

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207960Orig1s000**

**OTHER REVIEW(S)**



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** December 4, 2015

**To:** Mitchell Mathis, M.D., Director  
Division of Psychiatry Products

**Through:** Michael Klein, Ph.D., Director  
Controlled Substance Staff

**From:** Martin S. Rusinowiz, M.D., Medical Officer  
Controlled Substance Staff

**Subject:** QuilliChew ER/Methylphenidate Extended-Release Tablet  
NDA 207960  
Indication: Treatment of Attention Deficit Hyperactivity  
Disorder  
Dosages: Extended release tablets/ [REDACTED] (b) (4)  
[REDACTED] (20 mg, 30 mg, 40 mg equivalent salt)  
Sponsor: Pfizer, Inc.

**Materials reviewed:** Sponsor's Clinical Overview; January 21, 2015  
DARRTS, NDA 207960 CDTL Team Leader Review;  
Kempf, Lucas 11/24/2015

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## **I. Background**

Methylphenidate (MPH) was first approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in 1955. It was originally formulated as an immediate release (IR) tablet and later as an extended release (ER) tablet. ER formulations provide convenience and adherence for this mostly pediatric population that would require repeated dosing in school with IR formulations. The current application is for a new formulation that provides once daily extended

release in a tablet that may be chewed or swallowed for patients who may not swallow pills whole, such as young children.

QuilliChew consists of [REDACTED] (b) (4) [REDACTED] This formulation utilizes the same drug release mechanism as MPH ER powder for oral suspension (Quillivant XR®), which is a [REDACTED] (b) (4) ER [REDACTED] (b) (4) formulation (20% IR and 80% ER) of MPH HCl.

The Sponsor proposed that the dosage form be ‘chewable tablets’. However, USP <1151> states that a chewable tablet is one that must be chewed rather than one that may be chewed. As the drug product [REDACTED] (b) (4) the dosage form designation is ‘tablets’ rather than ‘chewable tablets’. Labeling negotiations have just been completed.

## II. Conclusions and Recommendations

1. QuilliChew ER contains methylphenidate, a Schedule II controlled substance and is therefore subject to Schedule II regulations and penalties.
2. The product’s Label and Medication Guide provide adequate instructions to minimize dosing errors.
3. Standard Periodic Adverse Event Reports (PADERS) are adequate for reviewing and reporting abuse related adverse events from the unknown ease of manipulation and extractability of the product’s MPH API.

## III. Discussion

Even though QuilliChew ER will remain a Schedule II controlled substance, CSS voiced concerns with the Sponsor about the potential for additional abuse liability of this MPH formulation. The ease of manipulation and extractability of the MPH API, compared with other available formulations, has not been studied. Additionally, we had been concerned about the possibility of dosing errors given that ‘may be chewed or swallowed’ will not be in the Dosage and Administration section of the label. This could potentially result in over- or under-dosing from misunderstanding the label. There may be cases of under-dosing if the tablet is spit out before being completely chewed, while there may also be cases of over-dosing if the patient swallows the tablet before complete chewing and then mistakenly takes another dose in an attempt to compensate. (These assumptions might be based on patients/parents assumption that the product consists of a chewing gum type resin.)

As labeling negotiations between the Division of Psychiatry Products (DPP) and the Sponsor have progressed it is now clear that in addition to the proprietary name (which implies the tablet is chewable) the Dosage Forms and Strengths section of the label as well as the Medication

Guide describe the chewability of the product, along with it being swallowed whole. The Sponsor will plan standard PADERS for reviewing and reporting adverse events related to the unknown ease of manipulation and extractability of the MPH API.

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/s/  
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MARTIN S RUSINOWITZ  
12/04/2015

MICHAEL KLEIN  
12/04/2015



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

*If not a PMR, skip to 4.*

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Pharmacokinetic study in ADHD patients aged 4-5 years old Study population: ADHD patients 4-5 years old Study design: multiple dose, open label Sample size: <span style="background-color: #cccccc; padding: 2px;">(b) (4)</span>
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Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

*Continuation of Question 4*

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

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

Agreed upon:

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

- 
- Other  
Pharmacokinetic study in ADHD patients aged 4-5 years old.
- 

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

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

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

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

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

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**PMR/PMC Development Coordinator:**

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

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/s/  
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HIREN PATEL  
12/04/2015

MITCHELL V Mathis  
12/04/2015



Psychostimulants, including methylphenidate, are the most common class of medication used to treat ADHD. The same stimulants used to treat ADHD in school-aged children are also widely used in the treatment of preschoolers with ADHD. Currently, methylphenidate is not approved by the FDA for treatment of children below 6 years of age. (b) (4)

The goal of this PMR is to evaluate the safety and efficacy of QuilliChew ER for the treatment of ADHD in children 4 to < 6 years of age.

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

*If not a PMR, skip to 4.*

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

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

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

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

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

**Clinical Trial:** A 6-week, double-blind, placebo-controlled, randomized, parallel-group safety and efficacy study in children with ADHD 4-5 years of age using methylphenidate ER formulation (QuilliChew ER)

**Subpopulation:** 4 to < 6 year old patients with ADHD

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

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

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

- Quality study without a safety endpoint (e.g., manufacturing, stability)
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- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
- 

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

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- There is not enough existing information to assess these risks
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- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

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

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/s/  
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HIREN PATEL  
12/04/2015

MITCHELL V Mathis  
12/04/2015



Psychostimulants, including methylphenidate, are the most common class of medication used to treat ADHD. The same stimulants used to treat ADHD in school-aged children are also widely used in the treatment of preschoolers with ADHD. Currently, methylphenidate is not approved by the FDA for treatment of children below 6 years of age. (b) (4)

The goal of this PMR is to evaluate the longer term safety of Quillichew ER for the treatment of ADHD in children 4 to < 6 years of age.

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

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

**Clinical Trial:** A 6-month, open-label extension study to obtain additional information on safety and tolerability of methylphenidate ER formulation (QuilliChew ER) in children 4 to <6 years of age with ADHD

**Subpopulation:** 4 to < 6 year old patients with ADHD



Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other  
6-month, open-label extension study to further define safety and tolerability of QuilliChew in 4 to < 6 year olds with ADHD
- 

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

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HIREN PATEL  
12/04/2015

MITCHELL V Mathis  
12/04/2015

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

**PATIENT LABELING REVIEW**

Date: November 18, 2015

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

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Marcia Williams, PhD  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Sharon W. Williams, MSN, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Susannah O'Donnell, MPH, RAC  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

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

Drug Name (established name): QuilliChew Extended-Release (ER) (methylphenidate hydrochloride)

Dosage Form and Route: extended-release chewable tablet

Application Type/Number: NDA 207960

Applicant: Pfizer, Inc.

## 1 INTRODUCTION

On February 4, 2015, Pfizer, Inc. submitted for the Agency's review an original New Drug Application (NDA) for methylphenidate hydrochloride extended- release chewable tablets as a treatment for Attention Deficit Hyperactivity Disorder (ADHD). On October 14, 2015, the Agency granted the sponsor's request for approval of the proprietary name, QuilliChew ER.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on February 23, 2015 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for QuilliChew ER (methylphenidate hydrochloride) chewable tablets.

## 2 MATERIAL REVIEWED

- Draft QuilliChew ER (methylphenidate hydrochloride) chewable tablet MG, received on February 4, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on November 10, 2015.
- Draft QuilliChew ER (methylphenidate hydrochloride) chewable tablet MG received on February 4, 2015, and received by OPDP on November 10 2015.
- Draft QuilliChew ER (methylphenidate hydrochloride) chewable tablet Prescribing Information (PI) received on February 4, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on November 10, 2015.
- Draft QuilliChew ER (methylphenidate hydrochloride) chewable tablet Prescribing Information (PI) received on February 4, 2015, revised by the Review Division throughout the review cycle, and received by OPDP on November 10, 2015.
- Approved Quillivant <sup>(b) (4)</sup> (methylphenidate hydrochloride) comparator labeling dated April 17, 2015.

## 3 REVIEW METHODS

In 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible

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

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

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

Please let us know if you have any questions.

