

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202100Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 202100	NDA Supplement #:	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: methylphenidate Dosage Form: extended-release powder for oral suspension Strengths: 25 mg/ 5 ml		
Applicant: Nextwave Pharmaceuticals, Inc.		
Date of Receipt: March 30, 2012		
PDUFA Goal Date: September 30, 2012		Action Goal Date (if different):
Proposed Indication(s): Attention Deficit Hyperactivity Disorder in patients aged 6 years and older		

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 or by reliance on published literature. *(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 referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Methylin (methylphenidate HCl) Oral Solution (NDA 21419)	Clinical Pharmacology, Nonclinical Toxicology

*each source of information should be listed on separate rows

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

Relative Bioavailability study (Study S09-0238; RLD: Methylin Oral Solution)
Single-dose PK study in children and adolescent patients with ADHD (Study NWP06-PPK-101)

RELIANCE ON PUBLISHED LITERATURE

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

YES NO

If “NO,” proceed to question #5.

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

YES NO

If “NO,” proceed to question #5.

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

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

YES NO

RELIANCE ON LISTED DRUG(S)

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

- 5) Regardless of whether the applicant has explicitly referenced the 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/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Methylin Oral Solution	NDA 21419	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 Oral Solution

- 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 monograph?

YES NO

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

Name of drug(s) described in a 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 a change in dosage form, from immediate release oral solution to extended-release oral powder for suspension

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 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)).*

***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?
YES NO

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)?
YES NO

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), Concerta extended-release tablets

PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s): 7691880

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): 7691880
- (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): *October 15, 2010*

- (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

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

/s/

SHIN-YE CHANG
09/27/2012

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

Product Title	QUILLIVANT XR (methylphenidate hydrochloride) for extended-release oral suspension, CII
Applicant	NextWave Pharmaceuticals, Incorporated
Application/Supplement Number	202100/1
Type of Application	Original NDA - Resubmission Class 2
Indication(s)	Treatment of Attention Deficit Hyperactivity Disorder
Established Pharmacologic Class ¹	Central Nervous System Stimulant
Office/Division	ODE I/DPP
Division Project Manager	Shin-Ye Chang
Date FDA Received Application	March 30, 2012
Goal Date	September 30, 2012
Date PI Received by SEALD	September 24, 2012
SEALD Review Date	September 24, 2012
SEALD Labeling Reviewer	Debra Beitzell
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

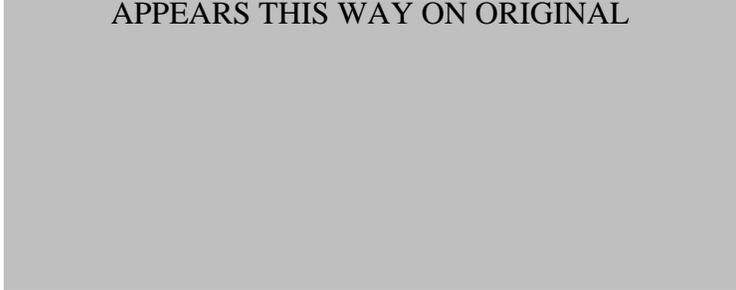
The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

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

Selected Requirements of Prescribing Information

APPEARS THIS WAY ON ORIGINAL



Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

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

Comment:

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

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

➤ **For the Filing Period (for RPMs)**

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

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*

Selected Requirements of Prescribing Information

• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

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

Comment:

Highlights Limitation Statement

NO

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment: Remove white space above Highlights Limitation Statement.

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

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

Comment:

Boxed Warning

YES

12. All text must be **bolded**.

Comment:

YES

13. Must have a centered 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**”).

Comment:

Selected Requirements of Prescribing Information

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

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

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(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, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. 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

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Selected Requirements of Prescribing Information

Comment:

Adverse Reactions

- YES** 25. 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

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

Comment: *Insert a horizontal line in between the TOC and FPI.*

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *Remove “Information on the Medication Guide” from the TOC.*

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Selected Requirements of Prescribing Information

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. 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:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)

Selected Requirements of Prescribing Information

12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. 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 patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see *Warnings and Precautions (5.2)*]”.

Comment:

- N/A** 41. 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

Boxed Warning

- YES** 42. All text is **bolded**.

Comment:

- YES** 43. 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**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is 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 clinical practice.”

Selected Requirements of Prescribing Information

Comment:

- YES** 47. When postmarketing adverse reaction data is 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

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

DEBRA C BEITZELL
09/24/2012

LAURIE B BURKE
09/25/2012

Materials Reviewed:

- Pregnancy, Nursing Mothers, and Pediatrics subsections of methylphenidate labeling.
- 21 CFR 201.57(c)(9)(iv) 8.4 *Pediatric use*
- Pediatric Review Committee minutes on Quillivant (May 18, 2011)
- PREA Waiver Request, Deferral Request/Pediatric Plan and Assessment Template for Quillivant (May 18, 2011)

Consult Question: Please review the Pregnancy, Nursing Mothers, and Pediatric subsections of methylphenidate labeling. DPP plans to use this labeling as a model for future labeling updates of methylphenidate products.

INTRODUCTION

On July 29, 2010, NextWave Pharmaceuticals, Inc. submitted an NDA for Quillivant (methylphenidate HCl) with the proposed indication of treatment for Attention Deficit Hyperactivity Disorder (ADHD) for patients age 6 years and above. During the initial review of the application, the applicant was sent a complete response letter on August 30, 2011 stating the application could not be approved due to deficiencies at one of the manufacturing facilities. The application was resubmitted on March 30, 2012.

The Division of Psychiatry Products (DPP) consulted the Pediatric and Maternal Health Staff (PMHS) to review and update pregnancy, nursing mothers, and pediatric use information for Quillivant labeling. Because stimulant medications such as amphetamines and methylphenidate are considered first line treatment for ADHD and have similar mechanism of action, DPP plans to use standard labeling language for these products. In addition to product specific data, data reviewed previously regarding amphetamine exposures during pregnancy has been incorporated into the standard labeling (see review by Leyla Sahin, MD, March 31, 2008). This dual review provides recommendations from both the Maternal Health team and Pediatric team for standardized labeling for stimulant products and product specific labeling for methylphenidate.

BACKGROUND

Methylphenidate is a central nervous system stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) for adults and children. The mode of therapeutic action for ADHD is not known although it is thought to be mediated through blocking the reuptake of norepinephrine and dopamine.¹ ADHD is a major public health problem that affects approximately 4% of the adult population and 8%² of the pediatric population. Because of the behavioral problems in patients with ADHD, females with

¹ 2010 Methylphenidate labeling

² Summary Health Statistics for US Children: National Health Interview Survey, 2010, Dec 2011;10(250):5 (http://www.cdc.gov/nchs/data/series/sr_10/sr10_247.pdf)

ADHD could potentially be at an increased risk for unplanned pregnancies and exposure to methylphenidate.³

REVIEWED MATERIALS

Applicant's Proposed Labeling (Pregnancy, Nursing Mothers, & Pediatrics)



(b) (4)

³ Resnick, R. Attention Deficit Hyperactivity Disorder in Teens and Adults: They don't outgrow it. J Clin Psychol. 2005;61:529-533.

MATERNAL HEALTH TEAM REVIEW

A Pub Med search was conducted to review published data regarding methylphenidate in pregnancy and lactation. The following sections of this review summarize the limited published studies and case reports.

Methylphenidate and Pregnancy

In retrospective chart review, Debooy⁴ et al. identified 38 women who used intravenous pentazocine and methylphenidate during pregnancy. In addition to using pentazocine and methylphenidate, the majority of women used alcohol and smoked cigarettes. Ten women used other drugs in addition to pentazocine and methylphenidate.

Among 39 infants (including one set of twins) exposed in utero, 21% delivered prematurely (less than 37 weeks at birth), 31% were small for gestational age (weight less than tenth percentile), and 28% had withdrawal symptoms including one infant noted to have seizures due to drug withdrawal. Four infants (10%) had congenital anomalies including one infant with a ventricular septal defect, one with polydactyly, and the set of twins both diagnosed with fetal alcohol syndrome.

The authors had follow-up developmental data from 30 infants. Of these, 22 infants had formal evaluations, and 18% of the formally evaluated infants had below normal scores.

Reviewer comments:

This study was confounded by the lack of a control group and the concomitant exposure from multiple substances that occurred in the majority of the pregnancies. Additionally, the majority of infants were placed in foster care or in the social services system after birth and may have had social circumstances that adversely affected their development.

