

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208398Orig1s000**

**OTHER REVIEW(S)**

**505(b)(2) ASSESSMENT**

| <b>Application Information</b>   |                                      |                              |
|--|--------------------------------------|------------------------------|
| NDA # 208398   | NDA Supplement #: S-                 | Efficacy Supplement Type SE- |
| Proprietary Name: Vermox<br>Established/Proper Name: mebendazole<br>Dosage Form: Chewable tablets<br>Strengths: 500 mg   |                                      |                              |
| Applicant: Janssen Pharmaceuticals Inc.  |                                      |                              |
| Date of Receipt: April 19, 2016  |                                      |                              |
| PDUFA Goal Date: October 19, 2016  | Action Goal Date (if different): N/A |                              |
| RPM: Alison Rodgers  |                                      |                              |
| Proposed Indication(s): Treatment of Trichuris trichiura (whipworm); Ascaris lumbricoides (large roundworm); <span style="background-color: gray; color: gray;">(b) (4)</span> |                                      |                              |

**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>Published literature</i>   | <i>Label Section 1 Indications and Usage –</i><br>(b) (4)                        |
| <i>Published literature</i>   | <i>Label Section 12.4 Microbiology –</i><br>(b) (4)                              |
| <i>Published literature</i>   | (b) (4)  |

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

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature<sup>1</sup>. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

*The Sponsor is relying on supportive efficacy data from the published literature for a single-dose mebendazole 500 mg regimen (any formulation) for the treatment of soil transmitted helminth infections, including *A. lumbricoides*, *T. trichiura* (b) (4) in adults and children. Multiple published studies, including those with placebo-control designs, conducted by different investigators demonstrate superiority of a single-dose mebendazole 500 mg regimen (any formulation) to placebo for the treatment of soil transmitted helminth infections in adults and children. The Sponsor proposes the same dose and dosing regimen for VERMOX™ CHEWABLE (mebendazole chewable tablet) as reported in the literature studies referenced (i.e. single dose mebendazole 500 mg).*

**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 as labeled without the published literature)?

YES X NO   
 If "NO," proceed to question #5.

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

YES  NO X  
 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 X  
 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) |
|---------------------|-------|--|
|                     |       |  |
|                     |       |  |

*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 X 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").

*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):

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): ANDA 073580 Mebendazole 100 mg Chewable Tablets

### 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):

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.*
- X 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):

(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):

*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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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALISON K RODGERS  
10/19/2016

## Division of Anti-Infective Products (DAIP) Associate Director for Labeling (ADL) Memo of the Prescribing Information

|                                      |   |
|--------------------------------------|---|
| <b>Product Title</b>                 | <b>VERMOX™ CHEWABLE (mebendazole chewable tablets), for oral use</b>  |
| <b>Applicant</b>                     | Janssen Pharmaceuticals, Inc  |
| <b>Application Number</b>            | NDA 208398  |
| <b>Type of Application</b>           | 505 (b)(2) NDA-New 500 mg Formulation   |
| <b>Proposed Indication</b>           | VERMOX™ Chewable (mebendazole) 500 mg chewable tablets is an anthelmintic indicated for the treatment of (b)(4) gastrointestinal (b)(4) by <i>Trichuris trichiura</i> (whipworm); <i>Ascaris lumbricoides</i> (large roundworm); (b)(4) |
| <b>Approved Indication</b>           | VERMOX™ CHEWABLE is indicated for the treatment of patients one year of age and older with gastrointestinal infections caused by <i>Ascaris lumbricoides</i> (roundworm) and <i>Trichuris trichiura</i> (whipworm).                     |
| <b>Date FDA Received Application</b> | April 19, 2016  |
| <b>Action Goal Date</b>              | October 19, 2016  |
| <b>Review Date</b>                   | October 17, 2016  |
| <b>ADL</b>                           | Abimbola O. Adebowale PhD   |

This Associate Director for Labeling (ADL) memo includes a high-level summary of the key labeling changes and recommendations provided by Eric Brodsky, Associate Director, Labeling Development Team (LDT) in the Office of New Drugs (OND).

On October 7<sup>th</sup>, 2016, DAIP requested further clarification from LDT on the CDER labeling policy that states that age groups should be included in the indications statement in the Prescribing Information (PI), as it relates to VERMOX CHEWABLE 500 mg tablets. DAIP was concerned that the VERMOX CHEWABLE 500 mg, tablet PI was not providing consistent clear communication about the age groups for the indicated population throughout the PI.

Although, the age groups studied in clinical trials were clearly identified as pediatric patients 1 to 16 years of age in subsection 8.4 (Pediatric Use) and section 14 (Clinical Studies). The applicant did not include the age groups in the indication statement for VERMOX CHEWABLE 500 mg tablets. However, the applicant included dosing recommendations for VERMOX CHEWABLE 500 mg tablets in a broader population (i.e. adults and pediatrics (b)(4) 1 years of age)) than the studied population, in the Dosing and Administration section.

In addition, the applicant did not clearly summarize the information supporting the adult indication in the PI. Although the applicant submitted supporting publications for the adult indication, it was not too clear as to how many adults were included or whether the outcomes were different in adults versus children. Therefore, this information was not appropriate for inclusion in section 14 (Clinical Studies) of the PI.

However, use of VERMOX CHEWABLE 500 mg in adults was adequately supported by evidence from the adequate and well-controlled study in pediatric patient's ages 1 to 16 years old, pharmacokinetic data in adults and additional evidence from published literature (see Division Director's Memo by Sumathi Nambiar MD MPH). Although the applicant did not propose including labeling language for any of the supportive evidence for adults in the PI, to ensure consistency throughout the PI, DAIP was able to propose an appropriate location for this information in the PI. The age group (patients one year of age and older) were also included in the appropriate sections of the PI. This decision was based on key labeling recommendations proposed by Eric Brodsky, MD in LDT (e-mails dated 10/7/16 and 10/12/16).

Basically, the key labeling recommendation by LDT (specifically, Eric Brodsky, MD) for approval of the product for patients one year of age and older were as follows (see attached e-mail communications for further details):

1. Include the age group (patients one year of age and older) in the INDICATIONS and USAGE and the DOSAGE and ADMINISTRATION sections of the PI.
2. Create an "Adult Use" subsection in the USE IN SPECIFIC POPULATIONS of the PI section as per 21 CFR 201.57 (c) (9) (vi). We note that Dr. Brodsky made it clear that he was not aware of any labeling that has an "Adult Use" subsection.
3. Provide a description and the results of the one adequate and well-controlled trial in pediatric patients in the CLINICAL STUDIES section of the PI

The applicant was sent the revised PI (on 10/13/16) with LDT's key labeling recommendations plus some additional revisions to the adverse reactions section included to ensure consistent communication of the age groups for the intended population.

Additional recommendations for an alternative situation where the VERMOX CHEWABLE 500 mg tablet indication is intended to mirror the age of the studied population (i.e. pediatric patients one year of age and older) was also provided by Eric Brodsky, MD. This recommendation was not applicable to this situation since VERMOX CHEWABLE 500 mg tablets is being approved for adults and pediatric patients (one year of age and older).

E-mail communications between DAIP and LDT incorporating the final recommendations from the LDT are attached below.

From: [Brodsky, Eric](#)  
To: [Nambiar, Sumathi](#); [Adebowale, Abimbola O](#)  
Cc: [Sohrabi, Farrokh](#); [Brodsky, Eric](#)  
Subject: RE: Pediatric Information in the Indications and Usage Section of the Vermox PI  
Date: Wednesday, October 12, 2016 3:09:34 PM

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Hi Sumati and Abi,

I made a slight change to my recommendations below. According to the draft unpublished I&U section of labeling guidance:

*“Limitations of use should be distinguished from contraindications. A contraindication is required when a drug should not be used in a certain situation because the risks clearly outweigh any possible therapeutic benefit (§ 201.57(c)(5)). However, there are cases in which the evidence falls short of requiring a contraindication, but suggests the use of the drug is inadvisable. There are also cases in which there is sufficient uncertainty about the drug’s benefits in certain clinical situations to suggest that the drug should generally not be used in those settings. In these cases, a limitation of use may be appropriate. **To avoid redundancy within the labeling, contraindications should not be restated as limitations of use in the INDICATIONS AND USAGE section.**”*

Thus, my revised proposal includes moves the contraindication in pediatric patients to the CONTRAINDICATIONS section. Note, you may decide that this is not a true contraindication (the EMVERM labeling does not have this contraindication).