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/s/  
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SHARON W WILLIAMS  
11/18/2015

SUSANNAH O'DONNELL  
11/18/2015

MARCIA B WILLIAMS  
11/18/2015

LASHAWN M GRIFFITHS  
11/18/2015

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

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

## Memorandum

**Date:** November 18, 2015

**To:** Hiren Patel, PharmD, MS, RAC  
Senior Regulatory Health Project Manager  
Division of Psychiatry Products (DPP)

**From:** Susannah K. O'Donnell, MPH, RAC  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** **NDA 207960**  
QuilliChew ER™ (methylphenidate hydrochloride) extended-release chewable tablets, for oral use, CII

---

OPDP has reviewed the draft product labeling (PI), Medication Guide (MG), and carton/container labeling for QuilliChew ER™ (methylphenidate hydrochloride) extended-release chewable tablets, for oral use, CII (QuilliChew ER) as requested in the consult from DPP dated March 2, 2015.

OPDP's comments on the draft PI for QuilliChew ER are based on the version provided by Hiren Patel via email on November 10, 2015. Combined OPDP and Division of Medical Policy Programs (DMPP) comments on the proposed MG will be provided to DPP under separate cover.

OPDP has reviewed the proposed carton/container labeling, obtained from the EDR (<\\CDSESUB1\evsprod\NDA207960\207960.enx> Seq. 0022) on November 17, 2015, and has no comments at this time.

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at [Susannah.ODonnell@fda.hhs.gov](mailto:Susannah.ODonnell@fda.hhs.gov).

OPDP appreciates the opportunity to provide comments on these materials.  
Thank you!

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/s/  
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SUSANNAH O'DONNELL  
11/18/2015

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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:** November 13, 2015  
**Requesting Office or Division:** Division of Psychiatry Products  
**Application Type and Number:** NDA 207960  
**Product Name and Strength:** QuilliChew ER (methylphenidate hydrochloride)  
Extended-release Chewable Tablets  
20 mg, 30 mg, and 40 mg  
**Submission Date:** November 11, 2015  
**Applicant/Sponsor Name:** Pfizer  
**OSE RCM #:** 2015-892-2  
**DMEPA Primary Reviewer:** Deborah Myers, RPh, MBA  
**DMEPA Team Leader:** Danielle Harris, PharmD, PCPS

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#### 1 PURPOSE OF MEMO

The Division of Psychiatry Products (DPP) requested that we review the revised container labels for QuilliChew ER (Appendix A) to determine if they are 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 QuilliChew ER are acceptable from a medication error perspective. We have no further recommendations at this time.

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<sup>1</sup> Holmes L. Label and Labeling Review Memorandum for QuilliChew ER (NDA 207960). 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); 2015 NOV 05. 3 p. OSE RCM No.: 2015-892-1.

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/s/  
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DEBORAH E MYERS  
11/13/2015

DANIELLE M HARRIS  
11/13/2015

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** 11/5/2015

**TO:** Hiren Patel, Regulatory Project Manager  
Christina Burkhart, M.D., Medical Officer and Clinical Reviewer  
Lucas Kempf, M.D., Medical Team Leader  
Division of Psychiatry Products (DPP)

**FROM:** Jenn Sellers, M.D., Ph.D. F.A.A.P.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

**THROUGH:** Susan D. Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.,  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 207960/SN000

**APPLICANT:** NextWave Pharmaceuticals, Inc. (a subsidiary of Pfizer Inc.)

**DRUG:** Methylphenidate HCl Extended-Release Chewable Tablets

**NME:** No

**REVIEW:** Standard Review

**INDICATION:** ADHD

**CONSULTATION REQUEST DATE:** 03/23/2015

INSPECTION SUMMARY GOAL DATE: November 6, 2015

DIVISION ACTION GOAL DATES: December 4, 2015

PDUFA DATES: December 4, 2015

## I. BACKGROUND

The sponsor, NextWave Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, developed an extended-release chewable tablet formulation of methylphenidate, also known as NWP09, for the treatment of ADHD. They submitted this 505(b) (2) application (NDA # 207960). The reference listed drug (RLD) was an immediate release formulation of methylphenidate, Methylin chewable tablet, which was approved by FDA on April 15, 2003.

This 505(b) (2) application includes a randomized, double-blind, placebo-controlled trial in 90 pediatric ADHD subjects aged 6 to 12 years in a laboratory classroom setting (Protocol# NWP09-ADHD-300). In the study, eligible enrolled subjects took open-label NWP09 orally once daily for 6 weeks to achieve a stable dose of 20 - 60 mg/day. After completing the Open-label Dose Optimization Period, subjects were evaluated for ADHD symptoms and signs using the Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) and the Permanent Product Measure of Performance (PERMP) assessment in a laboratory classroom setting at multiple time points (abbreviated laboratory classroom day or Visit 8). Subjects who achieved a stable dose of NWP09 and successfully completed the pre-dose and 0.75- and 2-hour post-dose laboratory classroom sessions during Visit 8 were randomized to take double-blind study drug (NWP09 or placebo) orally once daily for 1 week. At the end of the 1-week Double-blind Treatment Period, subjects were evaluated for ADHD symptoms and signs using the SKAMP and PERMP assessments in a laboratory classroom setting at multiple time points throughout the day (complete laboratory classroom day or Visit 9).

The primary efficacy endpoint was the average of all post-dose SKAMP-combined scores collected during the double-blind laboratory classroom day (0.75, 2, 4, 8, 10, 12, and 13 hours after dosing). The key secondary efficacy endpoints were onset and duration of clinical effect of NWP09 versus placebo using the SKAMP-Combined scores at 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose on the classroom study day (Visit 9). According to the sponsor, NWP09 demonstrated a statistically significant treatment effect in ADHD. The Division of Psychiatry Products (DPP) requested inspections of the following clinical investigator sites based primarily on large subject enrollment.

**II. RESULTS (by Site):**

<b>Name of Clinical Investigator Location</b>	<b>Protocol Study Site Number of Subjects Enrolled (n)</b>	<b>Inspection Date</b>	<b>Classification*</b>
Andrew J. Cutler, M.D. Florida Clinical Research Center, LLC 8043 Cooper Creek Blvd., Suite 107 Bradenton, FL 34201	NWP09-ADHD-300  Site # 03 N = 15	05/13/2015 to 05/15/2015	NAI
Matthew N. Brams, M.D. Bayou City Research, Ltd. 550 Westcott, Suite 310 Houston, Texas 77007	NWP09-ADHD-300  Site # 04 N = 14	4/29/2015, 4/30/2015, 5/1/2015, and 5/4/2015	NAI
John M. Giblin, M.D. Clinical Study Centers, LLC 11215 Hermitage Road, Suites 200 and 201 Little Rock, AR 72211	NWP09-ADHD-300  Site # 07 N = 13	The inspection was cancelled	

**\*Key to Classifications**

NAI = No deviation from regulations. Data acceptable

VAI = Deviation(s) from regulations. Data acceptable

OAI = Significant deviations from regulations. Data unreliable

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;  
EIR has not been received from the field and complete review of EIR is pending.**CLINICAL INVESTIGATOR (CI)**1. **Andrew J. Cutler, M.D.**

8043 Cooper Creek Blvd., Suite 107, Bradenton, FL 34201

- a. **What was inspected:** At this site, 17 subjects were screened, 15 were enrolled, and 14 completed the study. A complete review of all 17 subject records was conducted.
- b. **General observations/commentary:** No significant regulatory violations were noted, and no Form FDA 483 (List of Inspectional Observations) was issued. All primary and key secondary efficacy data were verifiable. There was no evidence of under-reporting of AEs.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and data generated by this site appear acceptable in support of the respective indication.

2. **Matthew N. Brams, M.D.**  
550 Westcott, Suite 310, Houston, Texas 77007
  - a. **What was inspected:** At this site, 14 subjects were screened, 14 were enrolled, and 14 completed the study. An audit of study records, patient histories, lab results, concomitant medications, sponsor correspondence, progress notes, and 100% of the informed consent forms was conducted.
  - b. **General observations/commentary:** It was verified that the subjects enrolled who participated in the clinical study met the inclusion criteria/exclusion criteria prior to randomization. All primary and the key secondary efficacy data were verifiable. There was no evidence of under-reporting of AEs. No significant regulatory violations were noted and no Form FDA 483 was issued.
  - c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.
3. **John M. Giblin, M.D.**  
No valid address was found

The FDA Dallas District informed OSI on 6/17/2015 that the FDA investigator discovered that the contact information provided by the sponsor for Dr. John Giblin was invalid when the investigator attempted to pre-announce the inspection. In addition, the Dallas District examined the FY14 BIMO assignment list and found that the assignment for Dr. Giblin in 2014 (FACTS #8765555) was cancelled because neither the Dallas District nor the sponsor could find Dr. Giblin.