The National Collaborative Perinatal Project⁵ monitored 50,282 women with medication exposure during pregnancy and collected data on malformations of the offspring. The study reported on 11 women who had first trimester exposure to methylphenidate. For all sympathomimetics included in the study, the crude relative risk for fetal malformations was

⁴ Debooy VD, Seshia MM, Tenenbein M, et al. Intravenous pentazocine and methylphenidate abuse during pregnancy: Maternal lifestyle and infant outcome. Am J Dis Child. 1993;147(10):1062-65.

⁵ Heinonen OP et al. Birth Defects and Drugs in Pregnancy. Littleton Publishing Sciences Group. 1977. p8-15,345-355.

1.27 ($p < 0.001$). The data for methylphenidate was reported with the “other sympathomimetics” drugs, a category that included methylphenidate with sixteen other drugs, and had a crude relative risk of 1.13 (95% CI not provided).

Reviewer comments

The data are difficult to interpret because the methylphenidate exposed patients comprised a small portion (11 of 96 total patients) and a separate analysis of these patients was not performed.

Methylphenidate and Lactation

In 2006, Hackett et al.⁶ reported a case of a lactating patient breastfeeding a six-month old infant who was started on treatment for ADHD with methylphenidate taking 40 mg twice daily for five days of each week. Five weeks after initiation of treatment, the patient took methylphenidate daily for seven days. Subsequently, breast milk and plasma samples were obtained during a twenty-four hour period from the mother at eight time points. The calculated infant dose was 2.3 $\mu\text{g}/\text{kg}/\text{day}$ or 0.2% of the weight-adjusted maternal dose. In a single sample obtained five hours after the first maternal dose, methylphenidate was undetectable in the infant plasma. The authors noted that the mother reported that the infant was feeding, sleeping, and had adequate weight gain.

In another report by Spigset et al.⁷, a lactating patient treated with methylphenidate for narcolepsy was breastfeeding an 11-month old infant. Analysis of breast milk was conducted during a 24-hour period to determine whether methylphenidate transferred into breast milk. The patient took a total of 15 mg daily of methylphenidate (5 mg in the am and 10 mg at noon). Breast milk (first three samples from foremilk and last two from hind milk) and maternal serum concentrations were determined at five time points in the day. In this patient, the infant dose was 0.38 $\mu\text{g}/\text{kg}/\text{day}$ or 0.16% of the maternal weight based dose.

Reviewer comments

These case reports indicate that methylphenidate is present in the breast milk of treated nursing mothers, but the amount of drug transferring into the breast milk cannot be generalized to all nursing mothers. Clear conclusions cannot be drawn from these data because these reports are of individual patients rather than of a series of patients treated similarly. Furthermore, because these patients have older infants that are not fully reliant on breast milk as the primary source of nutrition, the composition of the breast milk changes and the levels of drug in breast milk may not reflect the levels in women who are breastfeeding younger infants. Finally, the reports have scant follow-up data regarding infant well-being after chronic exposure to methylphenidate and are of limited use in evaluation of the overall long-term safety risk.

⁶ Hackett LP, Kristensen JH, Hale TW et al. Methylphenidate and Breastfeeding. The Annals of Pharmacotherapy. 2006;40:1890-91.

⁷ Spigset O, Brede WR, Zahlén K. Excretion of Methylphenidate in Breast Milk. Am J Psychiatry. 2007. 164:2;348.

DISCUSSION

Stimulants, such as methylphenidate and amphetamines, are first line therapy for treatment of ADHD. The Division of Psychiatry Products (DPP) consulted the Pediatric and Maternal Health Staff, both pediatrics and maternal health team, to develop standard labeling for Pregnancy, Nursing Mothers, and Pediatric subsections of labeling for stimulant products. Product specific labeling for Quillivant (methylphenidate HCl) was also requested.

Pregnancy and Nursing Mothers Labeling

Females of reproductive potential are likely to be treated with stimulants for treatment of ADHD and therefore, have exposure during pregnancy. Stimulant medications cause in vasoconstriction in the human placenta.⁸ Despite the length of time that methylphenidate products have been available, the published literature regarding methylphenidate use during pregnancy is limited and is not sufficient to inform labeling. Either the studies are confounded by use of illicit drugs, alcohol, and tobacco or have few patients. However, studies indicate that infants born to amphetamine dependent mothers have an increased risk of low birth weight and neonatal complications.⁹ Although the drug specific data for methylphenidate are limited, MHT recommends that the data available regarding pregnancy outcomes should be used in the stimulant labeling and the current pregnancy category C should be maintained. Additionally, further edits to the animal data sections of labeling will be made after Pharmacology Toxicology review is completed.

MHT recommends contraindicating breastfeeding in lactating patients who are using stimulants. The case reports indicate that methylphenidate, like other stimulants, is present in breast milk and can result in exposures to the infant. However, the individual reports have minimal data regarding infant outcome after exposure to methylphenidate through breast milk. The American Academy of Pediatrics Committee on Drugs 2001 recommends that amphetamines should be contraindicated in nursing mothers because of reports of adverse effects such as irritability and poor sleep patterns in exposed infants. 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.

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow

⁸ Ganapathy V. Drugs of abuse and human placenta. *Life Sciences*.2011;88:926-30.

⁹ Methamphetamine Abuse in Women of Reproductive Age. ACOG Committee Opinion, March 2011, number 279

provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in breastmilk is considered relevant and presented in the label, not the level detected in breastmilk. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

Pediatrics

The Pediatric Research Equity Act (PREA) requires that all NDAs, BLAs, or supplemental applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration contain a pediatric assessment unless a pediatric plan has been submitted and a request for a waiver or deferral has been granted. This application triggers PREA based on the new dosage form. The applicant requested a waiver of pediatric studies in children less than age 6 years citing studies would be “impossible or highly impracticable because assessment measures for determining treatment effect in children less than 6 years old are not well defined.” The applicant also believes the product would not represent a meaningful therapeutic benefit compared to other approved products and would unlikely be used in a substantial number of children less than 6 years old since behavioral approaches are generally recommended initially for children in this age group. Additionally, the applicant asserts that other (non-methylphenidate) products with an FDA-approved indication are available for pharmacological therapy when appropriate. DPP presented a pediatric assessment of a clinical trial of Quillivant in patients age 6 to 12 years and a waiver request to the Pediatric Review Committee (PeRC) on May 18, 2011. DPP proposed a partial waiver in patients less than 6 years old citing the product does not represent a meaningful benefit and is not likely to be used in a substantial number of pediatric patients in this age group because diagnostic criteria and efficacy measures are not well defined for children less than 6 years old. Additionally, DPP believed that pharmaceutical treatment is uncommon in this age group. DPP has concluded that data from studies in patients 6 to 17 years of age fulfilled the pediatric assessment for that age group. Efficacy was established in children 6 to 12 years of age based on a clinical trial, which was used to support the extrapolation of efficacy in adolescents age 13-17 years. Pharmacokinetic data in adolescents using Quillivant and safety data leveraged from other methylphenidate products additionally supported the extrapolation of efficacy in patients 13-17 years of age. The PeRC concurred that the assessment in patients 6 to 17 has been fulfilled and agreed with DPP to grant a waiver of pediatric study requirements in patients 0 to 6 years of age (see PeRC meeting minutes, May 18, 2011).

Pediatric Use Labeling

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. When a pediatric indication is based on extrapolation from adequate and

well-controlled studies in adults (or from data in younger or older pediatric patients) with additional data supporting pediatric use, the following statement or a reasonable alternative that adequately conveys the required information must be included:

“The safety and effectiveness of (*drug name*) have been established in the age groups ___ to ___ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (*drug name*) in these age groups is supported by evidence from adequate and well-controlled studies of (*drug name*) in adults with additional data (*insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population*).”

Efficacy from adequate and well-controlled trials may be extrapolated from one population if the disease process and the effect of the drug are sufficiently similar between the populations. However, while efficacy can be extrapolated, dosing and safety cannot. Thus, extrapolation of efficacy needs to be supplemented with safety information as well as other data such as pediatric pharmacokinetic studies to establish appropriate dose and dosing regimens.

Additionally, data summarized in the above statement must be discussed in more detail in appropriate sections of labeling. Any differences between pediatric and adults responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the product pediatric patients must be cited briefly in the Pediatric Use subsection and in the appropriate section of labeling. If juvenile animal toxicology studies were conducted to support pediatric clinical trials, a concise summary of the data including the human dose exposure equivalents used in the study as well as pertinent study endpoints should be described in the Pediatric Use subsection.