Thanks.

Eric

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From: Brodsky, Eric  
Sent: Friday, October 07, 2016 6:24 PM  
To: Nambiar, Sumathi  
Cc: Sohrabi, Farrokh; Adebowale, Abimbola O; Brodsky, Eric  
Subject: RE: Pediatric Information in the Indications and Usage Section of the Vermox PI

Hi Sumati,

Nice speaking to you today about the labeling considerations for the VERMOX (mebendazole) chewable tablets labeling, under pending NDA 208398. CDER labeling policy is to include age groups in the indications statement for new indications unless the product does not or rarely occurs in pediatric patients. This policy is to:

- Provide clear and consistent communication to healthcare providers about the indicated populations for which we are granting approval (we have heard from multiple stakeholders that sometimes our labeling are internally inconsistent and the

approved age groups are not clear)

- Improve FDA's ability to take enforcement actions against application holders for misleading promotion (if the indication statement is broad and the rest of the labeling narrow, it is legally more difficult to take an enforcement action against an application holder who promotes the broad indication)

As you know, you can consider the generalizability of the evidence, consistencies in the disease process across different groups, and the drug's overall benefits and risks when deciding if you have sufficient information to broaden the indicated population beyond the studied population.

[REDACTED] (b) (4)

Please double check the accuracy of the proposed wording below including the basis for approval in adults. Also note, best labeling practice is incorporate limitations of use (e.g., contraindication in pediatric patients less than one years old) directly in the indications statement. According to 21 CFR 201.57(c)(9)(vi), additional subsections in the USE IN SPECIFIC POPULATIONS section may be created (although I am not aware of labeling that have an "Adult Use" subsection, creation of this subsection would improve internal labeling consistency and would provide a clearer communication about the indicated population):

## 1 INDICATIONS AND USAGE

VERMOX indicated for the treatment of patients one year of age and older with [REDACTED] (b) (4) gastrointestinal [REDACTED] (b) (4) by *Trichuris trichiura* (whipworm); *Ascaris lumbricoides* (large roundworm); [REDACTED] (b) (4)

## 2 DOSAGE AND ADMINISTRATION

[REDACTED] (b) (4)

## 4 CONTRAINDICATIONS

[REDACTED] (b) (4)

## 8 USE IN SPECIFIC POPULATIONS

### 8.6 Adult Use

The safety and effectiveness of VERMOX have been established in adults for the treatment of [REDACTED] (b) (4) gastrointestinal [REDACTED] (b) (4) by *Trichuris trichiura* (whipworm); *Ascaris lumbricoides* (large roundworm);

(b) (4) Use of VERMOX in adults for these indications are supported by evidence from an adequate and well-controlled study in pediatric patients ages 1 to 16 years old [see *Clinical Studies (14.1)*], pharmacokinetic data in adults [see *Clinical Pharmacology (12.3)*], and the evidence from literature.

## 14 CLINICAL STUDIES

*[provides a description and results from one adequate and well-controlled study in pediatric patients]*

If you decide that you cannot broaden the studied population and the **VERMOX indication should mirror the studied population** (approve VERMOX in pediatric patients greater than one years old) consider the following.

### 1 INDICATIONS AND USAGE

VERMOX indicated for the treatment of pediatric patients one year of age and older with (b) (4) gastrointestinal (b) (4) by *Trichuris trichiura* (whipworm); *Ascaris lumbricoides* (large roundworm); (b) (4)

(b) (4)

### 2 DOSAGE AND ADMINISTRATION

(b) (4)

### 4 CONTRAINDICATIONS

(b) (4)

## 14 CLINICAL STUDIES

*[provides a description and results from one adequate and well-controlled study in pediatric patients]*

Either way, I recommend that the division document the rationale for the scope of the indication in the administrative record (this could be very brief).

Thanks.

Eric

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**From:** Adebowale, Abimbola O  
**Sent:** Friday, October 07, 2016 1:03 PM  
**To:** Brodsky, Eric; Sohrabi, Farrokh  
**Cc:** Nambiar, Sumathi

**Subject:** Pediatric Information in the Indications and Usage Section of the Vermox PI

Hi Eric and Farrokh,

Thank you for all your advice on the inclusion of age groups in the prescribing information. The information was helpful, however, we would appreciate further clarification with regards to how we apply this policy to the pending Vermox PI. In this particular instance, the clinical trials were conducted in pediatric patients between the ages of 1 to 16 years old. The supporting publications submitted by the applicant were not too clear as to how many adults were included or whether the outcomes were different in adults versus children. There is a statement in subsection 12.3 (Pharmacokinetics) that compares the pediatric exposure to the adult exposure. However, because the drug is non-absorbable, the PK exposures do not correlate with clinical outcomes. Basically section 8.4 (Pediatric Use) and 14 (Clinical Studies) clearly identify the age groups studied as 1 to 16 years of age. Please note that the applicant proposed the same dose for a broader age group (Adults and Pediatrics (b) (4) 1 years of age) in the Dosing and Administration section but this age group was not included in the indication statement by the applicant (see below).

Therefore, DAIP's question to LDT is as follows:

Should the age group studied (i.e. 1-16 years of age) be included in the indication statement or is this an instance where we could consider expanding the indication statement to include an age group (i.e. adults) broader than the pediatric population that was studied in the applicant's trials?

The proposed labeling Language by the applicant for the Indications and Usage section is as follows:

## **1 INDICATIONS AND USAGE**

VERMOX™ Chewable is indicated for the treatment of gastrointestinal infections caused by *Ascaris lumbricoides* (roundworm); *Trichuris trichiura* (whipworm); (b) (4)

Thank you for all your help.

Abi

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ABIMBOLA O ADEBOWALE  
10/18/2016



**DEPARTMENT OF HEALTH & HUMAN SERVICES**      Public Health Service

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Division of Pediatric and Maternal Health  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

**PLLR Labeling Memorandum**

**Date:** October 14, 2016                      **Date consulted:** August 8, 2016

**From:** Tamara Johnson, MD, MS, Team Leader, Maternal Health  
Division of Pediatric and Maternal Health

**Through:** Lynne P. Yao, MD, OND, Division Director  
Division of Pediatric and Maternal Health

**To:** Division of Anti-Infective Products (DAIP)

**Drug:** VERMOX (mebendazole) chewable tablets

**NDA:** 208398

**Applicant:** Janssen Pharmaceuticals, Inc.

**Subject:** Pregnancy and Lactation Labeling

**Indication:** Treatment of (b) (4) gastrointestinal (b) (4) infections caused by:

- Trichuris trichiura (whipworm),
- Ascaris lumbricoides (large roundworm); (b) (4)

(b) (4)

**Materials Reviewed:**

- Applicant's sNDA submission, dated April 19, 2016
- Proposed annotated label
  - FDA approved label for mebendazole 100 mg chewable tablet
  - Summary of Clinical Safety, Module 2.7.4, section 5.4

**Consult Question:** DAIP requests input regarding PLLR labeling, specifically Section 8.1 and 8.2 of the proposed label.

## PURPOSE

The purpose of the memorandum is to acknowledge the input of the Division of Pediatric and Maternal Health (DPMH) on labeling recommendations for Vermox (mebendazole) chewable tablets, a new formulation for donation to the World Health Organization single-dose mass drug administration programs for soil-transmitted helminths in adults and pediatrics (b) (4) 1 year of age).

The Division of Anti-Infective Products (DAIP) consulted DPMH to provide input regarding Pregnancy and Lactation Labeling Rule formatted labeling, specifically Section 8.1 and 8.2 of the proposed labeling.

## REGULATORY HISTORY

Mebendazole was initially approved in 1974 for the treatment of single or mixed gastrointestinal infestations by *Trichuris trichiura* (whipworm); *Ascaris lumbricoides* (large roundworm); and *Ancylostoma duodenale* (common hookworm) and *Necator americanus* (American hookworm). The applicant has developed 500 mg chewable tablets for donation to the World Health Organization single-dose mass drug administration programs for soil-transmitted helminths in adults and pediatrics (>1 year of age). The proposed dosing regimen is a 500 mg chewable tablet as a single dose.

## BACKGROUND

### Drug Characteristics<sup>1</sup>

Mebendazole is a benzimidazole molecule that functions as an anti-helminthic agent. The drug interferes with cellular tubulin formation in the helminth and causes ultrastructural degenerative changes in its intestine. As a result, its glucose uptake and the digestive and reproductive functions are disrupted, leading to immobilization, inhibition of egg production and death of the helminth.