OSI review team requested Pfizer Inc., the sponsor of NDA 207960, for the contact information of Dr. John Giblin and the location of the study records on 06/18/2015. The sponsor responded on 06/29/2015 that they could not locate the study records but were able to find the contact information in the website of Arkansas State Medical Board. OSI reviewer called the phone number provided and left a voice message for Dr. Giblin but no response received to date.

OSI requested the sponsor, Pfizer Inc., on 10/27/2015 to address how they determined that the data from Dr. Giblin's site is valid for submission of NDA 207960 (Protocol NWP09-ADHD-300), since the investigator and his records still cannot be located for inspectional verification. Pfizer responded on 11/2/2015. In the response, the sponsor stated that they had regular contact with Dr. Giblin and his study staff (a.k.a. Clinical Study Centers, LLC) during the conduct of the Study Protocol NWP09-ADHD-300 (the study initiation date was 07/02/2012 and the study completion date was 10/27/2012). In the response, the sponsor also provided the evidence of adequate monitoring of the clinical trial conducted in the site of Dr. Giblin. They concluded that the clinical trials conducted at Dr. Giblin's site were conducted in accordance with GCPs and other clinical study conduct guidelines and the study protocol.

OSI cancelled the inspection of Dr. Giblin's site based on the fact that Dr. Giblin and the study records cannot be located. DPP agreed with the cancellation and did not propose another site to be inspected.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigator sites were inspected in support of this NDA and no significant regulatory violations were noted at these sites. Since the records for Dr. Giblin could not be located for inspection, OSI cannot confirm that the data from this site are reliable.

Based on results of these inspections, it appears that the data submitted by the Applicant in support of the requested indication are acceptable and the studies appear to have been conducted adequately.

*{See appended electronic signature page}*

Jenn W. Sellers, M.D., Ph.D., F.A.A.P.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

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Kassa Ayalew, M.D., M.P.H.  
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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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JENN W SELLERS  
11/05/2015

SUSAN D THOMPSON  
11/05/2015

KASSA AYALEW  
11/05/2015

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**MEMORANDUM**  
**REVIEW OF REVISED LABELS**

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:** November 5, 2015  
**Requesting Office or Division:** Division of Psychiatry Products (DPP)  
**Application Type and Number:** NDA 207960  
**Product Name and Strength:** QuilliChew ER (Methylphenidate HCl) Extended-release  
Chewable Tablets  
20 mg, 30 mg and 40 mg  
**Submission Date:** September 9, 2015  
**Applicant/Sponsor Name:** Pfizer Inc.  
**OSE RCM #:** 2015-892-1  
**DMEPA Primary Reviewer:** Loretta Holmes, BSN, PharmD  
**DMEPA Team Leader:** Danielle Harris, PharmD, BCPS

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**1 PURPOSE OF MEMO**

The Division of Psychiatry Products (DPP) requested that we review the revised container labels for QuilliChew ER (Appendix A) to determine if they are 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 are unacceptable from a medication error perspective because the Medication Guide (MG) statement was not revised according to our recommendation.

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<sup>1</sup> Holmes L. Label and Labeling Review for Methylphenidate HCL Extended-release Chewable Tables (NDA 207960). 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); 2015 JUL 14. 5 p. OSE RCM No.: 2015-892.

Additionally, the recently proposed name “QuilliChew ER” was found conditionally acceptable for this product and is not accurately reflected on the container labels.

### 3 RECOMMENDATIONS FOR PFIZER INC.

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

#### A. All Container Labels

1. As proposed, the Medication Guide (MG) statement does not state **how** the MGs are provided [see 21 CFR 208.24(d)]. Please state how the MGs are provided (e.g., accompanying, enclosed, etc.).
2. Replace the name “(b) (4)” with the conditionally approved proprietary name, “QuilliChew ER”.
3. We note that the words (b) (4) appear in the lower right corner of the container labels. We find this misleading as it is inconsistent with the conditionally approved proprietary name, QuilliChew ER. Additionally, as presented, it only contains a portion of the approved proprietary name. It is unclear what the intent is for including this statement on the labels. To minimize the potential for confusion, remove the words (b) (4), or revise the statement to accurately reflect the full proprietary name, “QuilliChew ER”.

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

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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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LORETTA HOLMES  
11/05/2015

DANIELLE M HARRIS  
11/05/2015



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

### **Division of Pediatric and Maternal Health Memorandum**

**Date:** October 19, 2015      **Date consulted:** February 23, 2015

**From:** Miriam Dinatale, D.O., Medical Officer, Maternal Health  
Division of Pediatric and Maternal Health

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

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

**To:** Division of Psychiatry Products (DPP)

**Drug:** Methylphenidate Hydrochloride Extended-Release Chewable Tablets

**NDA:** 207960

**Applicant:** Pfizer, Inc.

**Subject:** Pregnancy and Lactation Labeling

**Indication:** Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

**Materials  
Reviewed:**

- DPMH consult request dated February 23, 2015, DARRTS Reference ID 3709903
- Sponsor's submitted background package for NDA 207960, Methylphenidate HCl ER
- DPMH consult review of Quillivant (methylphenidate HCl) Extended-Release Powder for Oral Suspension-NDA 202100 Upasana Bhatnager, M.D. and Erica Radden, M.D. September 20, 2012, DARRTS Reference ID 3192069.
- DPMH consult review of Aptensio XR-NDA 205831. Miriam Dinatale, D.O. March 16, 2015, DARRTS Reference ID 3715876.

- DPMH consult review of [REDACTED] (b) (4)
- Pregnancy and Nursing Mothers subsections of Aptensio XR (NDA 205831) (b) (4) [REDACTED] (methylphenidate) labeling

**Consult Question:**

DPP requests DPMH to “review labeling to ensure that it conforms to the Pregnancy Rule.”

**INTRODUCTION**

The Division of Psychiatry Products (DPP) consulted the Division of Pediatric and Maternal Health (DPMH) on February 23, 2015, to provide input for appropriate labeling of the pregnancy and lactation subsections of Methylphenidate HCL ER labeling to comply with Pregnancy and Lactation Labeling Rule format.

**REGULATORY HISTORY**

Methylphenidate hydrochloride (HCL) extended-release (ER) is central nervous system (CNS) stimulant. On February 4, 2015, Pfizer, Inc. submitted a 505 (b)(2) New Drug Application (NDA 207960) for methylphenidate HCL ER to obtain approval to market methylphenidate HCL ER for the proposed indication of the treatment of patients with Attention-Deficit Hyperactivity Disorder (ADHD). The reference listed drug for this application is the orally administered Methylin (methylphenidate HCl), NDA 21475, and Quillivant XR (methylphenidate HCl ER powder for oral suspension), NDA 202100.