Adequate and well-controlled studies of Quillivant were conducted in patients 6 to 12 years of age. Pediatric information is thus appropriately included throughout the proposed labeling based on the 2-week placebo-controlled trial in children aged 6-12 years with Quillivant. This information appears to be correctly placed for clinician accessibility. However, the applicant has proposed pediatric use language under subsection 8.4 (b)(4) that does not meet the specified regulatory requirements. Section 8.4 should describe the pediatric populations for which safety and effectiveness have been established, and the data used to support that determination when a pediatric indication is supported by studies that allow extrapolation to that pediatric population.

Extrapolation of efficacy from the studies conducted in younger pediatric patients was used to support approval of Quillivant in patients 12 to 17 years of age, along with pharmacokinetic data in adolescents. Furthermore, existing safety information from other methylphenidate-containing products was leveraged to support approval of Quillivant in patients 12 to 17 years of age. Thus, safety and effectiveness have been established for Quillivant in patients 6 to 17 years old. Therefore, labeling will need to reflect that safety and efficacy has been established in this broader age group and describes the studies used to support extrapolation (although the term extrapolation need not be used since practitioners will not likely understand the use of the phrase). Of note, when extrapolation is used, PREA

requires that the medical reviews for the product contain the scientific rationale for extrapolation. Justification for the extrapolation of efficacy in adolescents is supported by the fact that efficacy findings for ADHD in children and adolescents have not differed for methylphenidate products (Ritalin, Metadate, Focalin, Concerta and Daytrana). Furthermore, efficacy in ADHD has also been confirmed by adolescent studies of non-stimulant products such as Strattera (atomoxetine), Intuniv (guanfacine) and Kapvay (clonidine). Additionally, treatment recommendations are similar in children and adolescents.¹⁰

With respect to safety, discussion of the potential for long term growth suppression is included in the Pediatric Use subsection and the Warnings and Precautions section is cross-referenced. This is similar to Vyvanse labeling, (b) (4)

(b) (4) Also, a summary and a more detailed description of the available juvenile animal data for methylphenidate are included in the Pediatric Use subsection. The Pediatric Use statement in the Highlights of Prescribing Information may be deleted since there is no clinically significant difference in response or use of the drug in a pediatric population.

The applicant's proposed labeling in the Warnings and Precautions section includes the following subsections: Serious Cardiovascular Events, Psychiatric Adverse Events (b) (4), (b) (4) Long Term Suppression of Growth. DPP and PMHS agree that potential for new psychotic or manic symptoms, particularly hallucinations; serious cardiovascular reactions and increases in blood pressure and heart rate should be included in labeling in the Warnings and Precautions section per Pediatric Advisory Committee (PAC) recommendations in March 2006. However, DPP has decided to remove (b) (4)

Aggression and seizures, along with suicidality have been among pediatric postmarketing adverse events discussed at several Pediatric Advisory Committee (PAC) meetings. In March 2006, the Pediatric Advisory Committee (PAC) discussed suicidality and aggression along with other psychiatric adverse events noted with ADHD products. Clinical trial data suggested an increased frequency of aggression relative to placebo for some methylphenidate drugs, specifically Daytrana and Ritalin LA. In contrast, clinical data did not confirm a signal for suicidality, except for atomoxetine, which includes a boxed warning for this serious adverse reaction. Moreover, the number completed suicide events is consistent with the background rate of completed suicide based on CDC data. Thus, no changes to the current labeling for suicidality were recommended. The committee recommended that labeling should advise patients or caregivers to contact the physician for unexpected changes

¹⁰ Pliszka S; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007 Jul;46(7):894-921.

in behavior, new aggression or if symptoms of aggression worsen with therapy. The PAC noted that aggression is often a feature of ADHD.

Subsequent pediatric-focused safety reviews for Daytrana, Focalin and Vyvanse also identified postmarketing reports of aggression, seizures and suicidality. Although depression and suicidality may be comorbid conditions with ADHD, the PAC has recommended strengthening labeling language regarding suicidality for these medications. Of note, suicidality was not seen in adverse events for the non-stimulant ADHD medications guanfacine and clonidine. Although the population for which these non-stimulant medications are used to treat ADHD may be similar to that for stimulant medications, the use of non-stimulants is probably less. The reason for this finding is unclear and its existence is concerning.

Although there is no postmarketing safety experience with Quillivant, the longer-term safety is supported by the findings from other methylphenidate products. Therefore, PMHS recommends acknowledging the association of aggression and seizures with other methylphenidate products in the adverse events section of labeling. Additionally, with regards to the noted psychiatric adverse events seen in postmarketing reports with other methylphenidate products, PMHS recommends adding a statement in the adverse events section that suicidality has also been reported.

RECOMMENDATIONS

- The PMHS labeling recommendations are following. See Appendix A for the track changes version and Medication Guide recommendations.
- Please refer to Appendix B for labeling for the stimulant class.

PMHS Labeling Recommendations

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Nursing Mothers: Discontinue drug or discontinue nursing, taking into consideration the importance of the drug to the mother (8.3)

6 ADVERSE REACTIONS

6.2 Postmarketing experience

Postmarketing experience for other methylphenidate products in pediatric patients includes reports of aggression, seizures and suicidality.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate or well-controlled studies with QUILLIVANT in pregnant women. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been reported in mothers dependent on other stimulant products such as amphetamines. Rabbits treated with methylphenidate during organogenesis had an increased incidence of spina bifida (at 40 times the MRHD), and an increase in fetal skeletal variations was seen in treated rats (at 7 times the MRHD). [*Pharm Tox to add Seg 3 data sentence*]. QUILLIVANT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Stimulant medications, such as QUILLIVANT, cause vasoconstriction and thereby decrease placental perfusion. Infants born to amphetamine dependent mothers have an increased risk of premature delivery and low birth weight. Monitor infants for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness.

Animal Data

In studies conducted in rats and rabbits, methylphenidate had teratogenic effects on embryofetal development when administered orally to pregnant rabbits and rats throughout the period of organogenesis at doses of up to 200 and 75 mg/kg/day, respectively. In rabbits, an increased incidence of spina bifida was seen at doses approximately 40 times the maximum recommended human dose given to adolescents, on a mg/m² body surface area basis. In rats, the fetal skeletal variations were seen at the highest dose level (which was 7 times the MRHD on a mg/ m² basis) that were maternally toxic. [*Pharm Tox to edit this section*]

8.3 Nursing Mothers

Methylphenidate is present in human milk. Long-term neurodevelopmental effects on infants from stimulant exposure are unknown. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of QUILLIVANT have been established in pediatric patients ages 6 to 17 years. Use of QUILLIVANT in pediatric patients 6 to 12 years of age is supported by adequate and well-controlled studies [*see Clinical Studies (14)*]. Use in 12 to 17 year olds is supported by the adequate and well-controlled studies of QUILLIVANT in younger pediatric patients and additional pharmacokinetic data in adolescents, along with safety information from other methylphenidate-containing products. The long-term efficacy of methylphenidate in pediatric patients has not been established. Safety and efficacy in pediatric patients below the age of 6 years have not been established.

Long Term Suppression of Growth

Growth should be monitored during treatment with stimulants, including QUILLIVANT. Children who are not growing or gaining weight as expected may need to have their treatment interrupted [*see Warnings and Precautions (5.5)*].

Juvenile Animal Data

[Data from juvenile animal study for methylphenidate will be added here].

17 PATIENT COUNSELING INFORMATION

Pregnancy

Instruct patients to inform their healthcare provider if they become pregnant or intend to become pregnant during treatment with QUILLIVANT. Advise patients of the potential fetal effects from treatment with QUILLIVANT during pregnancy.

Nursing mothers

Advise nursing mothers to discontinue breastfeeding or discontinue QUILLIVANT.

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/s/

UPASANA BHATNAGAR
09/20/2012

ERICA D RADDEN
09/20/2012

MELISSA S TASSINARI
09/24/2012

HARI C SACHS
09/25/2012

the appended labeling does not include

(b) (4)

LYNNE P YAO
09/26/2012

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

PATIENT LABELING REVIEW

Date: **September 10, 2012**

To: Thomas Laughren, MD
Director
Division of Psychiatry Products (DPP)

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

From: Shawna Hutchins, MPH, BSN, RN
Reviewer, Patient Labeling
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling (Medication Guide)

Drug Name (established name): **QUILLIVANT (methylphenidate hydrochloride)**

Dosage Form and Route: **For extended-release oral suspension**

Application Type/Number: **NDA 202100**

Applicant: **Next Wave Pharmaceuticals**

1 INTRODUCTION

On July 29, 2010 Next Wave Pharmaceuticals submitted New Drug Application (NDA 202100) for QUILLIVANT (methylphenidate hydrochloride) for extended-release oral suspension, indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). On August 30, 2011, the Agency issued a Complete Response (CR) letter citing manufacturing deficiencies. On March 30, 2012, Next Wave Pharmaceutical re-submitted NDA 202100 for QUILLIVANT (methylphenidate hydrochloride) for extended-release oral suspension, in response to the CR letter issued by the Agency.