- Molecular weight: 295.30
- (b) (4) it exerts its action locally in the gastrointestinal tract
- 90-95% plasma protein bound,
- Half-life is 3-6 hours
- Known serious adverse events include cases of agranulocytosis and neutropenia with higher doses used for prolonged periods, and very rare cases of convulsions in children

### Helminthic Infection and Pregnancy

Helminthic infection is not a condition that is endemic in the US, as the prevalence is less than 20%. For areas of the world where helminthic infection is endemic, the benefits of treating the infection outweigh the potential risks to the pregnant women and developing fetus.

Potential risks to the pregnancy from untreated helminthic infection include iron deficiency anemia, low birth weight, and perinatal mortality.<sup>2</sup> The World Health Organization (WHO)

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<sup>1</sup> Proposed annotated labeling for mebendazole chewable 500 mg tablet, submitted with NDA April 19, 2016.

<sup>2</sup> Crompton DW. Preventive Chemotherapy in Human Helminthiasis: Coordinated Use of Anthelmintic Drugs In Control Interventions: A Manual for Health Professionals and Programme Managers. World Health Organization; 2006; sections 5.2.2. and 5.5.4.

recommends treatment with anti-helminthic medications, such as mebendazole or albendazole during the second and third trimesters, and praziquantel at any time during pregnancy. Because none of these anti-helminthics are licensed for use during the first trimester of pregnancy, women have the option to refuse treatment during pregnancy. However, iron supplementation would continue for medical management of the pregnancy.

#### Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”<sup>3</sup> also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule<sup>4</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation.

#### **LABELING RECOMMENDATIONS**

DPMH revised sections 8.1 and 8.2 of labeling for compliance with the PLLR. DPMH discussed our labeling recommendations with the Division at labeling meetings on August 18th and 19th, 2016. DPMH recommendations are below and reflect the discussions with the Division. DPMH refers to the final NDA action for final labeling.

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<sup>3</sup> *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

<sup>4</sup> *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

## DPMH Proposed Pregnancy and Lactation Labeling

### FULL PRESCRIBING INFORMATION

#### 8 USE IN SPECIFIC POPULATIONS

##### 8.1 Pregnancy

###### Risk Summary

The available published literature on mebendazole use in pregnant women has not reported a clear association with mebendazole and a potential risk of major birth defects or miscarriages [see Data]. There are risks to the mother and fetus associated with untreated helminthic infestation during pregnancy [see Clinical Considerations]. In animal reproduction studies, adverse developmental effects (i.e., skeletal malformations, decreased pup weight) were observed when mebendazole was administered to pregnant rats during the period of organogenesis at single oral doses as low as 10 mg/kg (approximately 0.2-fold the maximum recommended human dose (MRHD)). Maternal toxicity was present at these doses [see Data]. Based on findings in animal studies, advise a pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

###### Clinical Considerations

###### *Disease-Associated Maternal and/or Embryo/Fetal Risks*

Untreated helminthic infestation in pregnancy is associated with adverse outcomes including maternal iron deficiency anemia, low birth weight, neonatal and maternal death.

###### Data

###### *Human Data*

Several published studies, including prospective pregnancy registries, case-control, retrospective cohort, and randomized controlled studies, have reported no association with mebendazole use and a potential risk of major birth defects or miscarriage. Overall, these studies did not identify a specific pattern or frequency of major birth defects with mebendazole use. However, these studies cannot definitely establish the absence of any mebendazole-associated risk because of methodological limitations, including recall bias, confounding factors and, in some cases, small sample size or exclusion of first trimester mebendazole exposures.

### *Animal Data*

Embryo-fetal developmental toxicity studies in rats revealed no adverse effects on dams or their progeny at doses up to 2.5 mg/kg/day. Dosing at  $\geq 10$  mg/kg/day resulted in maternal toxicity as evidenced by a lowered body weight gain and a decreased number of pregnancies at termination. At 10 mg/kg/day, increased embryo-fetal resorption (100% at 40 mg/kg/day), decreased pup weight and increased incidence of malformations (primarily skeletal) were observed. Mebendazole was also embryotoxic and teratogenic in pregnant rats at single oral doses as low as 10 mg/kg (approximately 0.2-fold the MRHD, based on mg/m<sup>2</sup>).

In embryo-fetal developmental toxicity studies in mice, doses of 10 mg/kg/day and higher resulted in decreased body weight gain at 10 and 40 mg/kg/day and a higher mortality rate at 40 mg/kg/day. At doses of 10 mg/kg/day (approximately 0.1-fold the MRHD, based on mg/m<sup>2</sup>) and higher, embryo-fetal resorption increased (100% at 40 mg/kg) and fetal malformations were present. Dosing of hamsters and rabbits did not result in embryotoxicity or teratogenicity at doses up to 40 mg/kg/day (0.6 to 1.6-fold the MRHD, based on mg/m<sup>2</sup>).

In a peri- and post-natal toxicity study in rats, mebendazole did not adversely affect dams or their progeny at 20 mg/kg/day. At 40 mg/kg (0.8-fold the MRHD, based on mg/m<sup>2</sup>), a reduction of the number of live pups was observed and there was no survival at weaning. No abnormalities were found.

## **8.2 Lactation**

### **Risk Summary**

Limited data from case reports demonstrate that a small amount of mebendazole is present in human milk following oral administration. There are no reports of effects on the breastfed infant, and the limited reports on the effects on milk production are inconsistent. The limited clinical data during lactation precludes a clear determination of the risk of VERMOX Chewable to a breastfed infant; therefore, developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VERMOX Chewable and any potential adverse effects on the breastfed infant from VERMOX Chewable or from the underlying maternal condition.

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/s/  
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TAMARA N JOHNSON  
10/14/2016

LYNNE P YAO  
10/14/2016

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Memorandum:** September 19, 2016  
**Requesting Office or Division:** Division of Anti-Infective Products (DAIP)  
**Application Type and Number:** NDA 208398  
**Product Name and Strength:** Vermox Chewable (mebendazole Chewable Tablets)  
500 mg  
**Submission Date:** September 15, 2016  
**Applicant/Sponsor Name:** Janssen Pharmaceuticals, Inc.  
**OSE RCM #:** 2016-997-3  
**DMEPA Primary Reviewer:** Deborah Myers, RPh, MBA  
**DMEPA Team Leader:** Vicky Borders-Hemphill, PharmD

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#### 1 PURPOSE OF MEMO

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label for Vermox Chewable (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>a</sup>

#### 2 RECOMMENDATION/CONCLUSION

The revised container label for Vermox Chewable is acceptable from a medication error perspective. We have no further recommendations at this time. However, we note that the placeholder for the time to discard after opening still states "XX months" on the primary display panel. We have communicated this and defer to the Office of Pharmaceutical Quality (OPQ) to provide the correct time to discard that aligns with the results of the on-going stability testing.

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<sup>a</sup> Myers D. Label and Labeling Review Memo for Vermox Chewable (NDA 208398). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 SEP 08. 2 p. OSE RCM No.: 2016-997-2.

**RECOMMENDATION TO DAIP**

Please ensure that the time to discard after opening, as proposed on the primary display panel, is revised from “XX months” to align with the Office of Pharmaceutical Quality (OPQ) review of the stability testing results.

**APPENDIX A. LABEL AND LABELING SUBMITTED ON SEPTEMBER 15, 2016**

**Container label (not to scale)**



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/s/  
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DEBORAH E MYERS  
09/19/2016

BRENDA V BORDERS-HEMPHILL  
09/19/2016

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Memorandum:** September 8, 2016  
**Requesting Office or Division:** Division of Anti-Infective Products (DAIP)  
**Application Type and Number:** NDA 208398  
**Product Name and Strength:** Vermox Chewable (mebendazole Chewable Tablets), 500 mg  
**Submission Date:** September 6, 2016  
**Applicant/Sponsor Name:** Janssen Pharmaceuticals, Inc.  
**OSE RCM #:** 2016-997-2  
**DMEPA Primary Reviewer:** Deborah Myers, RPh, MBA  
**DMEPA Team Leader:** Vicky Borders-Hemphill, PharmD

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#### 1 PURPOSE OF MEMO

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label for Vermox Chewable (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to label suggestions that were made by the Office of Pharmaceutical Quality (OPQ).