**BACKGROUND**

**ADHD and Pregnancy**

ADHD affects 4.4% of adults in the United States and is associated with an elevated risk of poorer general and mental health, substance abuse, impaired work performance. There have been no studies evaluating the course of ADHD in pregnancy and the postpartum period. While many women with ADHD can stop their medications during pregnancy without adverse effects, for other women, functional impairment may be severe. Some women with ADHD may be at an increased risk of motor vehicle accidents and have severe impairments in occupational, school and work functioning.<sup>1</sup>

It is estimated that 30% of patients continue ADHD medications into adulthood. In an ongoing case-control surveillance study, Slone Epidemiology Center’s Birth Defects Study (BDS), the prevalence of ADHD medication use was analyzed. In this study, 29,540 women were interviewed between 1998 and 2014, and there were 87 reported exposures to an ADHD medication. Although the overall prevalence of use of any ADHD medication was 0.3%, there was a marked increase in the prevalence of use over the period of the study, from 0.2% for women with last menstrual period (LMP) dates in 1997-1998 to 1.3% for women with LMP dates in 2013. The most commonly reported ADHD medication was amphetamine mixed salts (57.5%), followed by methylphenidate (29.9%). Of the 87 women who were exposed to an ADHD medication, all but one used it during the first trimester; 18 continued use into the second trimester, and 11 continued use into the third trimester. In a recent letter to the editor, Louik *et al.*, noted that although the use of ADHD medications in

<sup>1</sup> Freeman, MP. ADHD and pregnancy. *Am J Psychiatry*. 2014; 171 (7): 723-8.

pregnancy is increasing, there is lack of information regarding potential fetal risks in humans.<sup>2</sup>

### **Methylphenidate and Drug Characteristics**

Methylphenidate HCl, which is a type of CNS stimulant, is indicated for the treatment of ADHD in adults and children. Methylphenidate HCl is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of monoamines into the extraneuronal space. Methylphenidate has a molecular weight of 269.77 Daltons, (b) (4).<sup>3</sup>

Common adverse events seen in children and adults who take methylphenidate products, regardless of immediate-release or extended-release formulations, include: decreased appetite, weight loss, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, affect lability, agitation, irritability, dizziness, vertigo, tremor, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis, and pyrexia.

### **Pregnancy and Nursing Mothers Labeling**

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”<sup>4</sup> also known as the Pregnancy and Lactation Labeling Rule (PLLR). 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>5</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation.

## **DISCUSSION**

### **Nonclinical Experience**

The applicant did not perform additional nonclinical studies for methylphenidate HCL ER and relied on literature included in the approved drug, Quillivant XR (methylphenidate), NDA 202100, to satisfy nonclinical requirements.

Overall, oral administration of methylphenidate to pregnant rabbits and rats during organogenesis was associated with an increased incidence of fetal spina bifida in rabbits at a dose 40 times the maximum recommended human dose (MRHD) and an increased incidence of fetal skeletal variations in rats at 7 times the MRHD (Maternal toxicity was seen at this

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<sup>2</sup> Louik et al. Increasing use of ADHD medications in pregnancy. *Pharmacoepidemiology and Drug Safety*. 2015; 24: 218-220.

<sup>3</sup> Applicant proposed methylphenidate HCl ER labeling. Section 12 Clinical Pharmacology.

<sup>4</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>5</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).

dose). A decrease in body weight gain was seen in the offspring of rats treated with methylphenidate throughout pregnancy and lactation at 4 times the MRHD. The reader is referred to the full Pharmacology/Toxicology review by Ikram Elayan, Ph.D.

### **Methylphenidate and Pregnancy**

The applicant performed a search of its post-marketing safety database, clinical database and published literature through July 31, 2015 to identify cases involving methylphenidate use during pregnancy.

Overall, there were 20 pregnancies associated with methylphenidate use that were part of the post-marketing database review. A search of the clinical trials database did not identify any cases involving methylphenidate exposure during pregnancy. The following outcomes were seen:

- Two congenital anomalies (cleft lip and palate and neonatal behavioral syndrome<sup>6</sup>) were reported. The mothers were also taking other medications (citalopram, ferric carboxymaltose, fluoxetine, olanzapine, pantoprazole)
- Four post-marketing cases reporting complications in neonates following exposure to methylphenidate. The following symptoms were seen: apnea, drug withdrawal syndrome, tremor, agitation, bradycardia, feeding disorder, hypertonia, and irritability. The mothers had received other drugs (alprazolam, amoxapine, bromazepam, bromperidol, citalopram, clomipramine, ethyl loflazepate, flunitrazepam, fluvoxamine, paroxetine, venlafaxine) in addition to methylphenidate
- One elective termination (no reason given)
- Two spontaneous abortions (no information regarding fetal malformations was given)
- Two cases of premature birth (There was no further information about fetal outcome)
- Four healthy infants
- Five cases with fetal outcome pending or with no information

#### *Reviewer comments:*

*The Slone Epidemiology Center's Birth Defects Study reviewed above noted that the overall prevalence of ADHD medication use in pregnant woman has increased. However, the applicant noted that only 20 methylphenidate-exposed pregnancies were reported in the post-marketing database, which seems to be a small number of methylphenidate-exposed pregnancies. The applicant's review of the post-marketing database may not have been complete or there may have been underreporting of pregnancies in women taking methylphenidate.*

A review of the published literature was provided by the applicant, and there was one additional study related to methylphenidate and pregnancy that had not previously been reviewed by DPMH.<sup>14,15</sup> The study is described below.

#### Haervig, et al. (2014)

In a retrospective study (Haervig, et al.), the authors looked at ADHD medication use during pregnancy in Denmark from 1999 to 2010. Of the 1,054,494 registered pregnancies, 480

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<sup>6</sup> Neonatal behavioral syndrome: includes tachypnea, cyanosis, tremors, increased muscle tone and feeding disturbances commonly seen in neonates exposed to Selective Serotonin Reuptake Inhibitors *in utero*.



pregnancies were exposed to ADHD medication (methylphenidate (81.88% of patients), atomoxetine (9.38% of patients) and modafinil (8.75% of patients)) at any time from 28 days prior to the first day of the last menstrual period (LMP) until the end of pregnancy. The usage of medications for ADHD during pregnancy increased from 5 to 533 per 100,000 person-years during the period from 2003 to the first quarter of 2010, and the trend was similar in the Danish women of childbearing age. Women using ADHD medication were young, single and nulliparous.

The study showed that exposed pregnancies were more likely to result in elective abortions per maternal requests (odds ratio [OR] = 4.70, 95 % CI: 3.77-5.85) or elective abortions due to special indications (reason not specified) (OR = 2.99, 95 % CI: 1.34-6.67), and miscarriage (OR = 2.07, 95 % CI: 1.51-2.84) compared with unexposed pregnancies. However, these observed effects were not confirmed in the additional case-crossover analysis. Only three pregnancies exposed to ADHD medication resulted in fetal malformation (rate of 0.6%, 95% CI= 0.6%-8.7% compared to a 3.9% rate of fetal malformations among all pregnancies). The authors did not describe what the fetal malformation included and concluded that the use of ADHD medication in pregnancy was associated with different indicators of maternal disadvantage and with an increased risk of induced abortion and miscarriage.<sup>7</sup>

*Reviewer comments:*

*Compared to women who were not exposed to ADHD medications, women who were exposed to ADHD medications had higher rates of induced abortion and miscarriage. However, further analysis of the results with case-crossover analysis did not reproduce the results that the authors had found. The increased rates of induced abortions and miscarriages seen in the study above may not be due to use of ADHD medications, but may be related to other factors, including factors related to socioeconomic status (age, marital status, education, income) or use of other medications. The women who were on ADHD medications were younger, single, had a history of a prior induced abortions, had less schooling, had low income and were more likely to be on anti-anxiety and anti-depressant medications, which makes it difficult to attribute increased rates of induced abortions and miscarriage to taking ADHD medications alone. These socioeconomic factors may have contributed to the increased rates of induced abortions and miscarriages observed in the above study making the results of this study less reliable.*

**Discussion**

Overall, there are limited controlled data on the use of methylphenidate in pregnancy. Studies that have described an increased risk of fetal malformations, prematurity and small-for-gestational age, also have confounders that make it difficult to associate methylphenidate use with these conditions.<sup>8,9</sup> Other studies have not found an increased rate of fetal malformations or spontaneous abortions, but there were not enough methylphenidate-

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<sup>7</sup> Haervig KB, Mortensen LH, Hansen AV, et al. Use of ADHD medication during pregnancy from 1999 to 2010: a Danish register-based study. *Pharmacoepidemiol Drug Saf* 2014; 23(5):526-33.

<sup>8</sup> Bro, et al. Adverse pregnancy outcomes after exposure to methylphenidate or atomoxetine during pregnancy. *Clin Epidemiol*. 2015; 29: 139-47.