This review is written in response to a request by the Division of Psychiatry Products (DPP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for QUILLIVANT (methylphenidate hydrochloride) for extended-release oral suspension.

2 MATERIAL REVIEWED

- Draft QUILLIVANT (methylphenidate hydrochloride) MG received on March 30, 2012, revised by the review division throughout the review cycle, and sent to DMPP on September 07, 2012.
- Draft prescribing information (PI) received March 30, 2012, revised by the Review Division throughout the current review cycle, and received by DMPP on September, 07, 2012.
- Approved CONCERTA (methylphenidate hydrochloride) comparator labeling approved November 23, 2010.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DMPP 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.

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

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/s/

SHAWNA L HUTCHINS
09/10/2012

MELISSA I HULETT
09/10/2012

LASHAWN M GRIFFITHS
09/10/2012



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

Date: August 16, 2012

To: Thomas Laughren, MD, Director
Division of Psychiatry Products (DPP)

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

From: Stephen Sun, MD, Medical Officer
Controlled Substance Staff

Subject: Methylphenidate HCl Extended-Release Powder for Oral Suspension
NDA-202100
Indication: Attention Deficit and Hyperactivity Disorder
Dosages: 300mg, 600mg, 900mg, 1200mg, 1500mg, 1800mg strength bottles containing powder to be reconstituted with water by a pharmacist administered at 25mg/5mL
Sponsor: NextWave Pharmaceuticals

Materials reviewed: 1. Sun S. FDA / Controlled Substance Staff Memorandum. Methylphenidate HCl Extended-release powder for oral suspension. NDA 202100. April 8, 2011.
2. Sun S., Tolliver J. FDA / Controlled Substance Staff Memorandum. Reference Listed Products and Generic Equivalents: Methylphenidate products and Amphetamine and related products. Multiple NDA. July 19, 2012.

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B. CONCLUSIONS:	2
C. RECOMMENDATIONS (TO BE CONVEYED TO THE SPONSOR VIA DIVISION):	2

I. Summary

A. Background:

This memorandum is a response to a consult request dated May 4, 2012, from the Division of Psychiatry Products (DPP) pertaining to NDA202100 for Methylphenidate HCl ER Powder for Oral Solution under development by NextWave Pharmaceuticals. In

addition to requesting CSS participation in milestone and labeling meetings, the consult requested CSS to provide input to assist in the review of the abuse and dependence information in the Quillivant[®] label.

In response to a prior consult request, an April 8, 2011 memorandum with recommendations of this product was provided. In response to a separate stimulant class labeling consult request, a July 19, 2012 memorandum with recommendations on the labeling language of all stimulants, including methylphenidates, amphetamines, and related products, was provided. This memorandum represents a follow-up memorandum to the consult dated May 4, 2012, with recommendations specific to this formulation that is in addition to the stimulant class labeling.

B. Conclusions:

1. The proposed product is an extended-release powder formulation of methylphenidate for pharmacist-facilitated oral suspension preparation. The Sponsor submits this as a 505(b)(2) application using Methylin Oral Solution as the reference drug product. The product is to be dispensed in bottles with varying strengths (300mg, 600mg, 900mg, 1200mg, 1500mg, and 1800mg) with each bottle to be reconstituted with water by pharmacy staff (per the sponsor's directions) in order to yield a final concentration of 25mg/5mL suspension (5mg/mL).
2. Methylphenidate is a Schedule II substance that requires management and handling according to regulations of the Controlled Substances Act (CSA). Therefore, all respective institutional and legal requirements for schedule II substance management apply to DEA registrants. All patient-level safeguards against misuse, abuse, and diversion are also recommended.
3. The proposed product in a large quantity suspension bottle is distributed as a powder from the manufacturer to the pharmacy, followed by reconstitution by a pharmacist and dispensing to the patient (and/or caregiver) for oral administration. Therefore, specific abuse-related safety concerns apply to both the powder and the liquid form.

C. Recommendations (to be conveyed to the Sponsor via Division):

1. Abuse and dependence sections in the product label should contain the recommended elements as described in the stimulant class label memorandum.
2. A discussion in the quarterly periodic safety reports should provide numbers and trends based upon MSSO's Standardized MedDRA Query (SMQ): "Drug Abuse, Dependence and Withdrawal" while the drug is marketed. As a new formulation of methylphenidate powder and higher-strength liquid as dispensed, abuse-related adverse events associated with this product should be reported as a 15-day important medical event.

3. Sponsor should be actively engaged in the surveillance of the potential known and unknown methods for misuse of this new formulation.
4. Sponsor should highlight all precautions against misuse, abuse, and diversion for any materials seen by patients and healthcare professionals.
5. Sponsor should employ safeguards against unintended distribution of the powdered methylphenidate by the pharmacist to the patient, e.g. Sponsor should highlight instructions to the pharmacists that the drug should be reconstituted only by the pharmacist and not to permit distribution of the product in powder form to allow patient- or caregiver self-reconstitution.

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/s/

STEPHEN W SUN
08/16/2012

MICHAEL KLEIN
08/16/2012



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

Date: July 19, 2012

To: Thomas Laughren, MD, Director
Division of Psychiatry Products (DPP)

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

From: Stephen Sun, M.D., Medical Officer
James Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: **Reference Listed Products and Generic Equivalents:**
Methylphenidate products: Quillivant (NDA 202100), Concerta (NDA 21121), Daytrana (NDA 21514), Focalin (NDA 21278), Focalin XR (NDA 21802), Metadate CD (NDA 21259), Methylin Chewable Tabs (NDA 21475), Methylin Oral Soln (NDA 21419), Ritalin (NDA 10187), Ritalin LA (NDA 21284), Ritalin SR (NDA 18029)
Amphetamine and related products: Adderall (NDA 11522), Adderall XR (NDA 21303), Dexedrine Spansules (NDA 17078); Methamphetamine: Desoxyn (NDA 05378); Lisdexamfetamine: Vyvanse (NDA 21977)
Indication: Attention Deficit and Hyperactivity Disorder
Dosages: Multiple strengths
Sponsor: Nextwave Pharmaceuticals, Shire, Duramed, Ortho McNeil Jansen, Lundbeck, GSK, Novartis, UCB, Mallinckrodt

Materials reviewed: All current methylphenidate and amphetamine reference listed drug product labels.

I. Summary

A. Background

This memorandum is in response to a consult request dated May 14, 2012, from the Division of Psychiatry Products (DPP) pertaining to multiple applications for stimulant products indicated for the treatment of Attention Deficient Hyperactivity Disorder (ADHD). Included are methylphenidate products (Quillivant, Concerta, Daytrana, Focalin, Focalin XR, Metadate CD, Methylin Chewable Tabs, Methylin Oral Soln, Ritalin, Ritalin LA, Ritalin SR) as well as products containing

amphetamine (Adderall, Adderall XR, Dexedrine Spansules), methamphetamine (Desoxyn), and lisdexamfetamine (Vyvanse) products involving different Sponsors (Nextwave, Shire, Duramed, Ortho McNeil Jansen, Lundbeck, GSK, Novartis, UCB, and Mallinckrodt) for the drug class of prescription stimulants. Specifically, the Division requested the assistance of CSS in the review and development of the Boxed Warning and abuse and dependence sections of a model label for the class of ADHD stimulants. In addition the Division is requesting CSS participation in the internal meeting and industry meeting.

B. Conclusions:

1. Methylphenidate, amphetamine, methamphetamine, and lisdexamfetamine are Schedule II substances under the federal Controlled Substances Act (CSA) and are designated under this statute as having a high potential for abuse and dependence development.
2. Current product labels approved over the past several years are varied in defining the risks of abuse of stimulants. A current class label for all prescription stimulant products may help to prevent, detect, and minimize the misuse, abuse, addiction, and diversion of these drugs.

C. Recommendations:

The proposed stimulant class label is as follows:

BOXED WARNING

WARNING: MISUSE, ABUSE, ADDICTION, AND DIVERSION

See full prescribing information for complete boxed warning

BRANDNAME (API) is a Schedule II controlled substance. Stimulants, such as amphetamines and methylphenidates, are subject to misuse, abuse, addiction, and criminal diversion. (9)

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

[Brandname] ([API]) is a Schedule II controlled substance within the federal Controlled Substances Act. Under this statute, [Brandname] is considered to have a high potential for abuse.