#### 2 CONCLUSION

The revised container label is unacceptable from a medication error perspective. As presented, there is lack of differentiation of the statement "Discard after   /  /  . Discard unused portion XX months after first opening." from the other text on the principal display panel. We recommend changing the font color, surrounding this information with a box, or highlighting the information, to draw attention to this important information and to minimize the potential of medication errors involving the dispensing or administration of deteriorated drug product.

#### 3 RECOMMENDATIONS FOR JANSSEN PHARMACUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA 208398:

To minimize the risk of medication errors involving the dispensing or administration of deteriorated drug product, revise the statement “Discard after   /  /  . Discard unused portion XX months after first opening.” on the principal display panel of the container label. We recommend changing the font color, surrounding this information with a box, or highlighting the information, to draw attention to this important information and the need to complete/fill-in this information to provide an accurate expiration date after opening.

**APPENDIX A. LABEL AND LABELING SUBMITTED ON SEPTEMBER 6, 2016**

Container label (not to scale)



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/s/  
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DEBORAH E MYERS  
09/08/2016

BRENDA V BORDERS-HEMPHILL  
09/08/2016

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

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

**Memorandum**

**Date:** September 6, 2016

**To:** Alison Rodgers  
Regulatory Project Manager  
Division of Anti-Infective Products (DAIP)

**From:** Adam George, Pharm.D.  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Through:** Amy Toscano, Pharm.D, RAC, CPA  
Team Leader  
Office of Prescription Drug Promotion (OPDP)

**Subject:** **NDA 208398 VERMOX™ Chewable (mebendazole chewable tablets), chewable tablet for oral use**

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This consult review is in response to DAIP's May 17, 2016, request for OPDP's review of the draft package insert (PI) for NDA 208398 VERMOX™ Chewable (mebendazole chewable tablets), chewable tablet for oral use (Vermox). OPDP's review of the PI is based on the substantially complete version titled "NDA 208398 draft label sponsor submitted 071216.docx" accessed via SharePoint on September 5, 2016. We had two comments. One comment for the Highlights of Prescribing Information regarding the warning and precaution for risk of convulsions and one comment for section 5.1. These comments have been uploaded into SharePoint and a copy of the reviewed PI is attached to this consult response for your reference.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Adam George at 301-796-7607 or adam.george@fda.hhs.gov.

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

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/s/  
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ADAM N GEORGE  
09/06/2016

## 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 # 208398   | NDA Supplement #: S-<br>BLA Supplement #: S- | Efficacy Supplement Category:<br><input type="checkbox"/> New Indication (SE1)<br><input type="checkbox"/> New Dosing Regimen (SE2)<br><input type="checkbox"/> New Route Of Administration (SE3)<br><input type="checkbox"/> Comparative Efficacy Claim (SE4)<br><input type="checkbox"/> New Patient Population (SE5)<br><input type="checkbox"/> Rx To OTC Switch (SE6)<br><input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7)<br><input type="checkbox"/> Labeling Change With Clinical Data (SE8)<br><input type="checkbox"/> Manufacturing Change With Clinical Data (SE9)<br><input type="checkbox"/> Animal Rule Confirmatory Study (SE10) |
| Proprietary Name: Vermox Chewable<br>Established/Proper Name: mebendazole<br>Dosage Form: Tablet<br>Strengths: 500 mg  |  |   |
| Applicant: Janssen Pharmaceuticals, Inc.<br>Agent for Applicant (if applicable): N/A   |  |   |
| Date of Application: April 19, 2016<br>Date of Receipt: April 19, 2016<br>Date clock started after Unacceptable for Filing (UN): N/A   |  |   |
| PDUFA/BsUFA Goal Date: October 19, 2016  |  | Action Goal Date (if different):  |
| Filing Date: June 18, 2016   |  | Date of Filing Meeting: May 16, 2016  |
| Chemical Classification (original NDAs only) :<br><input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination<br><input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination<br><input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination<br><input type="checkbox"/> Type 4- New Combination<br>X Type 5- New Formulation or New Manufacturer<br><input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA<br><input type="checkbox"/> Type 8- Partial Rx to OTC Switch<br><input type="checkbox"/> Type 9- New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval)<br><input type="checkbox"/> Type 10- New Indication or Claim (will be marketed as a separate NDA after approval) |  |   |
| Proposed indication(s)/Proposed change(s): Treatment of single or mixed gastrointestinal infestations by Trichuris trichiura (whipworm), Ascaris lumbricoides (large roundworm), and Ancylostoma duodenate and Necator americanus (hookworm).  |  |   |
| Type of Original NDA:<br>AND (if applicable)<br>Type of NDA Supplement:  |  | X 505(b)(1)<br><input type="checkbox"/> 505(b)(2)<br><input type="checkbox"/> 505(b)(1)<br><input type="checkbox"/> 505(b)(2)   |
| <b><i>If 505(b)(2) NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i></b><br><a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> .  |  |   |

|  |   |
|--|---|
| Type of BLA  | <input type="checkbox"/> 351(a)<br><input type="checkbox"/> 351(k)  |
| <b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b>  |   |
| Review Classification:   | <input type="checkbox"/> Standard<br>X Priority   |
| <b>The application will be a priority review if:</b>   | <input type="checkbox"/> Pediatric WR<br><input type="checkbox"/> QIDP<br><input type="checkbox"/> Tropical Disease Priority Review Voucher<br><input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher  |
| <ul style="list-style-type: none"> <li>• A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</li> <li>• The product is a Qualified Infectious Disease Product (QIDP)</li> <li>• A Tropical Disease Priority Review Voucher was submitted</li> <li>• A Pediatric Rare Disease Priority Review Voucher was submitted</li> </ul> |   |
| Resubmission after withdrawal? <input type="checkbox"/>  | Resubmission after refuse to file? <input type="checkbox"/>   |
| Part 3 Combination Product? <input type="checkbox"/>   | <input type="checkbox"/> Convenience kit/Co-package<br><input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.)<br><input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.)<br><input type="checkbox"/> Device coated/impregnated/combined with drug<br><input type="checkbox"/> Device coated/impregnated/combined with biologic<br><input type="checkbox"/> Separate products requiring cross-labeling<br><input type="checkbox"/> Drug/Biologic<br><input type="checkbox"/> Possible combination based on cross-labeling of separate products<br><input type="checkbox"/> Other (drug/device/biological product) |
| <b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b>   |   |

|   |   |
|---|---|
| <input type="checkbox"/> Fast Track Designation<br><input type="checkbox"/> Breakthrough Therapy Designation<br><i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i><br><input type="checkbox"/> Rolling Review<br>X Orphan Designation<br><input type="checkbox"/> Rx-to-OTC switch, Full<br><input type="checkbox"/> Rx-to-OTC switch, Partial<br><input type="checkbox"/> Direct-to-OTC | <input type="checkbox"/> PMC response<br><input type="checkbox"/> PMR response: <ul style="list-style-type: none"> <li><input type="checkbox"/> FDAAA [505(o)]</li> <li><input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B)</li> <li><input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)</li> <li><input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)</li> </ul> |
| Other:  |   |

Collaborative Review Division (if OTC product): N/A

List referenced IND Number(s): 115959

| Goal Dates/Product Names/Classification Properties   | YES | NO | NA | Comment |
|--|-----|----|----|---------|
| PDUFA/BsUFA and Action Goal dates correct in the electronic archive?<br><br><b>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</b>  | X   |    |    |         |
| Are the established/proper and applicant names correct in electronic archive?<br><br><b>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 electronic</b> | X   |    |    |         |