<sup>9</sup> Bolea-Alamanac, et al. Methylphenidate use in pregnancy and lactation: a systemic review of evidence. *BJCP*. 2014; 77(1): 96-101.

exposed pregnancies in these studies to allow risk estimates of specific malformations.<sup>10,11,12,13</sup> Therefore, it is premature to conclude that methylphenidate is associated with an increased risk for spontaneous abortions or adverse fetal outcomes. DPMH does not recommend incorporation of the data reviewed above in current labeling. The reader is referred to DPMH reviews on Aptensio XR (b) (4) (methylphenidate) by Miriam Dinatale, DO for further details.<sup>14,15</sup>

### **Methylphenidate and Lactation**

The applicant performed a literature search to evaluate the effects of methylphenidate during lactation. DPMH also performed a search of the Drugs and Lactation Database (LactMed)<sup>16</sup> and Pubmed. Limited evidence indicates that methylphenidate levels in breast milk are low, and there is no evidence of adverse effects on nursing infants. The effects of methylphenidate in breast milk on the neurological development of the infant have not been well studied. The reader is referred to DPMH reviews on Aptensio XR (b) (4) (methylphenidate) by Miriam Dinatale, DO, for a complete review of the published literature related to methylphenidate use during lactation.<sup>17,18</sup>

### The American Academy of Pediatrics Committee on Drugs (2013)

The American Academy of Pediatrics Committee on Drugs 2013 reports that amphetamine exposure in the breastfeeding infant has resulted in cases of infant hypertension, tachycardia and seizures. In animal studies of postnatal exposure, long-term behavioral effects (learning and memory deficits), as well as altered locomotor activity, have been observed. Because current published data are insufficient to determine the long-term effects on infants exposed to stimulants through breast milk, physicians must counsel patients about the potential risks to an infant balanced with the risk of stopping the medication in the mother.<sup>19</sup>

<sup>10</sup> Pottegard, et al. First-Trimester Exposure to Methylphenidate: A Population-Based Cohort Study. The Journal of Clinical Psychiatry. 2014; 75(1): e88-e93.

<sup>11</sup> Dideriksen, et al. First Trimester In Utero Exposure to Methylphenidate. Basic and Clinical Pharmacology & Toxicology. 2013; 112 (2): 73-76.

<sup>12</sup> Wajnberg, et al. Pregnancy outcome after in-utero exposure to methylphenidate: A prospective comparative cohort study. Reproductive Toxicology. 2011; 21: 255-268.

<sup>13</sup> Heinonen OP et al. Birth Defects and Drugs in Pregnancy. Littleton Publishing Sciences Group. 1977. p8-15,345-355.

<sup>14</sup> DPMH consult review of Aptensio XR-NDA 205831. Miriam Dinatale, D.O. March 16, 2015, DARRTS Reference ID 3715876.

<sup>15</sup> DPMH consult review of (b) (4)

<sup>16</sup> <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

<sup>17</sup> DPMH consult review of Aptensio XR-NDA 205831. Miriam Dinatale, D.O. March 16, 2015, DARRTS Reference ID 3715876.

<sup>18</sup> DPMH consult review of (b) (4)

<sup>19</sup> American Academy of Pediatrics: Committee on Drugs. The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on Selected Topics. Pediatrics. 2013; 132 (3): e796-809.

### Medications and Mother's Milk: A Manual of Lactational Pharmacology (2012)

In Hale's Medication and Mother's Milk, Dr. Thomas Hale, a breastfeeding expert, classifies breastfeeding as "probably safe" with maternal use of methylphenidate. Dr. Hale reviewed the same published articles that were reviewed by DPMH in previous consult reviews.<sup>20</sup>

#### **Discussion**

The characteristics of methylphenidate suggest that methylphenidate is present in breast milk. Methylphenidate has low protein-binding of (b) (4) % (medications with protein-binding less than (b) (4) % are more extensively excreted into breastmilk), a low molecular weight of 269.7 Daltons (drugs with molecular weights less than 800 Daltons are more readily transferred to the milk compartment), and a high pH of (b) (4) (a higher pH means that more drug will be present in breast milk than in plasma).<sup>21</sup>

There are insufficient data to recommend that breastfeeding be contraindicated during maternal use of methylphenidate. Although, there have been reports of infant adverse events with exposure to amphetamines, which are also CNS stimulants, there have been no reported adverse events seen in infants of mothers who have taken methylphenidate while breastfeeding. If women choose to breastfeed while taking methylphenidate, they should be aware of potential side effects (agitation, insomnia, anorexia, and reduced weight gain) in their infants.<sup>22</sup>

#### **Methylphenidate and Females and Males of Reproductive Potential**

In animal studies, methylphenidate did not impair fertility in male or female mice at doses up to 8 times the maximum recommended human dose of methylphenidate (160mg/kg/day) in 18-week continuous breeding studies. The reader is referred to the full Pharmacology/Toxicology review by Ikram Elayan, Ph.D. for further details.

The applicant and DPMH performed a literature search evaluating the effects of methylphenidate on females and males of reproductive potential. The applicant did not find any available articles. In a prior review of methylphenidate, DPMH reviewed a case report of idiopathic testicular failure that discussed long-term methylphenidate use and delayed puberty. The reader is referred to the DPMH review on (b) (4) (methylphenidate) by Miriam Dinatale, DO, for further details on this case report. Overall, DPMH included the case report for completeness but noted that the information was not sufficient to conclude a drug-associated risk or to include the information in section 8.3, Females and Males of Reproductive Potential, of labeling.<sup>23</sup>

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<sup>20</sup> Hale, Thomas. Medications and Mother's Milk: A Manual of Lactational Pharmacology, 15<sup>th</sup> edition. Hale Publishing, L.P. 2012

<sup>21</sup> Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94.

<sup>22</sup> Hale, Thomas. Medications and Mothers' Milk: 15<sup>th</sup> edition. Hale Publishing, L.P. 2012

<sup>23</sup> DPMH consult review of (b) (4)

## CONCLUSIONS

Methylphenidate HCl ER has been updated to comply with the PLLR. A review of the literature revealed no new data with methylphenidate use in pregnant or lactating women. DPMH has the following recommendations for Methylphenidate HCl ER labeling:

- **Pregnancy, Section 8.1**

- The “Pregnancy” subsection of methylphenidate HCl ER labeling was formatted in the PLLR format to include: “Risk Summary,” “Clinical Considerations,” and “Data” subsections<sup>24</sup>.

- **Lactation, Section 8.2**

- The “Lactation” subsection of methylphenidate HCl ER labeling was formatted in the PLLR format to include: the “Risk Summary” and “Clinical Considerations” subsections<sup>25</sup>.

## RECOMMENDATIONS

DPMH revised sections 8.1 and 8.2 of Methylphenidate HCl ER labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling. (See Appendix A for the applicant’s proposed pregnancy and lactation labeling.)

## FULL PRESCRIBING INFORMATION

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

##### Risk Summary

Limited published studies report on the use of methylphenidate in pregnant women; however, the data are insufficient to inform any drug-associated risks. No teratogenic effects were observed in embryo-fetal development studies with oral administration of methylphenidate to pregnant rats and rabbits during organogenesis at doses 2 and 11 times, respectively, the maximum recommended human dose (MRHD). However, spina bifida was observed in rabbits at a dose 40 times the MRHD. (b) (4)

[see Data].

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

###### *Fetal/Neonatal adverse reactions*

CNS stimulants, such as TRADE NAME, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the

<sup>24</sup> Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

<sup>25</sup> Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

## Data

### *Animal Data*

In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 40 times the maximum recommended human dose (MRHD) on a mg/m<sup>2</sup> basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m<sup>2</sup> basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the MRHD on a mg/m<sup>2</sup> basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD on a mg/m<sup>2</sup> basis). (b) (4)

[Redacted text block]

## **8.2 Lactation**

### Risk Summary

Limited published literature reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. Long-term neurodevelopmental effects on infants from stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

### Clinical Considerations

Monitor breastfeeding infants for adverse reactions, such as agitation, insomnia, anorexia, and reduced weight gain.