9.2 Abuse

[Brandname] can be abused in a manner similar to other stimulants by intentional non-therapeutic use for its rewarding effects as well as other effects (e.g. staying awake).

The repeated use of stimulants may result in addiction characterized by an overwhelming desire to take a drug for reasons other than a therapeutic purpose together with an inability to control, or stop its use despite harmful consequences. Addiction to stimulants may develop following repeated administration by ingestion (mouth), chewing, snorting, smoking, or injection. Often there is an escalation of dose due to development of tolerance (diminished effect to a dose of drug due to repeated drug exposure) to the desired, non-therapeutic effects. Individuals become preoccupied with the repeated administering of the stimulant, experiencing the desired effects of the stimulant, and obtaining additional supplies of the stimulant for continued abuse. This preoccupation continues despite the development of adverse psychological and physical effects, as well as possible adverse legal, societal, and family consequences. Upon termination of stimulant abuse, individuals experience a withdrawal syndrome that may be severe (called the “crash”) depending upon the intensity of stimulant abuse. Termination of stimulant abuse is frequently associated with intense craving to obtain more drug and restart the cycle of stimulant abuse. As a result, termination (abstinence) of stimulant abuse is difficult to achieve.

Individuals displaying addiction to stimulants are in frequent need of supplies of the drug and will utilize various means to obtain the drug. These “drug-seeking” tactics include but are not limited to emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions, reluctance to provide prior medical records or contact information for other treating healthcare providers, and “doctor shopping” (visiting multiple prescribers).

Prior to prescribing stimulants, prescribers should assess the likelihood of misuse, abuse, addiction, and diversion. Patients treated with stimulants require periodic re-evaluation for need of therapy and careful monitoring for signs of abuse, addiction, and overdose.

Careful record-keeping of prescriptions, including quantity, frequency, and renewal requests is strongly advised. Healthcare professionals should contact their State Medical Board, State Board of Pharmacy, or State Control Board for information on how to prevent and detect theft and diversion and comply with security requirements for proper storing, handling, and disposal.

Abuse and addiction are separate and distinct from dependence and tolerance. Addiction may not be accompanied by tolerance and physical dependence in all addicts.

[Human Abuse-Potential Studies]

[Language on the studies do not apply to all products]

[Animal Abuse-Potential Studies]

[Language on the studies do not apply to all products]

9.3 Dependence

Abuse of stimulants may lead to physical dependence characterized as a state of adaptation by the body to the continued exposure to a drug and is manifested by a withdrawal syndrome following discontinuation of drug exposure. Upon termination of stimulant abuse, individuals experience a withdrawal syndrome characterized by such symptoms as unpleasant mood swings,

agitation, motor retardation, fatigue, increased appetite, and hypersomnia or insomnia. Following episodes of intense, high-dose use (called a "binge" or "speed run"), the withdrawal syndrome may be particularly severe (called the "crash") resulting in feelings of lassitude and depression, requiring several days of rest.

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a reduction of one or more of the drug's desired and undesired effects over time. Tolerance development is associated with the abuse of stimulants resulting in escalation of dose.

16 HOW SUPPLIED / STORAGE AND HANDLING

16.3 Disposal

Any remaining, used or unused [Brandname] from a prescription should be disposed by a medicine take-back program. If this is unavailable, the remaining unused product should be disposed in a manner consistent with current laws, regulations, and guidelines to minimize the risk of accidental exposure to an unintended population or criminal theft and diversion.

17 PATIENT COUNSELING INFORMATION

17.1 Controlled Substance Status / Drug Abuse and Dependence

Advise patients and their caregivers of the following [*see Drug Abuse and Dependence (9)*]:

- [Brandname] is a federally controlled substance and it can be abused and lead to addiction and dependence.
- Do not give [Brandname] to anyone else.
- Store [Brandname] in a safe place, preferably locked, to prevent misuse, abuse, and diversion.
- Discard any unused remaining [Brandname] down the toilet to prevent diversion or handled in a consistent manner based on FDA guidelines.

II. Review

A. Chemistry

1. The class of products used to treat attention deficit and hyperactivity disorder includes: stimulants (methylphenidate, dexamethylphenidate and mixed amphetamine salts, dextroamphetamine sulfate, lisdexamfetamine), clonidine, guanfacine, and atomoxetine. This review is a focus on the prescription stimulant class and subclasses of methylphenidate and amphetamine and their respective related compounds.

B. Integrated assessment

1. Review of the Literature

- a. Literature search consisted primarily of US studies from the past 5 years that included separated data for the subclasses of amphetamines and methylphenidates. The limitation of this literature review is that several products, each with distinctive formulations and safety risk profiles, were approved in the past several years and therefore, may not represent the current product formulations. As an example, a large sample study published in 2006 appears useful but study data is gathered from a 2002 conducted study¹. Most manuscripts generalized the misuse and abuse risks to stimulants (or occasionally “prescription stimulants” from the National Survey on Drug Use and Health²) versus other category of products; therefore, subclass comparisons and categorizations were difficult.
- b. In a 2005 survey of college students resulting in 4,580 responses, 75% (204 of 269) of past-year illicit stimulant users were using amphetamine-dextroamphetamine products whereas the remainder 25% (66 of 269) used only methylphenidate. 18% (48 of 269) students reported using both classes of drugs (Teter et al., 2006)³.
- c. (Table 1) In a 2009 review of 8 years of the American Association of Poison Control’s National Poison Data System for the years of 1998-2005 for all cases involving people aged 3 to 19 years, the number of amphetamine prescriptions increased 133-141% from 2.2 million to 5.2 million whereas the call volume increased 476%. In contrast, methylphenidate and related prescriptions increased 52-57% but the call volume decreased by 30%. Explanations for the higher number of calls for amphetamine products and fewer calls for methylphenidate products were not further elaborated.

Table 1: Call Volume of Amphetamine and Methylphenidate Relative to Prescriptions from the American Association of Poison Control Centers’ (AAPCC) National Poison Data System (NPDS)⁴

	1998	2005	Change
Amphetamine and Related			
Prescriptions (3 to 19 y/o)	2.2M	5.2M	133%
Prescriptions (10 to 19 y/o)	1.5M	3.6M	141%
# of poison control center calls (all)	71	409	476%

¹ White BP, Becker-Blease KA, Grace-Bishop K. Stimulant medication use, misuse, and abuse in an undergraduate and graduate student sample. *J Am Coll Health*. 2006 (54): 261-268.

² Kroutil LA, VanBrunt DL, Herman-Stahl MA, et al. Nonmedical use of prescription stimulants in the United States. *Drug Alcohol Dep*. 2006; 84: 135-143.

³ Teter CJ, McCabe SE, LaGrange K, et al. Illicit use of specific prescription stimulants among college students: Prevalence, motives, and routes of administration. *Pharmacotherapy*. 2006. 26(10): 1501-1510.

⁴ Setlik J, Bond GR, Ho M. Adolescent prescription ADHD medication abuse is rising along with prescriptions for these medications. *Ped*. 2009. 124(3): 875-880.

# of poison control center calls (10 to 19 y/o)	48	115	140%
Methylphenidate and Related			
Prescriptions (3 to 19 y/o)	4.3M	6.6M	52%
Prescriptions (10 to 19 y/o)	2.7M	4.3M	57%
# of poison control center calls	246	172	-30%
# of poison control center (10 to 19 y/o) calls	91	41	-55%

2. Product Labels

- a. In this analysis, a review of all approved products listed as the Reference Listed Drug (RLD) for ADHD were identified based upon a search of the FDA’s Orange Book listings as of 10/26/11. ANDAs were not included in this review as they are expected to follow the brand product’s label. Table 2 is a listing of DEA-scheduled products that are approved for the treatment of ADHD and their respective unique label highlights and differences amongst the other labels. Table 3 is a listing of non-scheduled products that are approved for the treatment of ADHD.
- b. In the review, amphetamines and related products generally contained a boxed warning for abuse, whereas the methylphenidates and related products carried the boxed warning for drug dependence. Rationale for separation of the subclasses may be difficult to support.
- c. Several of the reviewed product labels, whether recently approved or not, are formatted to the current Structured Product Labeling (SPL) guidelines.
- d. A few of the reviewed product labels had revision dates for the full prescribing information and the medication guide were not reviewed at the same time and message may or may not differ slightly.
- e. Some of the reviewed product labels had section “15 Reference” removed while others contained template language from the American Psychiatric Association DSM IV criteria.
- f. A few of the reviewed product labels had different updated versions from the NIH “DailyMed” repository and their corporate website.