|   |  |           |           |   |
|---|--|-----------|-----------|---|
| <i>archive.</i>   |  |           |           |   |
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i><br><a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a><br><i>If no, ask the document room staff to make the appropriate entries.</i> | X  |           |           |   |
| <b>Application Integrity Policy</b>   | <b>YES</b>   | <b>NO</b> | <b>NA</b> | <b>Comment</b>                          |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i><br><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a><br><b>If yes, explain in comment column.</b>  |  | X         |           |   |
| <b>If affected by AIP, has OC been notified of the submission? If yes, date notified:</b>   |  |           | X         |   |
| <b>User Fees</b>  | <b>YES</b>   | <b>NO</b> | <b>NA</b> | <b>Comment</b>                          |
| Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?   | X  |           |           |   |
| <u>User Fee Status</u><br><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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>   | Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ):<br><input type="checkbox"/> Paid<br><input checked="" type="checkbox"/> Exempt (orphan, government)<br><input type="checkbox"/> Waived (e.g., small business, public health)<br><input type="checkbox"/> Not required |           |           |   |
| <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. Contact the User Fee Staff. If appropriate, send UN letter.</i>  | Payment of other user fees:<br><input checked="" type="checkbox"/> Not in arrears<br><input type="checkbox"/> In arrears   |           |           |   |
| <u>User Fee Bundling Policy</u><br><i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i><br><a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>   | Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i><br><input type="checkbox"/> Yes<br><input type="checkbox"/> No   |           |           |   |
| <b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>   | <b>YES</b>   | <b>NO</b> | <b>NA</b> | <b>Comment</b>                          |
| Is the application a 505(b)(2) NDA? ( <i>Check the 356h form, cover letter, and annotated labeling</i> ). <b>If yes, answer the bulleted</b>  |  | X         |           | The application's status as a 505(b)(1) |

| questions below:  |                 |                  |                        | versus a 505(b)(2) is under discussion. |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|---|-----------------|------------------|------------------------|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
| <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> </ul>  |                 |                  |                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <ul style="list-style-type: none"> <li>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)].</li> </ul>   |                 |                  |                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <ul style="list-style-type: none"> <li>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)]?</li> </ul> <p><i>If you answered yes to any of the above bulleted 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 for advice.</i></p>   |                 |                  |                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <ul style="list-style-type: none"> <li>Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</li> </ul> <p><b>Check the Electronic Orange Book at:</b><br/> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1"> <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                  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Application No.   | Drug Name       | Exclusivity Code | Exclusivity Expiration |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   |                 |                  |                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   |                 |                  |                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   |                 |                  |                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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 orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>   |                 |                  |                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>Exclusivity</b>  | <b>YES</b>      | <b>NO</b>        | <b>NA</b>              | <b>Comment</b>                          |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b><br><a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>  |                 | X                |                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  |                 |                  | X                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>  |                 |                  |                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?   |                 | X                |                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>If yes, # years requested:</b>   |                 |                  |                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>Note:</b> An applicant can receive exclusivity without requesting it;  |                 |                  |                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

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| <i>therefore, requesting exclusivity is not required.</i>  |  |   |   |  |
| <b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?   |  | X |   |  |
| <b>If yes,</b> 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)?<br><br><i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>  |  |   | X |  |
| <b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?<br><br><i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i><br><br><i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> |  |   | X |  |

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

<sup>1</sup> <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

|   |            |           |           |                |
|---|------------|-----------|-----------|----------------|
| X English (or translated into English)<br>X pagination<br>X navigable hyperlinks (electronic submissions only)  |            |           |           |                |
| <b>If no, explain.</b>  |            |           |           |                |
| <b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  |            |           |           |                |
| <b>If yes, BLA #</b>  |            |           |           |                |
|   |            |           |           |                |
|   |            |           |           |                |
|   |            |           |           |                |
|   |            |           |           |                |
|   |            |           |           |                |
| <b>Forms and Certifications</b>   |            |           |           |                |
| <i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i> |            |           |           |                |
| <b>Application Form</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?   | X          |           |           | ?? signature   |
| <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          |           |           |                |
| <b>Patent Information (NDAs/NDA efficacy supplements only)</b>  | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?   | X          |           |           |                |
| <b>Financial Disclosure</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| 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>   |            |           |           |                |
| <b>Clinical Trials Database</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| 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>  |            |           |           |                |

| <b>Debarment Certification</b>  | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b>                  |
|---|------------|-----------|-----------|---------------------------------|
| <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, <u>both</u> 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&amp;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          |           |           |                                 |
| <b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>  | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b>                  |
| <p><b>For paper submissions only:</b> 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         | Electronic submission           |
| <b>Controlled Substance/Product with Abuse Potential</b>  | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b>                  |
| <p><u>For NMEs:</u><br/>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><br/><i>Date of consult sent to Controlled Substance Staff :</i></p>   |            |           | X         |                                 |
| <b>Pediatrics</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b>                  |
| <p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i></p>   |            | X         |           | Product has orphan designation. |

2

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

Version: 4/12/2016

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|  |   |           |           |   |
|--|---|-----------|-----------|---|
| <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i> |   |           |           |   |
| <b>If the application triggers PREA</b> , is there an agreed Initial Pediatric Study Plan (iPSP)?<br><br><i>If no, may be an RTF issue - contact DPMH for advice.</i>  |   |           | X         |   |
| <b>If required by the agreed iPSP</b> , are the pediatric studies outlined in the agreed iPSP completed and included in the application?<br><br><i>If no, may be an RTF issue - contact DPMH for advice.</i>   |   |           | X         |   |
| <b><u>BPCA:</u></b><br><br>Is this submission a complete response to a pediatric Written Request?<br><br><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required<sup>3</sup>)</i>   |   | X         |           |   |
| <b>Proprietary Name</b>  | <b>YES</b>  | <b>NO</b> | <b>NA</b> | <b>Comment</b>  |
| Is a proposed proprietary name submitted?<br><br><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>  | X   |           |           | Proposed proprietary name submitted on April 29, 2016; submission was not part of NDA submission. |
| <b>REMS</b>  | <b>YES</b>  | <b>NO</b> | <b>NA</b> | <b>Comment</b>  |
| Is a REMS submitted?<br><br><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>   |   | X         |           |   |
| <b>Prescription Labeling</b>   | <input type="checkbox"/> Not applicable   |           |           |   |
| Check all types of labeling submitted.   | <input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI)<br><input type="checkbox"/> Patient Package Insert (PPI)<br><input type="checkbox"/> Instructions for Use (IFU)<br><input type="checkbox"/> Medication Guide (MedGuide)<br><input type="checkbox"/> Carton labeling<br><input checked="" type="checkbox"/> Immediate container labels<br><input type="checkbox"/> Diluent labeling<br><input type="checkbox"/> Other (specify) |           |           |   |
|  | <b>YES</b>  | <b>NO</b> | <b>NA</b> | <b>Comment</b>  |
| Is Electronic Content of Labeling (COL) submitted in SPL format?<br><br><i>If no, request applicant to submit SPL before the filing date.</i>  | X   |           |           |   |

3

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

|  |  |           |           |  |
|--|--|-----------|-----------|--|
| Is the PI submitted in Physician Labeling Rule (PLR) format? <sup>4</sup>  | X  |           |           |  |
| <b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?<br><br><i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>   |  |           | X         |  |
| <b>For applications submitted on or after June 30, 2015:</b><br>Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?<br><br>Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?   | X<br><br>X   |           |           | Section 8.3 will have to be added.                                 |
| <b>For applications submitted on or after June 30, 2015:</b><br><b>If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?<br><br><i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i> |  |           | X         |  |
| Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?  | X  |           |           |  |
| Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? ( <i>send WORD version if available</i> )  |  |           | X         | Submission does not contain Patient Information, MedGuide, or IFU. |
| Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?  | X  |           |           |  |
| <b>OTC Labeling</b>  | <b>X Not Applicable</b>  |           |           |  |
| Check all types of labeling submitted.   | <input type="checkbox"/> Outer carton label<br><input type="checkbox"/> Immediate container label<br><input type="checkbox"/> Blister card<br><input type="checkbox"/> Blister backing label<br><input type="checkbox"/> Consumer Information Leaflet (CIL)<br><input type="checkbox"/> Physician sample<br><input type="checkbox"/> Consumer sample<br><input type="checkbox"/> Other (specify) |           |           |  |
|  | <b>YES</b>   | <b>NO</b> | <b>NA</b> | <b>Comment</b>   |

4

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

|   |            |           |           |   |
|---|------------|-----------|-----------|---|
| Is electronic content of labeling (COL) submitted?<br><i>If no, request in 74-day letter.</i>   |            |           |           |   |
| Are annotated specifications submitted for all stock keeping units (SKUs)?<br><i>If no, request in 74-day letter.</i>   |            |           |           |   |
| If representative labeling is submitted, are all represented SKUs defined?<br><i>If no, request in 74-day letter.</i>   |            |           |           |   |
| All labeling/package sent to OSE/DMEPA?   |            |           |           |   |
| <b>Other Consults</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b>                          |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)<br><i>If yes, specify consult(s) and date(s) sent:</i> |            | X         |           |   |
| <b>Meeting Minutes/SPAs</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b>                          |
| End-of Phase 2 meeting(s)?<br><b>Date(s):</b> N/A   |            | X         |           | An End-of-Phase 2 meeting was not held. |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?<br><b>Date(s):</b> March 8, 2016   | X          |           |           |   |
| Any Special Protocol Assessments (SPAs)?<br><b>Date(s):</b> N/A   |            | X         |           | There were no requests for SPAs.        |

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** May 16, 2016

**BACKGROUND:** A Pre-IND meeting was held in October 2012. During the meeting, the Division suggested that the Sponsor develop a different, age-appropriate formulation for the pediatric population. Subsequently, the Sponsor developed a rapidly disintegrating chewable tablet. This new 500 mg chewable formulation was utilized in the Phase 3 study. The product was granted Orphan Drug Status on September 3, 2014, for the treatment of single or mixed gastrointestinal infestations by *T. trichiura* (whipworm), *A. lumbricoides* (large roundworm), and *A. duodenale* and *N. americanus* (hookworm). The new chewable tablet formulation of mebendazole will be donated to the World Health Organization to replace the current 500 mg solid tablet.