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/s/  
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MIRIAM C DINATALE  
10/19/2015

TAMARA N JOHNSON  
10/19/2015

LYNNE P YAO  
10/26/2015



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

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Food and Drug Administration  
Office of New Drugs, ODE-IV  
Division of Pediatric and Maternal Health  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9855

**MEMORANDUM TO FILE**

**From:** Ethan D. Hausman, MD, Medical Officer  
Division of Pediatric and Maternal Health (DPMH)

**Through:** Hari Cheryl Sachs, MD, Medical Team Leader  
Linda Lewis, MD, Acting Deputy Division Director  
DPMH

**NDA Number:** 207,960

**Sponsor:** Pfizer, Inc.

**Drug:** methylphenidate (proposed trade name: [REDACTED] (b) (4) )

**Dosage form and route of administration:** 20, 30, and 40 mg chewable tablets, oral (PO)

**Proposed Dosing regimen:** 20 to 60 mg/day

**Indication:** Attention Deficit Hyperactivity Disorder (ADHD)

**Division Consult Request:** The Division of Psychiatry Products (DPP) requests both Maternal Health and Pediatric labeling assistance for this original NDA for a methylphenidate product for treatment of ADHD.

## Background

This product (proposed tradename: [REDACTED] (b) (4) ) is a chewable, extended-release methylphenidate hydrochloride medication under development for treatment of attention deficit/hyperactivity disorder (ADHD) in affected patients 6 years and older.

A brief overview of ADHD and approved drug treatments is provided below, followed by a brief summary of the data submitted to support labeling, and the labeling review.

## Disease Background

ADHD is defined by the diagnostic and statistical manual 5<sup>th</sup> edition (DSM-V) of the American Psychiatric Association as a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development.<sup>1</sup> While prevalence figures in the United States population vary, data suggest that ADHD occurs in 3 to 10% of school aged children, 10 to 60% of whom have symptoms as adults (up to 4% of the adult population).<sup>2,3,4</sup>

Treatment includes a combination of behavioral therapy and drug therapy. Approved drug therapies fall into two broad categories: non-stimulant medications (e.g., clonidine, [NDA 22,331] and guanfacine [NDA 22,037]), for patients 6 years and older; atomoxetine [NDA 21,411] for patients 6 years and older) and stimulant medications (methylphenidate- and amphetamine-like products). Most stimulant medications for ADHD treatment are approved for use in patients 6 years and older; however, several products such as mixed amphetamine salts (ANDA 40,422) and two generic dextroamphetamine products (ANDA 203,644 and ANDA 84,051) are approved for patients 3 years and older.

## Clinical Program

This NDA was submitted as a 505(b)(2) application with reliance on four studies performed by the sponsor and upon data sources from entities other than the sponsor including, but not limited to, literature and right of reference to labeling for the reference listed drug [NDA 202,100, Quillivant XR oral suspension].

The sponsor conducted three bioavailability (BA) studies, including a food effects study, in healthy adult volunteers, and a clinical trial of safety and efficacy in 90 pediatric patients, ages 6 to 12 years. The pediatric safety and efficacy study is summarized below.

Pediatric Study: Ninety pediatric patients meeting DSM-IV criteria for ADHD enrolled in a two part, 7-week study. Part 1 was a 6-week open label dose optimization period where patients received 20 mg PO study drug (methylphenidate) in the morning. Based on response, dose of methylphenidate could be titrated up in 10 or 20 mg/day increments to a maximum of 60 mg/day. At the end of Part 1, patients entered a randomized, double-

<sup>1</sup> American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Arlington, VA., American Psychiatric Association, 2013.

<sup>2</sup> Wilens T, Faraone S, Biederman J, Attention-deficit/hyperactivity disorder in adults. JAMA. 2004 Aug 4;292(5):619-23.

<sup>3</sup> Kessler R, Adler L, Barkley R., et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry 2006; 163(4):716-723.

<sup>4</sup> Gentile J, Atig R, Gillig P. Adult ADHD Diagnosis, Differential Diagnosis, and Medication Management. Psychiatry (Edgmont). Aug 2006;3(8):25-30.



blind, placebo-controlled, withdrawal phase. Of 90 patients who enrolled in Part 1, 86 completed Part 1 and enrolled in and completed Part 2. At the end of Part 2, response in drug and placebo-treated patients was compared using standardized tests of class-room behavior.

*Reviewer comment 1: Per discussions with DPP, the differences between the current (DSM-V) and prior (DSM-IV) definitions of ADHD are qualitative in nature<sup>5</sup> and do not invalidate the study design, data quality, or the ability to draw clinical conclusions from the study. Review of safety and efficacy are deferred to DPP and Statistics; however, the overall study design is consistent with recent studies conducted in support of other stimulant medication products for treatment of ADHD [Aptensio XR, NDA 205,831]*

*Reviewer comment 2: Per discussions with the DPP team at the mid-cycle meeting of July 7, 2015, reliance on referenced data with similar products and the three BA studies and the single clinical study for this product would likely be adequate to assess efficacy and safety in patients six years and older. Review of the data is deferred to DPP and other consultant divisions.*

## **Labeling Review**

Except where otherwise noted, this labeling review is based on the labeling version located in SharePoint on June 30, 2015. The labeling is undergoing substantial revisions by multiple consultant disciplines and the comments below were shared with the review team in advance of the labeling meeting of July 15, 2015.

This labeling review is limited to review of the proposed Boxed Warning, sections 1 (Indications and Usage), 2 (Dosage and Administration), 4 (Contraindications), 5 (Warnings and Precautions), and section 8.4 (Pediatric Usage). Sections 8.1 and 8.3 will be addressed in the separate Maternal Health labeling consult.

For each section, the suggested labeling is presented first and is followed by suggested revisions which are noted in ***bold italics***.

Note: The highlights section of labeling has been reviewed and is consistent with the highlights section for other recently approved stimulant medications for treatment of ADHD (Aptensio XR, NDA 205,831; approved April 17, 2015). The reader is directed to final negotiated labeling (pending) for editorial changes which are not described in this review

Note: Sections 6 (Adverse Reactions) and 14 (Clinical Studies) have been reviewed in their entirety and appear generally consistent with other stimulant medication drugs approved for treatment of ADHD. Since sections 6 and 14 are still undergoing review by DPP and other consultant divisions for determination of safety and effectiveness, these two sections are not included in this review.

## **Boxed Warning**

### Proposed

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<sup>5</sup> Highlights of Changes from DSM-IV-TR to DSM-5. American Psychiatric Association. American Psychiatric Publishing, 2013; [<http://www.dsm5.org/Documents/changes%20from%20dsm-iv-tr%20to%20dsm-5.pdf>]; website accessed: October 6, 2015.

“CNS stimulants, including <TRADENAME>, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [see Warning and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)].”

*Reviewer comments: This proposed boxed warning matches the boxed warning for other recently approved stimulant medications intended for treatment of ADHD (e.g., Aptensio XR) and is appropriate.*

### 1. Indication

<TRADENAME> is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

*Reviewer comments: The proposed indication is consistent with the indication for Aptensio XR and is appropriate.*

### 2. Dosage and Administration

*Reviewer comment: This section has undergone substantial revision since initial DPMH comments were provided to DPP. The version that is in SharePoint as of August 25, 2015 reflects prior DPMH suggestions and is presented below without additional edits and is acceptable. Additional revisions, if needed, are deferred to Clinical Pharmacology and DPP.*

#### 2.1 Dos (b) (4)

The recommended starting dose of <TRADENAME> for patients 6 years and above is 20 mg once daily in the morning. The dose may be titrated weekly in increments of 10 mg, 15 mg or 20 mg. The 10 mg and 15 mg doses can each be achieved by breaking in half the functionally scored 20 mg and 30 mg tablets, respectively) (b) (4)

The dose should be individualized according to the needs and responses of the patient. Daily doses above 60 mg have not been studied and are not recommended.

Pharmacological treatment of ADHD may be needed for extended periods. Healthcare providers should periodically re-evaluate the long-term use of <TRADENAME>, and adjust dosage as needed.

*Reviewer comment: During the labeling meeting of October 5, 2015, Clinical Pharmacology and DPP determined that description in the above section is appropriate. DPP and Clinical Pharmacology stated that the sentence (b) (4)*

#### 2.2 Administration Instructions

<TRADENAME> should be orally administered once daily in the morning with or without food. (b) (4)  
[see Clinical Pharmacology (12.3)].