Table 1: Comparison of the Current Labels of New Drug Applications of methylphenidate, amphetamine, and related-compounds approved for the treatment of attention deficit and hyperactivity disorder

Proprietary	Active (form)	Appl #	Applicant	(Version reviewed) Highlights
Adderall XR	amphetamine, mixed salts (ER capsule)	N021303	Shire	(08/2011) HPI: Boxed warning is about “Potential for Abuse”

				<p><u>FPI</u>: No Section 15</p> <p>(08/2011)</p> <p><u>MG</u>: [No comments]</p>
Concerta	methylphenidate (ER tablet)	N021121	Janssen Pharms	<p>(11/2010)</p> <p><u>HPI</u>: Boxed warning is about “Drug Dependence”</p> <p><u>FPI</u>: Section 15 makes reference to a citation of APA’s DSM IV; Section 9.2 contains Concerta human abuse potential study</p> <p>(11/2010)</p> <p><u>MG</u>: [No comments]</p>
Daytrana	methylphenidate (patch)	N021514	Noven Pharm	<p>(11/2010)</p> <p><u>HPI</u>: No reference to “CII”; Boxed warning is about “Drug Dependence”</p> <p><u>FPI</u>: Section 9.2 and 9.3 contains only a reference link to abuse and dependence, no language; Section 15 makes reference to a citation of APA’s DSM IV; Section 9.2</p> <p>(11/2010)</p> <p><u>MG</u>: CII language is only in the MG</p>
Desoxyn	methamphetamine (tablet)	N005378	Lundbeck	<p>(05/2009)</p> <p><u>FPI</u>: Not in SPL format; Abuse language different from other amphetamine products; no dependence language;</p> <p>(05/2009)</p> <p><u>MG</u>: Boxed language between HPI and MG is different</p>
Dexedrine Spanules	dextroamphetamine (ER capsule)	N017078	Amedra (under licence by GSK)	<p>(12/2010)</p> <p><u>FPI</u>: Available .pdf from website is small and</p>

				unreadable; Not in SPL format; No heading in boxed warning; CII is not highlighted in the dailymed version (12/2010) <u>MG</u> : Available .pdf from website is small and unreadable; Not in SPL format
Focalin	dexamethylphenidate (tablet)	N021278	Novartis	(12/2010 from DailyMed) <u>FPI</u> : Not in SPL format; no reference to CII, no headed boxed warning <u>MG</u> : Boxed warning on drug dependence within the middle of document; CII is highlighted within document
Focalin XR	dexamethylphenidate (ER capsule)	N021802	Novartis	(04/2011) <u>HPI</u> : Boxed warning is about “Drug Dependence”; no reference to numbered section; in SPL format <u>FPI</u> : Section 9.1 heading is “Controlled Substance Class”, Section 9.2 heading is “Abuse, Dependence, Tolerance”, there is no Section 9.3; Section 15 makes reference to a citation of APA’s DSM IV (04/2011) <u>MG</u> : [No comments]
Metadate CD	methylphenidate (ER capsule)	N021259	UCB	(09/2010) <u>FPI</u> : Not in SPL format; Boxed warning on “Drug Dependence” is embedded within the product label; Sections are entitled “Controlled Substance Class” and “Abuse, Dependence, and Tolerance”; no specific language on abuse, dependence,

				and tolerance in the section (06/2009) <u>MG</u> : [No comments]
Metadate ER	methylphenidate (ER tablet)		UCB	(08/2008) <u>FPI</u> : Not in SPL format; Boxed warning on “Drug Dependence” is embedded within the product label; no section on abuse and dependence; no CII identification (10/2008) <u>MG</u> : CII is identified in a boxed warning
Methylin	methylphenidate (oral solution)	N021419	Mallinckrodt	(10/2010) <u>FPI</u> : Not in SPL format; Boxed warning on “Drug Abuse and Dependence” is embedded within the product label; no section on abuse and dependence; no CII identification at the header (10/2010) <u>MG</u> : CII is identified in a boxed warning within the MG
Methylin	methylphenidate (chewable tablet)	N021475	Mallinckrodt	(10/2010) <u>FPI</u> : Not in SPL format; Boxed warning on “Drug Abuse and Dependence” is embedded within the product label; no section on abuse and dependence; no CII identification at the header (10/2010) <u>MG</u> : CII is identified in a boxed warning within the MG
Ritalin; Ritalin-SR	methylphenidate (tablet);	N010187 N018029	Novartis	(12/2010) <u>FPI</u> : Not in SPL format; Boxed

	methylphenidate (ER tablet)			warning on “Drug Dependence” is embedded within the product label; no other section on abuse and dependence <u>MG</u> : [No comments]
Ritalin LA	methylphenidate (ER capsule)	N021284	Novartis	(12/2010) <u>FPI</u> : Not in SPL format; Boxed warning on “Drug Dependence” is embedded within the product label; section called “Abuse and Dependence” is available; no textual information is provided except for specific DEA schedule <u>MG</u> : [No comments]

Note: FPI: Full Prescribing Information; HPI: Highlights of Prescribing Information; MG: Medication Guide

Table 2: Comparison of the Current Labels of New Drug Applications of non-methylphenidate and non-amphetamine products that are approved for the treatment of attention deficit and hyperactivity disorder and are not DEA-scheduled.

Appl #	Proprietary	Active (form)	Applicant	Highlights
N022037	Intuniv	Guanfacine (ER tablet)	Shire	(06/2011) <u>HPI</u> : [No comments] <u>FPI</u> : Section 9.2 and 9.3 is deleted; Section 15 is deleted <u>MG</u> : [No comments]
N022331	Kapvay	clonidine (ER tablet)	Shionogi	(09/2010) <u>HPI</u> : [No comments] <u>FPI</u> : Section 9.2 and 9.3 is deleted; Section 15 is deleted <u>MG</u> : [No comments]
N021411	Strattera	Atomoxetine	Lilly	(08/2011)

				<p><u>HPI</u>: [No comments]</p> <p><u>FPI</u>: Section 9 for Drug Abuse and Dependence contains information for 9.1, 9.2, and 9.3. Section 15 is deleted</p> <p><u>MG</u>: [No comments]</p>
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3. Other Surveillance Data on the Misuse, Abuse, and Diversion of Stimulants

- a. Drug Abuse Warning Network (DAWN).⁵ National Estimates document 4,782 emergency department (ED) visits for methylphenidate (26% of all CNS stimulant ED visits) in 2007. This number is second only to amphetamine substances in the CNS stimulant class: 6,372 ED visits (34.3% of all CNS stimulant ED visits) in 2007. From 2004 to 2007, CNS stimulant ED visits increased by 89%.
- b. According to DEA's recent National Drug Intelligence Report, the street value of methylphenidate was \$5.00 per tablet as identified in 5 states.⁶
- c. Of 1,047 surveyed individuals ≥ 12 year olds reporting nonmedical stimulant use in the National Survey on Drug use and Health (NSDUH), 19% had stimulant dependence⁷
- d. Of 10,904 randomly selected students surveyed from 119 four-year colleges, stimulant misuse was noted as 6.9% lifetime, 4.1% past-year, 2.1% in past-month⁸
- e. Oral administration of abuse was preferred route. Approximately 40% also used intranasal administration in 2 studies.^{9,10}

4. Harmonization of Current Stimulant Class Product Labels

Based on this information, one method to address prescription stimulant drug abuse is by harmonizing the various stimulant product labels that have been approved over the past several years with language on known current risks and methods to prevent, detect, and address misuse, abuse, and diversion.

⁵ SAMHSA. Drug Abuse Warning Network. National estimates of drug-related emergency department visits. 2007. Accessed: Jan 5, 2011. Link: <https://dawninfo.samhsa.gov/files/ED2007/DAWN2k7ED.pdf>.

⁶ DEA. National Drug Intelligence Center. National prescription drug threat assessment. April 2009. Product No. 2009-L0487-001.

⁷ Wu LT, Schlenger WE. Psychostimulant dependence in a community sample. *Subst Use Misuse*. 2003. 38: 221-248.

⁸ McCabe SE, Knight JR, Teter CJ et al. Non-medical use of prescription stimulants among US college students: prevalence and correlates from a national survey. *Addiction*. 2005. 99: 96-106.

⁹ White BP, Becker-Blease KA, Grace-Bishop K. Stimulant medication use, misuse, and abuse in an undergraduate and graduate student sample. *J Am Coll Health*. 2006. 54: 261-68.

