Verify from source documents that evaluations related to the primary endpoint were accurately reported in case report forms: _____
- Confirm that clinical assessments were conducted in a consistent manner and in accordance with the protocol: _____
- Confirm that SOPs were followed during study conduct: _____
- Examine correspondence files for any sponsor- or monitor-requested changes to study data or reports: _____
- Include a brief statement summarizing your findings (IRB approvals, study protocol and SOPs, protocol deviations, adverse events, concomitant medications, inclusion/exclusion criteria, adequacy of records, drug accountability

documents, and case report forms for dosing of subjects, etc.)

- Other Comments:
-
-

Collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

ANALYTICAL:

For the two studies:

Analytical Site: SUN Pharmaceutical Industries Ltd
Pharmacokinetics Department
Tandalja, Vadodara - 390 020
Gujarat, India
Tel: 91-265-2350789, 91-265-6615500
FAX: 91-265-2354896

Contact Person: Dr. T Rajamannar
Director & Executive Vice President
TEL: +91-265-6615500, 2350789
FAX: +91-265-2354897
Email: trajamannar@sunpharma.com

Methodology: UPLC-MS/MS

Please confirm the following during the inspection:

- Examine all pertinent items related to the analytical methods used for the measurement of **desvenlafaxine concentrations in human plasma**.
- Compare the accuracy of the analytical data provided in the NDA submission by the applicant with the original documents at the site.
- Determine if the validated analytical method was employed for the subject sample analysis.
- Compare the assay parameters (such as variability between and within runs, accuracy and precision, etc.) observed during the study sample analysis with those obtained during method validation.
- Confirm that the accuracy and precision in matrix were determined using standards and QCs prepared from separate stocks.

- Determine if the subject samples were analyzed within the validated stability period.
- **Confirm that freshly made calibrators and/or freshly made QCs were used for stability evaluations during method validation.**
- **Confirm that the precision and accuracy was demonstrated at least one time using QCs and calibrators prepared from separate stock solutions.**
- **Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria such as the number of freeze-thaw cycles sufficiently covered the stability of reanalyzed subject samples.**
- Examine correspondence files between the analytical site and the sponsor for their content.

Additional instructions to ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to the inspection. Therefore, we request that the DBGLPC POC be contacted for further instructions, inspection-related questions or clarifications before the inspection, and also regarding data anomalies or questions noted during review of study records on site.

Please fax/email a copy of Form FDA 483 if issued, as soon as possible. If at close-out of the inspection, it appears that the violations may warrant an OAI classification, please notify the DBGLPC POC as soon as possible. At completion of inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA 483. Please forward written response as soon as you receive it to Dr. Sam H. Haidar (Fax: 1-301-847-8748 or Email: sam.haidar@fda.hhs.gov) and DBGLPC POC. Please address the EIR to Dr. Haidar:

Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)
Office of Compliance
Bldg. 51 Rm. 5330
10903 New Hampshire Ave.
Silver Spring, MD 20993

Page 7 - BIMO Assignment, NDA 205583, Desvenlafaxine Fumarate
Extended-Release 50 mg and 100 mg Tablets

DBGLPC POC: Foreign: Arindam Dasgupta, Ph.D.
Email: arindam.dasgupta@fda.hhs.gov
TEL: (301)796-3326
FAX: (301)847-8748

cc:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Haidar/Skelly/Patel/Li/Dasgupta/Dejernett/CF

HFC-130/ORA HQ OMPTO DMPTI MPTTPB BIMO

CDER/OND/DPP/Chang,ShinYe/Kumi,Kofi/Zhu,Hao/Mathis,Mitchell

Draft: XFL 05/15/2013

Edit: JBP 05/20/2013

OSI file #: 6462; O:\BE\assigns\bio205583.doc

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Electronic Archive/BEB

FACTS: 1521275

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/s/

XINGFANG LI
05/29/2013

SAM H HAIDAR
05/30/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205583 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Desvenlafaxine Fumarate Dosage Form: extended-release tablets Strengths: 50 mg, 100 mg		
Applicant: Sun Pharma Global FZE Agent for Applicant (if applicable): Salamandra, LLC		
Date of Application: 03/28/2013 Date of Receipt: 03/28/2013 Date clock started after UN:		
PDUFA Goal Date: 01/28/2014	Action Goal Date (if different):	
Filing Date: 05/27/2013	Date of Filing Meeting: 05/09/2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): MDD		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 113361				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>X</p>																		

<p>Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>				
<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)				
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):		X		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE:

BLA/NDA/Supp #: 205583

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: Desvenlafaxine Fumarate

DOSAGE FORM/STRENGTH: extended-release 50 mg, 100 mg tablets

APPLICANT: Sun Pharma Global FZE

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): MDD

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Shin-Ye Sandy Chang	Y
	CPMS/TL:	Renmeet Grewal	N
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Christina Burkhart	Y
	TL:	Robert Levin	N
Clinical Pharmacology	Reviewer:	Kofi Kumi	Y
	TL:	Hao Zhu	Y
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Shiny Mathew	Y
	TL:	Linda Fossom	Y
Product Quality (CMC)	Reviewer:	Shastri Bhamidipati	Y

	TL:	Chhagan Tele	Y
Quality Microbiology	Reviewer:	Ericka Pfeiler	Y
	TL:		
Biopharmaceutics	Reviewer:	Elsbeth Chikhale	Y
	TL:	Angelica Dorantes	N
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO BA/BE studies
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments 	<input type="checkbox"/> Not Applicable

List comments:	
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: No clinical studies submitted</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CLINICAL MICROBIOLOGY	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p>Comments:</p> <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) 	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

Comments:	
<u>Facility Inspection</u> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>CMC Labeling Review</u> Comments:	<input type="checkbox"/> Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Mitchell Mathis</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 08/22/2013</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product

	Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

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

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

SHIN-YE CHANG
05/28/2013