**REVIEW TEAM:**

| Discipline/Organization                            | Names           |                       | Present at filing meeting? (Y or N) |
|--|-----------------|-----------------------|-------------------------------------|
| Regulatory Project Management                      | RPM:            | Alison Rodgers        | Y                                   |
|  | CPMS/TL:        | Maureen Dillon-Parker | Y                                   |
| Cross-Discipline Team Leader (CDTL)                | Hala Shamsuddin |                       | Y                                   |
| Division Director/Deputy                           | Sumathi Nambiar |                       | Y                                   |
| Office Director/Deputy                             | N/A             |                       |                                     |
| Clinical   | Reviewer:       | Sheral Patel          | Y                                   |
|  | TL:             | Hala Shamsuddin       | Y                                   |
| Social Scientist Review (for OTC products)         | Reviewer:       | N/A                   |                                     |
|  | TL:             | N/A                   |                                     |
| OTC Labeling Review (for OTC products)             | Reviewer:       | N/A                   |                                     |
|  | TL:             | N/A                   |                                     |
| Clinical Microbiology (for antimicrobial products) | Reviewer:       | Shukal Bala           | Y                                   |
|  | TL:             | Kalavati Suvarna      | Y                                   |
| Clinical Pharmacology                              | Reviewer:       | Abhay Joshi           | Y                                   |

|  |           |                        |   |
|--|-----------|------------------------|---|
|  | TL:       | Philip Colangelo       | Y |
| • Genomics   | Reviewer: | N/A                    |   |
| • Pharmacometrics  | Reviewer: | N/A                    |   |
| Biostatistics  | Reviewer: | Janelle Charles        | Y |
|  | TL:       | Karen Higgins          | N |
| Nonclinical<br>(Pharmacology/Toxicology)                                   | Reviewer: | Amy Nostrandt          | Y |
|  | TL:       | Wendelyn Schmidt       | Y |
| Statistics (carcinogenicity)   | Reviewer: | N/A                    |   |
|  | TL:       | N/A                    |   |
| Product Quality (CMC) Review Team:   | ATL:      | Dorota Matecka         | N |
|  | RBPM:     | Navi Bhandari          | N |
| • Drug Substance   | Reviewer: | Gaetan Ladouceur       | N |
| • Drug Product   | Reviewer: | George Lunn            | Y |
| • Process  | Reviewer: | Sateesh Sathigari      | N |
| • Microbiology   | Reviewer: | Sateesh Sathigari      | N |
| • Facility   | Reviewer: | Quallyna Porte         | N |
| • Biopharmaceutics   | Reviewer: | Mei Ou                 | Y |
| • Immunogenicity   | Reviewer: | N/A                    |   |
| • Labeling (BLAs only)   | Reviewer: | N/A                    |   |
| • Other (e.g., Branch Chiefs, EA Reviewer)                                 | N/A       |                        |   |
| OMP/OMPI/DMPP (MedGuide, PPI, IFU)   | Reviewer: | N/A                    |   |
|  | TL:       | N/A                    |   |
| OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling) | Reviewer: | N/A                    |   |
|  | TL:       | N/A                    |   |
| OSE/DMEPA (proprietary name, carton/container labeling)                    | Reviewer: | Deborah Myers          | Y |
|  | TL:       | Vicky Borders-Hemphill | N |
| OSE/DRISK (REMS)   | Reviewer: | N/A                    |   |
|  | TL:       | N/A                    |   |
| OC/OSI/DSC/PMSB (REMS)   | Reviewer: | N/A                    |   |

|                                  |                    |                |   |
|----------------------------------|--------------------|----------------|---|
|                                  | TL:                | N/A            |   |
| Bioresearch Monitoring (OSI)     | Reviewer:          | John Lee       | Y |
|                                  | TL:                | Janice Pohlman | N |
| Controlled Substance Staff (CSS) | Reviewer:          | N/A            |   |
|                                  | TL:                | N/A            |   |
| Other reviewers/disciplines      |                    |                |   |
| • <b>Discipline</b>              | Reviewer:          | N/A            |   |
|                                  | TL:                | N/A            |   |
| Other attendees                  | Abimbola Adebowale |                | Y |
|                                  | Joseph Toerner     |                | Y |
|                                  | Janet Higgins      |                | Y |
|                                  | Tim Jancel         |                | Y |

**FILING MEETING DISCUSSION:**

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

|   |   |
|---|---|
|   |   |
| <b>CLINICAL</b>   | X FILE  |
| <b>Comments:</b>  |   |
| <ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no</b>, explain:</p>   | X YES   |
| <ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></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"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><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></li> </ul> | X NO<br><br>Reason:                               |
| <ul style="list-style-type: none"> <li>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?</li> </ul> <p><b>Comments:</b></p>   | X Not Applicable                                  |
| <b>CONTROLLED SUBSTANCE STAFF</b>   | X Not Applicable                                  |
| <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>   |   |
| <b>CLINICAL MICROBIOLOGY</b>  | X FILE  |
| <b>Comments:</b> May have issues for 74-day letter.   | X Review issues for 74-day letter<br>*See comment |

|  |   |
|--|---|
| <p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p> <ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>   | <p>X FILE</p>   |
| <p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>  | <p>X NO</p>   |
| <p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> May have issue for 74-day letter.</p>  | <p>X FILE</p> <p>X Review issues for 74-day letter<br/>*See comment</p> |
| <p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>  | <p>X FILE</p>   |
| <p><b><u>New Molecular Entity</u> (NDAs only)</b></p> <ul style="list-style-type: none"> <li>• Is the product an NME?</li> </ul>   | <p>X NO</p>   |
| <p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no, was a complete EA submitted?</b></p> <p><b>Comments:</b></p> | <p>X YES</p>  |
| <p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> </ul> <p><b>Comments:</b></p>  | <p>X YES</p>  |

|  |   |
|--|---|
| <p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>   | <p>X Not Applicable</p>   |
| <p><b><u>CMC Labeling Review (BLAs only)</u></b></p> <p>Comments:</p>  | <p><input type="checkbox"/> Review issues for 74-day letter</p>     |
| <p><b>APPLICATIONS IN THE PROGRAM (PDUFA V)<br/>(NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• 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?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul> | <p>X N/A</p>  |
| <ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>  |   |
| <ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>  | <p><input type="checkbox"/> YES<br/><input type="checkbox"/> NO</p> |
| <ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>   | <p><input type="checkbox"/> YES<br/><input type="checkbox"/> NO</p> |
| <ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>   | <p><input type="checkbox"/> YES<br/><input type="checkbox"/> NO</p> |

| <b>REGULATORY PROJECT MANAGEMENT</b>  |   |
|---|---|
| <b>Signatory Authority: Sumathi Nambiar, MD, MPH</b>  |   |
| <b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V):  |   |
| <b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional): |   |
| <b>Comments:</b>  |   |
| <b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>  |   |
| <input type="checkbox"/>  | The application is unsuitable for filing. Explain why:  |
| <input type="checkbox"/>  | The application, on its face, appears to be suitable for filing.<br><br><u>Review Issues:</u><br><br><input type="checkbox"/> No review issues have been identified for the 74-day letter.<br><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.<br><br><u>Review Classification:</u><br><br><input type="checkbox"/> Standard Review<br><input checked="" type="checkbox"/> Priority Review |
| <b>ACTION ITEMS</b>   |   |
| <input checked="" type="checkbox"/>   | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).  |
| <input type="checkbox"/>  | If RTF, notify everyone who already received a consult request, OSE PM, and RBPM  |
| <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"/>  | If priority review, notify applicant in writing by day 60 (see CST for choices)   |
| <input type="checkbox"/>  | Send review issues/no review issues by day 74   |
| <input checked="" 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 applications in the Program)  |
| <input type="checkbox"/>  | Other   |