¹⁰ Teter CJ, McCabe SE, LaGrange K, et al. Illicit use of specific prescription stimulants among college students: prevalence, motives and routes of administration. *Pharmacotherapy*. 2006. 26: 1501-10.

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/s/

STEPHEN W SUN
07/19/2012

JAMES M TOLLIVER
07/19/2012

MICHAEL KLEIN
07/19/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

PATIENT LABELING REVIEW

Date: May 19, 2011

To: Thomas Laughren, M.D., Director
Division of Psychiatry Products (DPP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)
Melissa Hulett, RN, BSN, MSBA
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

From: Shawna Hutchins, MPH, BSN, RN
Patient Labeling Reviewer
Division of Risk Management (DRISK)

Subject: DRISK Review of Patient Labeling (Medication Guide and Instructions for Use)

Drug Name (established name): QUILLIVANT (methylphenidate hydrochloride)

Dosage Form and Route: For extended-release oral suspension

Application Type/Number: NDA 202100

Applicant: Next Wave Pharmaceuticals

OSE RCM #: 2010-1796

1 INTRODUCTION

This review is written in response to a request by the Division of Psychiatry Products (DPP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for Quillivant (methylphenidate hydrochloride) for extended-release oral suspension.

On July 29, 2010 the applicant submitted New Drug Application (NDA) 202100, indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). This original submission contained a voluntary proposed Risk Evaluation and Mitigation Strategy (REMS). DRISK conferred with DMEPA and a separate DMEPA review of the IFU was completed April 04, 2011.

On Friday, February 25, 2011, FDA published a draft Guidance that addresses when a Medication Guide will be required as part of a REMS. Based on the risks of a drug and public health concerns, FDA has the authority to determine whether a Medication Guide should be required as part of a REMS or should be required as labeling but not part of a REMS.

DPP and DRISK determined that a Medication Guide is required as part of labeling in accordance with 21 CFR part 208 but that the proposed REMS submitted on July 29, 2010 by the Applicant is not necessary for this drug product.

2 MATERIAL REVIEWED

- Draft QUILLIVANT (methylphenidate hydrochloride) Medication Guide (MG) and Instructions for Use (IFU) received on July 29, 2010, revised by the review division throughout the review cycle, and sent to DRISK on May 12, 2011.
- Draft prescribing information (PI) received July 29, 2010, revised by the Review Division throughout the current review cycle, and received by DRISK on May 12, 2011.
- Approved CONCERTA (methylphenidate hydrochloride) comparator labeling approved November 23, 2010.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 11.

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFU is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG and IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG and IFU are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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

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/s/

SHAWNA L HUTCHINS
05/19/2011

LASHAWN M GRIFFITHS
05/19/2011

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: May 17, 2011

To: Sandy Chang
Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Jessica Cleck Derenick, PhD
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC Comments on Quillivant (methylphenidate HCl) Extended-Release Powder for Oral Suspension**
NDA# 202100

DDMAC has reviewed the proposed product labeling (PI) for Quillivant (methylphenidate HCl) extended-release powder for oral suspension submitted for DDMAC review. The following comments, using the proposed PI posted in the Eroom on May 16, 2011, by Sandy Chang, are provided directly on the marked up version of the label attached below.

If you have any questions about DDMAC's comments, please do not hesitate to contact us.

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/s/

JESSICA N CLECK DERENICK
05/17/2011

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

Date: April 14, 2011
Application Type/Number: NDA 202100
To: Thomas Laughren, MD, Director
Division of Psychiatry Products
Through: Zachary Oleszczuk, Pharm.D., Team Leader
Kellie Taylor, Pharm.D., MPH, Associate Director
Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis
From: Yelena Maslov, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis
Subject: Label and Labeling Review
Drug Name(s): Methylphenidate HCl Extended-release Powder for Oral
Suspension 25 mg/5 mL
Applicant/sponsor: Next Wave Pharmaceuticals, Inc.
OSE RCM #: 2010-1854

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1 BACKGROUND

1.1 INTRODUCTION

This review summarizes our evaluation of the container labels, carton and prescribing information labeling, as well as the dosing device (oral syringe) and container closure system for Methylphenidate HCl Extended-release Powder for Oral Suspension, 25 mg/5 mL (NDA 202100). Additionally, on August 25, 2010, the Division of Psychiatry Products requested DMEPA provide answers to specific questions.

1.2 REGULATORY HISTORY

Methylphenidate HCl Extended-release Powder for Oral Suspension 25 mg/5 mL is a subject to 505 (b)(2) application submitted to the FDA on July 29, 2010, that references Methylin (Methylphenidate HCl) Oral Solution (NDA 021419). The Applicant submitted a Proprietary Name Review Request for the name (b) (4) on January 11, 2011.

1.3 PRODUCT INFORMATION

Methylphenidate HCl Extended-release Powder for Oral Suspension 25 mg/5 mL is a central nervous system stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder in patients aged 6 years and older. Methylphenidate HCl Extended Release Powder for Suspension is stable for 120 days after reconstitution. Methylphenidate HCl Extended-release Powder for Oral Suspension should be administered orally once daily in the morning with or without food. For adults, adolescents and children over 6 years of age and older the starting recommended dose is 20 mg once daily. Dosage may be increased by 10 to 20 mg per day at weekly intervals. Daily dosage above 60 mg is not recommended. The product will be supplied in a concentration of 25 mg/5 mL once reconstituted and will be marketed in containers of 300 mg, 600 mg, 900 mg, 1200 mg, 1500 mg, and 1800 mg of methylphenidate powder per container respectively. The product should be stored at room temperatures between 68°F and 77°F (20°C and 25°C).

2 METHODS AND MATERIALS

Since the referenced listed drug Methylin (Methylphenidate HCl) Oral Solution has been marketed since 2002, DMEPA conducted a search for medication errors involving Methylin Oral Solution using FDA Adverse Event Reporting System database. Identification of these errors may be indicative of potential issues with the proposed 505 (b)(2) Methylphenidate HCl Extended-release Powder for Oral Suspension.

Because the proposed Methylphenidate product is an oral powder for suspension, we also considered medication error cases involving other products (i.e., antibiotics) available as oral powders for reconstitution since these risks may apply to this formulation.

Additionally, we reviewed the specific questions posed by the Division to DMEPA and conducted a literature review in order to provide answers to these questions.

The following questions were posed by the Division:

- How common are reconstitution errors in general pharmacy practice for orally administered powder medications?
- What steps can be taken to ensure proper reconstitution and accurate delivery of this orally administered powder product?
- What safety risks are there to pharmacy staff in reconstituting this product (i.e., inhalation of powder while reconstituting?)

Additionally, DMEPA evaluated the proposed labels, labeling, container closure system, and oral syringe for Methylphenidate HCl Extended-release Powder for Oral Suspension using Failure

Mode and Effects Analysis¹ (FMEA), principles of human factors, and lessons learned from the post marketing experience to identify areas that can contribute to medication errors.

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH CRITERIA

The AERS search conducted on December 7, 2011, used the following MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues” along with the active ingredient “Methylphenidate”, the trade name “Methylin”, and the verbatims “Methyli%” and “Methylpheni%” without date limitations.

We eliminated reports not pertaining to medication errors (e.g., adverse events, suicide attempts, use of the expired drugs, drug interactions, and medication errors due to another concomitant drug product) and grouped duplicate reports into cases.

2.2 LITERATURE REVIEW

The literature review^{2,3,4} conducted on December 8, 2011, used the following terms and phrases “oral powder for reconstitution”, “oral powder”, “reconstitution medication errors”, “medication errors with oral powder”, “zithromax powder”, “amoxicillin powder”, “erythromycin powder”, “omnicef powder”, and “rate of medication errors with oral powders”.

In conducting the literature review, DMEPA eliminated reports and articles not pertaining to medication errors occurring with oral medications that require reconstitution prior to the administration. The remaining relevant articles were separated by the type of error and evaluated for the root cause.

2.3 LABELS, LABELING, AND PACKAGING RISK ASSESSMENT

This review focused on Methylphenidate HCl Extended-release Powder for Oral Suspension container labels, carton, prescribing information, and oral syringe labeling submitted to the FDA on February 7, 2011 as well as the container closure system (glass bottles, closure caps, dosing device adapter), and oral syringe submitted to the FDA on March 31, 2011 (See Appendices A, B, and C for container label, carton and dosing device labeling images):

- Container Labels and Carton Labeling: 300 mg per bottle, 600 mg per bottle, 900 mg per bottle, 1200 mg per bottle, 1500 mg pr bottle, and 1800 mg per bottle.
- Oral Syringe: capable of holding 12 mL of suspension
- Amber Glass Bottles with Child Resistant Caps: (b) (4) for holding 300 mg/60 mL, (b) (4) for holding 600 mg/120 mL and 900 mg/180 mL, and size (b) (4) for holding 1200 mg/240 mL, 1500 mg/300 mL, and 1800 mg/360 mL
- Dosing Device Adapter: capable of fitting into every bottle size and syringe tip

¹ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p 275.