#### 2.3 Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug. <TRADENAME> should be periodically discontinued to assess the child's condition. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

#### 4. Contraindications

*Reviewer comment: The sponsor's original contraindications statements are consistent with known contraindications for stimulant medications drugs for treatment of ADHD and are similar to Aptensio XR labeling. Upon discussion with DPP the following text is suggested for conformance with current labeling guidance,<sup>6</sup> and is acceptable.*

- Hypersensitivity to Methylphenidate or other Components of <TRADENAME>. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other methylphenidate products [see Adverse Reactions (6.2)].
- Concomitant treatment with monoamine oxidase inhibitors (MAOIs), and also within 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (MAOI), because of the risk of hypertensive crisis [see Drug Interactions (7.1)].

#### 5. Warnings and Precautions

*Reviewer comment: This section of labeling has been reviewed in its entirety and is similar to labeling for Aptensio XR and other recently approved stimulant medication drugs for treatment of ADHD. Since DPMH has no substantive comments, the list of Warnings and Precautions is provided below; however the reader is directed to the final negotiated labeling (pending) for the text of the individual Warnings and Precautions.*

- 5.1 Potential for Abuse and Dependence
- 5.2 Serious Cardiovascular Reactions
- 5.3 Blood Pressure and Heart Rate Increases
- 5.4 Psychiatric Adverse Reactions
- 5.5 Priapism
- 5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon
- 5.7 Long-term Suppression of Growth

*Reviewer comment: Pursuant to internal discussions after the labeling meeting of July 25, 2015, DPP and Clinical Pharmacology determined that presence of phenylalanine (PHE) in the formulation necessitated the following new warning for patients with phenylketonuria ((PKU) which appears consistent with labeling for at least some other PHE containing products (e.g., Augmentin ER-600, NDA 50,755; March 16, 2015).*

#### 5.8 Risk in Patients with Phenylketonuria

Phenylalanine can be harmful to patients with phenylketonuria (PKU). <TRADENAME> extended-release chewable tablets contains phenylalanine, a component of aspartame.

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<sup>6</sup> Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format.

Each 20 mg <TRADENAME> extended-release chewable tablet contains (b) (4)  
phenylalanine. (b) (4)

#### 8.4 Pediatric Use

##### Proposed

The safety and effectiveness of <TRADENAME> (b) (4) in pediatric patients (b) (4)

Long-term effectiveness of <TRADENAME> has not established [see *Clinical Pharmacology (12) and Clinical Studies (14)*].

##### Long Term Suppression of Growth

Growth should be monitored during treatment with CNS stimulants, including <TRADENAME>. (b) (4) who are not growing or gaining weight as expected may need to have their treatment interrupted [see *Warnings and Precautions (5.7)*].

##### Juvenile Animal Data

Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 6 times the maximum recommended human dose (MRHD) on a mg/m<sup>2</sup> basis.

In the study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal day 7) and continuing through sexual maturity (postnatal week 10). When these animals were tested as adults (postnatal weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] on a mg/m<sup>2</sup> basis) or greater, and a deficit in the acquisition of a specific learning task was observed in females exposed to the highest dose (12 times the MRHD on a mg/m<sup>2</sup> basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m<sup>2</sup> basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

*Reviewer comment: The description of long-term suppression of growth and animal toxicology are similar to other recently approved stimulant medications for treatment of ADHD; however the following revision is recommended for the introductory section of 8.4 for consistency across the drug class.*

The safety and effectiveness of <TRADENAME> in pediatric patients under six years have not been evaluated.

The safety and effectiveness of <TRADENAME> have been established in pediatric patients ages 6 to 17 years. Use of TRADENAME in these age groups is based on one adequate and well-controlled clinical study in pediatric patients 6 to 12 years old, pharmacokinetic data in adolescents and adults, and safety information from other methylphenidate-containing products

Long-term effectiveness of <TRADENAME> has not established [*see Clinical Pharmacology (12) and Clinical Studies (14)*].

### **Conclusions and Recommendations**

The above recommendations were discussed with the labeling review team at the first labeling meeting July 15, 2015. DPMH will continue to participate in labeling negotiations and the reader is directed to final negotiated labeling which may include changes not reflected in this document.

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/s/  
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ETHAN D HAUSMAN  
10/13/2015

HARI C SACHS  
10/16/2015  
I agree with these recommendations.

LINDA L LEWIS  
10/16/2015

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## **LABELS 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:** July 14, 2015  
**Requesting Office or Division:** Division of Psychiatry Products (DPP)  
**Application Type and Number:** NDA 207960  
**Product Name and Strength:** Methylphenidate HCl Extended-release Chewable Tablets  
20 mg, 30 mg and 40 mg  
**Product Type:** Single Ingredient Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Pfizer Inc.  
**Submission Date:** February 4, 2015  
**OSE RCM #:** 2015-892  
**DMEPA Primary Reviewer:** Loretta Holmes, BSN, PharmD  
**DMEPA Team Leader:** Danielle Harris, PharmD, BCPS

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## 1 REASON FOR REVIEW

The Division of Psychiatry Products asked the Division of Medication Error Prevention and Analysis to review the container labels, prescribing information (PI) and Medication Guide (MG) for Methylphenidate Hydrochloride Extended-release Chewable Tablets (NDA 207960) to determine if they can contribute to confusion that can lead to medication errors. This is a 505(b)(2) application and the referenced drug is Methylin (methylphenidate hydrochloride) Chewable Tablets (NDA 021475).

## 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 (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (NDA)
Other	F (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 labeling (PI and MG) did not identify any areas of vulnerability from a medication error perspective. However, our review of the container labels noted there is an area where the Medication Guide (MG) statement can be clarified by stating how the MGs are provided [in accordance with 21 CFR 208.24(d)].

We note that the product contains phenylalanine and the principal display panel of the labels has a statement regarding the amount of phenylalanine in each tablet. We defer to the Office of Pharmaceutical Quality (OPQ) to evaluate the presentation of the statement.

## 4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed labeling (PI and MG) is acceptable from a medication error perspective. However, we have identified an area of needed improvement in the MG statement on the container labels and provide recommendations for Pfizer in Section 4.1.



#### 4.1 RECOMMENDATIONS FOR PFIZER INC.

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

##### A. All Container Labels

1. The Medication Guide (MG) statement does not state how the MGs are provided [see 21 CFR 208.24(d)]. We recommend the following (or similar) language, dependent upon how the MG is supplied:


Attention Pharmacist: Dispense (b) (4) accompanying Medication Guide (b) (4)

2. Ensure that a sufficient number of MGs are provided with each bottle, given that multiple prescriptions can be filled from a single bottle.

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

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

Table 2 presents relevant product information for Methylphenidate Hydrochloride Extended-release Chewable Tablets that Pfizer submitted on February 4, 2015.

<b>Table 2. Relevant Product Information for Methylphenidate Hydrochloride Extended-release Chewable Tablets</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	Methylphenidate Hydrochloride
<b>Indication</b>	Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
<b>Route of Administration</b>	Oral
<b>Dosage Form</b>	Extended-release Chewable Tablets
<b>Strengths</b>	20 mg, 30 mg and 40 mg
<b>Dose and Frequency</b>	For patients 6 years and above (including adolescents and adults), the recommended starting dose is 20 mg given orally once daily in the morning (b) (4) 
<b>How Supplied</b>	100-count bottles The 20 mg and 30 mg extended-release chewable tablets are scored (bisected) and can be divided into equal halves for dose adjustments.
<b>Storage</b>	Store at 25°C (77°F); excursions permitted from 15°C to 30°C (59°F to 86°F).
<b>Container Closure</b>	Information not available

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/s/  
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LORETTA HOLMES  
07/14/2015

DANIELLE M HARRIS  
07/14/2015

### 505(b)(2) ASSESSMENT

Application Information		
NDA # 207960	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Methylphenidate Dosage Form: Extended-Release Chewable Tablets Strengths: 20 mg, 30 mg and 40 mg		
Applicant: Pfizer Inc.		
Date of Receipt: February 4, 2015		
PDUFA Goal Date: December 4, 2015		Action Goal Date (if different):
RPM: Hiren Patel, PharmD		
Proposed Indication(s): Attention Deficit Hyperactivity Disorder		

### GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

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

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

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

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
<a href="#">NDA 21475 Methylin</a>	<a href="#">Clinical Pharmacology, Clinical, Nonclinical</a>

\*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.](#)

Pfizer conducted a study entitled, “A Three-Way Crossover Relative Bioavailability Study Comparing Methylphenidate HCl Extended-Release Chewable Tablets and METHYLIN Chewable Tablets under Fasting Conditions and Determining the Effect of Food on 40 mg Methylphenidate ER Chewable Tablets.”