Annual review of template by OND ADRAAs completed: April 2016

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ALISON K RODGERS  
08/15/2016

MAUREEN P DILLON PARKER  
08/16/2016

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

---

**Date of This Memorandum:** June 9, 2016  
**Requesting Office or Division:** Division of Anti-Infective Products (DAIP)  
**Application Type and Number:** NDA 208398  
**Product Name and Strength:** Vermox Chewable (mebendazole) Chewable Tablets, 500 mg  
**Submission Date:** June 8, 2016  
**Applicant/Sponsor Name:** Janssen Pharmaceuticals, Inc.  
**OSE RCM #:** 2016-997-1  
**DMEPA Primary Reviewer:** Deborah Myers, RPh, MBA  
**DMEPA Team Leader:** Vicky Borders-Hemphill, PharmD

---

#### 1 PURPOSE OF MEMO

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label for Vermox Chewable (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1</sup>

#### 2 CONCLUSION

The revised container labels for Vermox Chewable are acceptable from a medication error perspective. We have no further recommendations at this time.

---

<sup>1</sup> Myers, D. Label and Labeling Review for Vermox Chewable (NDA 208398). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAY 26. 9 p. OSE RCM No.: 2016-997.

**APPENDIX A. LABEL AND LABELING SUBMITTED ON JUNE 8, 2016**

Container label (not to scale)



(b) (4)

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/s/  
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DEBORAH E MYERS  
06/09/2016

BRENDA V BORDERS-HEMPHILL  
06/09/2016

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## **LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** May 26, 2016  
**Requesting Office or Division:** Division of Anti-Infective Products (DAIP)  
**Application Type and Number:** NDA 208398  
**Product Name and Strength:** Vermox Chewable (mebendazole) Chewable Tablets, 500 mg  
**Product Type:** Single-Ingredient Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Janssen Pharmaceuticals, Inc.  
**Submission Date:** April 19, 2016  
**OSE RCM #:** 2016-997  
**DMEPA Primary Reviewer:** Deborah Myers, RPh, MBA  
**DMEPA Team Leader:** Vicky Borders-Hemphill, PharmD

---

## 1 REASON FOR REVIEW

This review is written in response to a request from the Division of Anti-Infective Products (DAIP) to review the container label and prescribing information labeling submitted for Vermox Chewable (mebendazole) Chewable Tablets, 500 mg [NDA 208398] for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

| <b>Material Reviewed</b>                    | <b>Appendix Section (for Methods and Results)</b> |
|---|---|
| Product Information/Prescribing Information | A   |
| Previous DMEPA Reviews                      | B   |
| Human Factors Study                         | N/A   |
| ISMP Newsletters                            | N/A   |
| FDA Adverse Event Reporting System (FAERS)* | N/A   |
| Other                                       | N/A   |
| Labels and Labeling                         | G   |

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed container label and prescribing information labeling identified areas that can be improved to increase clarity, improved readability, and add important information to minimize the risk of medication errors and promote the safe use of Vermox Chewable.

### Prescribing Information

We note that the intended route of administration and duration are not included in the Highlights of Prescribing Information, *Dose and Administration*, as well as Full Prescribing Information, Section 2, *Dose and Administration*, Section 2.1, *Adults and Pediatrics (>1years of age)*, which could increase the potential for wrong route of administration and wrong duration medication errors. In addition, in these sections we note the use “1” and to minimize the risk for misinterpretation we suggest consider replacing “1” with its intended meaning, “One.” and thus revised to read “One single tablet of Vermox Chewable 500 mg taken as a single oral dose”.

In the Highlights of Prescribing Information, *Dose and Administration*, Full Prescribing Information, Section 2, *Dose and Administration*, Section 2.1 *Adults and Pediatrics (>1years of age)*, and Section 2.3, *Dosage and Administration, Pediatrics <1 years of age*, we note the inclusion of “>” and “<”. Errors can result from the use of abbreviations, symbols, and dose designations and therefore Sponsors should avoid the use of abbreviations for dose designations in labeling.

In Highlights of Prescribing Information, *Dosage and Administration* and Full Prescribing Information, Section 2, *Dosage and Administration*, [REDACTED] (b) (4)

We have provided language to clarify that this information is only applicable to Vermox Chewable tablets, not all chewable tablets in general.

### **Container Label**

The submitted container label presents the incorrect proprietary name and dosage form as:

Vermox  
Chewable Tablets 500 mg  
(mebendazole)

This is not consistent with the order of presentation of the proprietary name, established name, strength, and dosage form for drug products on labels and labeling. The proposed name “Vermox Chewable” was found conditionally acceptable on May 26, 2016. As presented, the presentation includes “Tablets” as though it is part of the proprietary name, Vermox Chewable. We collaborated with the Office of Pharmaceutical Quality (OPQ) to determine the appropriate presentation and provide a recommendation in Section 4.2 to the Applicant to make the necessary changes to the container label.

We note that the product strength is not displayed prominently on the container label, which could potentially lead to wrong strength medication errors.

We note that the barcode is placed at the bottom of the principal display panel (PDP). Barcodes in a horizontal position may not scan due to the curvature of the container. Therefore we asked that the barcode be relocated and reoriented to a vertical position to improve the scannability.

## **4 CONCLUSION & RECOMMENDATIONS**

We identified areas of the label and labeling that can be revised to increase clarity, improve readability, and add important information to mitigate the potential for medication errors and

promote the safe use of Vermox Chewable. We provide recommendations in Sections 4.1 and 4.2 below and advise that they be implemented prior to the approval of this NDA.

#### 4.1 RECOMMENDATIONS FOR THE DIVISION

##### A. Highlights of Prescribing Information, *Dosage and Administration*

1. To provide clarity regarding the route of administration and duration of therapy consider adding the words “taken as a single oral dose” so that the Dosage statement reads:
  - 1 single tablet of Vermox Chewable 500 mg taken as a single oral dose.
2. To minimize the risk for misinterpretation, consider replacing “1” with its intended meaning, “One” in the statement “1 single tablet...” so that it instead reads, “One single tablet...”
3. The symbols ‘<’, ‘≤’, ‘>’, and ‘≥’ are dangerous abbreviations that appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because these symbols are often mistaken and used as opposite of intended.<sup>1</sup> As a part of a national campaign to reduce medication errors related to error-prone medical abbreviations, symbols, and dose designations, the FDA agreed not to approve labels and labeling that include error-prone abbreviations, symbols, and dose designations. The symbol ‘>’ appears in the statement “Adults and Pediatrics (>1 years of age)” and should be changed to instead read “(above 1 year of age)” or “(1 year of age and older).”
4. To improve clarity that this suggestion of the addition of water is applicable only to Vermox Chewable tablet, not to more than one Vermox chewable tablet nor to all chewable tablets in general, consider changing the current (b) (4)

[Redacted text block]

##### B. Full Prescribing Information, Section 2, *Dosage and Administration*, (b) (4)

[Redacted text block]

1. See A.1
2. See A.2
3. See A.3

---

<sup>1</sup> ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2015 Mar 3]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

C. Full Prescribing Information, Section 2, *Dosage and Administration*, (b) (4)

1. To provide clarity consider adding the quantity of measure after the “2” in the part of the statement, “...approximately 2 to 3 mL...” so that it instead reads, “...approximately 2 mL to 3 mL...”.

D. Full Prescribing Information, Section 2, *Dosage and Administration*, Section 2.3, *Pediatrics <1 years of age*

1. The symbols ‘<’, ‘≤’, ‘>’, and ‘≥’ are dangerous abbreviations that appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations because these symbols are often mistaken and used as opposite of intended. As a part of a national campaign to reduce medication errors related to error-prone medical abbreviations, symbols, and dose designations, the FDA agreed not to approve labels and labeling that include error-prone abbreviations, symbols, and dose designations. The symbol ‘<’ appears in the heading “2.3, *Pediatrics (<1 years of age)*” and should be changed to instead read “(below the age of 1 year)” or “(less than 1 year of age).”

#### 4.2 RECOMMENDATIONS FOR JANSSEN PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA 208398:

##### Container Label

1. We note that your container labels present the proprietary name, established name, strength, and dosage form as:



This layout is not consistent with the presentation of the proprietary name, established name, strength, and dosage form for drug products. (b) (4)

. The Office of Pharmaceutical Quality (OPQ) determined the presentation of the established name to include the dosage form. Thus, revise the presentation as follows:

Vermox Chewable  
(mebendazole chewable tablets)  
500 mg

2. Increase the prominence of the product strength, 500 mg, on the principal display panel (PDP) to help decrease the potential of wrong strength medication errors.
3. To improve readability, please add a period at the end of the sentence, “Each chewable tablet contains 500 mg of mebendazole.”
4. Barcodes placed in a horizontal position may not scan due to the curvature of the container. Consider relocating the barcode from the bottom of the PDP and reorient the barcode to a vertical position to improve the scannability.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Vermox Chewable that Janssen Pharmaceuticals, Inc. submitted on April 19, 2016.

| <b>Table 2. Relevant Product Information for Vermox Chewable</b> |  |
|--|--|
| <b>Initial Approval Date</b>                                     | N/A  |
| <b>Active Ingredient</b>   | mebendazole  |
| <b>Indication</b>  | treatment of single or mixed gastrointestinal infestations by <i>Trichuris trichiura</i> (whipworm); <i>Ascaris lumbricoides</i> (large roundworm); [REDACTED] (b) (4) |
| <b>Route of Administration</b>                                   | Oral   |
| <b>Dosage Form</b>   | Chewable Tablet  |
| <b>Strength</b>  | 500 mg   |
| <b>Dose and Frequency</b>  | One single 500 mg chewable tablet once.  |
| <b>How Supplied</b>  | Bottles of 200 tablets   |
| <b>Storage</b>   | [REDACTED] (b) (4)   |

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On May 5, 2016, we searched the L:drive and AIMS using the terms, Vermox to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified one previous review<sup>2</sup>, and we confirmed that our previous recommendations were implemented.

APPEARS THIS WAY ON ORIGINAL



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<sup>2</sup> Sheppard, J. Proprietary Name Review for Vermox Chewable (IND 115959). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 DEC 11. RCM No.: 2015-1115400.

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>3</sup> along with postmarket medication error data, we reviewed the following Vermox Chewable labels and labeling submitted by Janssen Pharmaceuticals, Inc. on April 19, 2016.

- Container label
- Prescribing Information (no image)

### **G.2 Label and Labeling Images**

- Container label

(b) (4)



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

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/s/  
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DEBORAH E MYERS  
05/26/2016

BRENDA V BORDERS-HEMPHILL  
05/31/2016

# REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 208398

**Application Type:** New NDA

**Drug Name(s)/Dosage Form(s):** Vermox (mebendazole) Chewable Tablets, 500 mg

**Applicant:** Janssen Pharmaceuticals, Inc.

**Receipt Date:** April 19, 2016

**Goal Date:** October 19, 2016

## 1. Regulatory History and Applicant's Main Proposals

A Pre-IND meeting was held in October 2012. During the meeting, the Division suggested that the Sponsor develop a different, age-appropriate formulation for the pediatric population. Subsequently, the Sponsor developed a rapidly disintegrating chewable tablet. This new 500 mg chewable formulation was utilized in the Phase 3 study. The product was granted Orphan Drug Status on September 3, 2014, for the treatment of (b)(4) gastrointestinal (b)(4) by *T. trichiura* (whipworm), *A. lumbricoides* (large roundworm), (b)(4). The new chewable tablet formulation of mebendazole will be donated to the World Health Organization to replace the current 500 mg solid tablet.

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

## 3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 23, 2016. The resubmitted PI will be used for further labeling review.

---

## 4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

# Selected Requirements of Prescribing Information

## Highlights

See Appendix for a sample tool illustrating Highlights format.

### HIGHLIGHTS GENERAL FORMAT

- 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 unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

**Comment:**

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
  - TOC from the Full Prescribing Information (FPI).

**Comment:**

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

**Comment:**

- YES** 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 for HL format.

**Comment:**

- NO** 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 is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:** *There is no reference following the Adverse Reactions topic.*

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

| Heading                           | 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                                  |

## Selected Requirements of Prescribing Information

|  |   |
|--|---|
| • 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 five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

### HIGHLIGHTS DETAILS

#### Highlights Heading

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

Comment:

#### Highlights Limitation Statement

- YES** 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:

#### Product Title in Highlights

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

Comment:

#### Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *There is a dash between Approval and 1974 instead of a colon.*

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

**N/A**

## Selected Requirements of Prescribing Information

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

Comment:

- N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

### Recent Major Changes (RMC) in Highlights

- YES 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- YES 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) --- 8/2015.”

Comment:

- YES 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

### Dosage Forms and Strengths in Highlights

- N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

### Contraindications in Highlights

- YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

### Adverse Reactions in Highlights

- YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at**

## Selected Requirements of Prescribing Information

(insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).”

Comment:

### Patient Counseling Information Statement in Highlights

**YES** 22. 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 (or will have)** 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

**NO** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment: *The revised date is not listed.*

## Selected Requirements of Prescribing Information

---

### Contents: Table of Contents (TOC)

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

- YES** 24. The TOC should be in a two-column format.  
*Comment:*
- YES** 25. 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:*
- N/A** 26. The same title 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** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- NO** 28. 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 (for, of, to) and articles (a, an, the), or conjunctions (or, and)].  
*Comment:* Under section 2.3, the first letters of the words years and age are not capitalized.
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS\***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. 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.

|  |
|--|
| <b>BOXED WARNING</b>   |
| <b>1 INDICATIONS AND USAGE</b>   |
| <b>2 DOSAGE AND ADMINISTRATION</b>   |
| <b>3 DOSAGE FORMS AND STRENGTHS</b>  |
| <b>4 CONTRAINDICATIONS</b>   |
| <b>5 WARNINGS AND PRECAUTIONS</b>  |
| <b>6 ADVERSE REACTIONS</b>   |
| <b>7 DRUG INTERACTIONS</b>   |
| <b>8 USE IN SPECIFIC POPULATIONS</b>   |
| 8.1 Pregnancy  |
| 8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery") |
| 8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")          |
| 8.4 Pediatric Use  |
| 8.5 Geriatric Use  |
| <b>9 DRUG ABUSE AND DEPENDENCE</b>   |
| 9.1 Controlled Substance   |
| 9.2 Abuse  |
| 9.3 Dependence   |
| <b>10 OVERDOSAGE</b>   |
| <b>11 DESCRIPTION</b>  |
| <b>12 CLINICAL PHARMACOLOGY</b>  |
| 12.1 Mechanism of Action   |
| 12.2 Pharmacodynamics  |
| 12.3 Pharmacokinetics  |
| 12.4 Microbiology (by guidance)  |
| 12.5 Pharmacogenomics (by guidance)  |
| <b>13 NONCLINICAL TOXICOLOGY</b>   |
| 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility  |
| 13.2 Animal Toxicology and/or Pharmacology   |
| <b>14 CLINICAL STUDIES</b>   |
| <b>15 REFERENCES</b>   |
| <b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>  |
| <b>17 PATIENT COUNSELING INFORMATION</b>   |

**Comment:**

- YES** 32. 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)*].”

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.  
*Comment: No RMC were included.*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.  
*Comment:*

#### BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.  
*Comment:*
- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.  
*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- N/A** 37. If no Contraindications are known, this section must state “None.”  
*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:  
  
“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** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), 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.”  
*Comment:*

## Selected Requirements of Prescribing Information

### PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
  - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

**Comment:**

- N/A** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) 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:**

# Selected Requirements of Prescribing Information

## Appendix: Highlights and Table of Contents Format

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol  
Initial U.S. Approval: YYYY

#### WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

#### RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y  
Section Title, Subsection Title (x.x) M/201Y

#### INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

#### DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

#### DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

#### CONTRAINDICATIONS

- Text (4)
- Text (4)

#### WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

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

#### DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

#### USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

### FULL PRESCRIBING INFORMATION: CONTENTS\*

#### WARNING: TITLE OF WARNING

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

#### 6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

#### 7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

#### 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 Subsection Title

14.2 Subsection Title

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALISON K RODGERS  
05/17/2016