**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  NO

*If “NO,” proceed to question #5.*

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

YES  NO

*If “NO”, proceed to question #5.*

*If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

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

YES  NO

<sup>1</sup>For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

**RELIANCE ON LISTED DRUG(S)**

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

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

YES  NO

*If "NO," proceed to question #10.*

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

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Methylin	21475	Yes

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

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

N/A  YES  NO

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

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

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

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

YES  NO

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

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

- b) Approved by the DESI process?

YES  NO

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

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

- c) Described in a final OTC drug monograph?

YES  NO

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

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

d) Discontinued from marketing?

YES  NO

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

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

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

YES  NO

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

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

This application provides for different strengths and dosing regimen.

*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): Daytrana Transdermal patches, Ritalin tablets (generic available), Ritalin LA capsules, Ritalin SR tablets (generic available), Metadate CD capsules, Metadate ER tablets (generic available), Methylin ER tablets (generic available), Methylin Chewable tablets (generic available), (b)(4) Quillivant XR

**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.*
- 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

APPEARS THIS WAY ON ORIGINAL

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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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HIREN PATEL  
12/04/2015

MITCHELL V Mathis  
12/04/2015

## 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 # 207960 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: N/A Established/Proper Name: Methylphenidate HCl Dosage Form: Extended-Release Chewable Tablets Strengths: 20 mg, 30 mg and 40 mg		
Applicant: Pfizer Inc. Agent for Applicant (if applicable):		
Date of Application: 2/4/2015 Date of Receipt: 2/4/2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: December 4, 2014	Action Goal Date (if different):	
Filing Date: April 5, 2015	Date of Filing Meeting: March 19, 2015	
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input checked="" type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Attention Deficit Hyperactivity Disorder		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> <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) <input type="checkbox"/> 351(k)
<b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b>	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <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 <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 111020

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</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> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<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> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If yes, explain in comment column.</b>			X	
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>	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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <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> <input checked="" type="checkbox"/> Yes <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,</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

cover letter, and annotated labeling). <b>If yes</b> , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• 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)].		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• 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)]?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<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>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>Check the Electronic Orange Book at: <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></i>					
<b>If yes</b> , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<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, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
<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? <i>Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm</a></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
<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)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>If yes</b> , # years requested: 3					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					



<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?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<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)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>  <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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b>Format and Content</b>				
<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) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<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> <i>If not, explain (e.g., waiver granted).</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<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, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<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>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <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>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i> <b>March 2, 2015</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b> Does the application trigger PREA?  <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

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<i>(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, is there an agreed Initial Pediatric Study Plan (iPSP)?</b>  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	An agreed to iPSP was not required of Pfizer by DPP for this application.
<b>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</b>  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b><u>BPCA:</u></b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <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?  <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

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

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

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End-of Phase 2 meeting(s)? <b>Date(s):</b> <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> October 2, 2014 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 3/19/2015

**BACKGROUND:**

Pfizer submitted this NDA under section 505(b)(2) of the Act. The referenced drug for this application is Methylin 10 mg Chewable Tablets (NDA 21475). This applicant is seeking approval of an extended-release chewable tablet formulation of methylphenidate hydrochloride. This formulation was developed under IND 111020 and a Pre-NDA meeting was held on October 2, 2014.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Hiren Patel	Y
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)	Lucas Kempf		Y
Division Director/Deputy	Mitchell Mathis		Y
Office Director/Deputy			
Clinical	Reviewer:	Lucas Kempf	Y
	TL:	Christina Burkhart	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Huixia Zhang	Y
	TL:	Hao Zhu	Y
Biostatistics	Reviewer:	George Kordzakhia	Y

	TL:	Peiling Yang	Y



Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ikram Elayan	Y
	TL:	Linda Fossom	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:		
	TL:	David Claffey	Y
Biopharmaceutics	Reviewer:		
	TL:		
Quality Microbiology	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Steven Fong	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Danielle Harris Deborah Myers	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Jenn Sellers	3/23/2015
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees	Ethan Hausman (PMHS)		

**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> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>Pfizer conducted a study entitled, “A Three-Way Crossover Relative Bioavailability Study Comparing Methylphenidate HCl Extended-Release Chewable Tablets and METHYLIN Chewable Tablets under Fasting Conditions and Determining the Effect of Food on 40 mg Methylphenidate ER Chewable Tablets.”</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><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> No comments</p>

<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<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>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <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>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>BIOSTATISTICS</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>IMMUNOGENICITY (protein/peptide products only)</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>New Molecular Entity (NDAs only)</b>	
<ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b><u>Environmental Assessment</u></b>	
<ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>If no, was a complete EA submitted?</b>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>If EA submitted, consulted to EA officer (OPS)?</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
<b><u>Quality Microbiology</u></b>	<input checked="" type="checkbox"/> Not Applicable

<ul style="list-style-type: none"> <li>Was the Microbiology Team consulted for validation of sterilization?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (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>	<input checked="" type="checkbox"/> N/A  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<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>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<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>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<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>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Mitchell Mathis (Division Director)</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter.  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product

	Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" 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 ADRA's completed: September 2014

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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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HIREN PATEL  
04/16/2015



**REGULATORY PROJECT MANAGER  
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW  
OF THE PRESCRIBING INFORMATION**

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

**Application:** NDA 207960

**Application Type:** New NDA

**Name of Drug/Dosage Form:** methylphenidate hydrochloride extended-release chewable tablets

**Applicant:** Pfizer Inc.

**Receipt Date:** February 4, 2015

**Goal Date:** December 4, 2015

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

Pfizer submitted this NDA under section 505(b)(2) of the Act. The referenced drug for this application is Methylin 10 mg Chewable Tablets (NDA 21475). This applicant is seeking approval of an extended-release chewable tablet formulation of methylphenidate hydrochloride. This formulation was developed under IND 111020 and a Pre-NDA meeting was held on October 2, 2014.

### **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 for Prescribing Information (SRPI)" checklist (see the Appendix).

### **3. Conclusions/Recommendations**

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

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 May 1, 2015. The resubmitted PI will be used for further labeling review.

# Selected Requirements of Prescribing Information

## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-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.

## Highlights

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

### 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:**
- NO** 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). A horizontal line must separate the TOC from the FPI.
- Comment:**
- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
- Comment:**
- 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 A for a sample tool illustrating white space in HL.
- Comment:**
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
- Comment:**
- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

## Selected Requirements of Prescribing Information

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

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

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

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

**Comment:**

#### Highlights Limitation Statement

- 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

- N/A** 10. Product title must be **bolded**.

**Comment:**

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

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

**Comment:**

#### Boxed Warning (BW) in Highlights

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

**Comment:**

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

## Selected Requirements of Prescribing Information

### Comment:

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

### Comment:

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

### Comment:

### Recent Major Changes (RMC) in Highlights

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

### Comment:

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

### Comment:

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

### Comment:

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

### Comment:

### Dosage Forms and Strengths in Highlights

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

### Comment:

### Contraindications in Highlights

**YES**

## Selected Requirements of Prescribing Information

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

Comment:

### Adverse Reactions in Highlights

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

Comment:

### Patient Counseling Information Statement in Highlights

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

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

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

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

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

Comment:

### Revision Date in Highlights

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

Comment:

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

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

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

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

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

<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>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<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** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:**

## Selected Requirements of Prescribing Information

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

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

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

*Comment:*

#### BOXED WARNING Section in the FPI

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

*Comment:*

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

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

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

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

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

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

*Comment:*

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

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

*Comment:*

#### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and



## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

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

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

#### RECENT MAJOR CHANGES

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

#### INDICATIONS AND USAGE

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

#### DOSAGE AND ADMINISTRATION

- [text]
- [text]

#### DOSAGE FORMS AND STRENGTHS

[text]

#### CONTRAINDICATIONS

- [text]
- [text]

#### WARNINGS AND PRECAUTIONS

- [text]
- [text]

#### ADVERSE REACTIONS

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

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

#### DRUG INTERACTIONS

- [text]
- [text]

#### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

#### 6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

#### 7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

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

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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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HIREN PATEL  
04/16/2015