² PubMed [Internet]. U.S. National Library of Medicine National Institutes of Health [cited January 18, 2011]. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/>

³ Google [Internet]. [cited January 18, 2010]. Available from <http://www.google.com/>

⁴ Institute of Safe Medication Practices [Internet]. Patient Safety Organization [cited January 18, 2011]. Available from <http://ismp.org/>

3 RESULTS

The following sections describe the results of the DMEPA's medication error searches and labels and labeling risk assessment.

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE CASES

3.1.1 *Methylin Results*

DMEPA retrieved 183 reports related to different formulations of Methylphenidate and Methylin. These reports were mostly related to the adverse events, suicide attempts, use of the expired drugs, drug interactions, and medication errors due to another concomitant drug. Thus, after excluding reports not related to medication errors involving Methylin, no relevant cases remained.

3.1.2 *Tamiflu Powder for Suspension Results*

We identified one AERS case related to Tamiflu Powder for Suspension in a previously conducted AERS search. The case (ISR #6232451-7) reported that Tamiflu was not reconstituted prior to dispensing and the 4 year old child received 1 teaspoonful of the unconstituted powder form instead of liquid oral suspension. Patient outcome was not reported. Although no additional details were provided, this error seems to be related to the labels and labeling as well as practice. The reconstitution instructions are listed on the side panel of the carton labeling among other text; thus, making it difficult to see that the product needs to be reconstituted prior to dispensing. Therefore, we believe an addition of the prominent statement to the carton labeling and container label of Methylphenidate HCl Extended-release Powder for Oral Suspension may help minimize this type of error.

3.2 LITERATURE REVIEW

Two medication error cases were identified in the literature search, one U.S. Pharmacist Journal and one from ISMP Website.

The article⁵ in the U.S. Pharmacist Journal described a case when a patient was dispensed amoxicillin powder for suspension 250 mg/5 mL unconstituted. The patient was administered 9 mL of the powder instead of reconstituted suspension. Thus, the patient received a 9 gram dose instead of 450 mg. The error was described to be related to the practice. However, we believe appropriate labeling that includes prominent and clear presentation of the diluent and the amount of diluent required for reconstitution in mg/mL is important to minimize this type of error.

A safety brief listed on the ISMP website⁶ reports reconstituting Amoxil with external use alcohol. Although no additional details are provided, this error re-iterates the importance of appropriate labeling that clearly presents the name and amount of diluent required.

3.3 LABELS, LABELING, AND PACKAGING RISK ASSESSMENT

The following sections describe the findings of the labels, labeling, and packaging evaluation in detail.

⁵ Grissinger, Mathew and Proulx, Susan. Not a Proper Mix. U.S. Pharmacist Journal [Internet], c 2000-2011; 2008 July 18 [Accessed January 20, 2011]. Available from http://www.uspharmacist.com/content/d/ismj - medication_safety/c/10946/

⁶Institute of Safe Medication Practices. [Internet]; 1999 Apr. 7 [Accessed January 20, 2011]. Available from <http://www.ismp.org/Newsletters/acutecare/archives/Apr99.asp>

3.3.1 Container Closure System and Dosing Device Adapter Risk Assessment

Our evaluation of the container caps and the dosing device adapter found that they are suitable for dosing and administration of this product. The container closure is child resistant; and thus, the entire manufacturer's bottles may be dispensed to a patient with this closure. Additionally, the dosing device adapter fits well on the bottles of every size and is appropriate for this product.

Our evaluation of the glass bottle containers noted that the bottles are appropriate in color and size. The bottles have transparent amber color, which protects Methylphenidate HCl Extended-release Powder for Suspension from light as well as allows healthcare practitioners and consumers to see the product in powder or liquid form through the glass. However, we identified the following areas of improvement that can be made to the bottle containers:

- The bottles use [REDACTED] (b) (4) [REDACTED] which may contribute to wrong strength selection errors.
- There are six different volumes of diluent needed for the different strengths of the product, which may result in the wrong amount of diluent used for reconstitution

3.3.2 Container, Carton, and Prescribing Information Labeling Risk Assessment

Our evaluation of the proposed container labels, carton, and prescribing information labeling identified the following areas of needed improvements in order to minimize the potential for medication errors:

- The prescribing information labeling contains lacks adequate information regarding reconstitution of Methylphenidate HCl Extended-release Powder for Oral Suspension.
- The prescribing information labeling does not contain information in the patients' instructions for use regarding measuring the dose using the oral syringe.
- The labeling does not have Patient Instructions for Use that patients will use to administer Methylphenidate HCl Extended-release Powder for Oral Suspension
- Some of the important information on the container labels and carton labeling such as product's net quantity once reconstituted, reconstitution statement, and storage information are not prominent, which may lead to the information being overlooked.

3.3.3 Dosing Device Risk Assessment

Our evaluation of the dosing device (oral syringe) and its design found that the device is adequate for the use with this product. The syringe contains clearly expressed 1 milliliter graduation marks, which in this case is suitable for a dosing device to help with accurate dosing of this product. Additionally, the volume of the oral syringe (12 mL) is appropriate as well because the highest dose of 60 mg corresponds to the volume of 12 mL. However, we identified the following area of needed improvements in order to minimize the potential for medication errors:

- The oral syringe contains manufacturer's name in place of the product's name and strength.

4 DISCUSSION

We considered all relevant information identified in Section 3 in order to answer the Division's questions regarding Methylphenidate HCl Extended-release Powder for Oral Suspension. The following Sections present the answers to questions in detail.

How common are reconstitution errors in general pharmacy practice for orally administered powder medications?

It is difficult to quantify the amount of medication errors that occur with orally administered powders due to the limitations of spontaneous reporting and the inherent under-reporting of medication errors. However, we have post-marketing evidence that there are several types of errors that may occur. An oral powder may inadvertently be dispensed without being reconstituted, which may result in the overdose evidenced by cases presented in Section 3.1.2 and 3.2.1. Additionally, the incorrect diluent may be added to the oral powder for suspension as presented in Section 3.2.2. Furthermore, the incorrect amount of diluent may be added leading to a final concentration that is less than or greater than the intended strength of the product. This incorrect concentration can lead to inaccurate doses for this product.

For Methylphenidate HCl Extended-release Powder for Oral Suspension, the risk of medication errors that occur with orally administered powders may be higher since this product is the first CII ADHD product that requires reconstitution. If a teaspoonful of the product is administered without being reconstituted, it may cause significant and severe adverse events since the powder is highly concentrated.

Additionally, Methylphenidate HCl Extended-release Powder for Suspension comes in six different strengths that all require a different amount of diluent for reconstitution of this product correctly. Eliminating strengths (i.e., 1200 mg and 1800 mg) that are achievable using other of the proposed strengths (i.e., 2 bottles containing 600 mg equals 1200 mg and 2 bottles containing 900 mg equal 1800 mg) would make the reconstitution of this product less error prone, because there would only be four different amounts of diluents needed for reconstitution of the product.

Furthermore, most reconstituted suspensions require refrigeration. However, this product should be stored at the room temperature, which may cause confusion among healthcare professionals and consumers. It is unknown what may happen to the product if it is refrigerated because the Applicant did not provide that information. However, clearly labeling this product to state that it should be stored at the room temperature may help minimize this risk of wrong storage.

What steps can be taken to ensure proper reconstitution and accurate delivery of this orally administered powder product?

The proposed dosage form of Oral Powder for Suspension of Methylphenidate HCl Extended-release cannot eliminate all medication errors related to the reconstitution and administration of the product. One solution to ensure that a proper amount and type of diluent is used to require the product already be in a solution or develop a novel closure system that is self encapsulated to activate in order to deliver the diluent prior to opening the bottle. However, DMEPA recognizes this may not be feasible at this time (b) (4). Additionally, even if such a system did exist, the resulting suspension would still need to be shaken well to ensure even distribution of the drug product; thus, even the closure system could not mitigate all risks during reconstitution. Appropriate labeling is important to minimize the risk of medication errors during reconstitution step of the dispensing process.

Additionally, this product is five times as concentrated as the reference listed drug, Methylin Oral Solution. Labeling this product as 5 mg/mL only may be misinterpreted as 5 mg/5 mL, which is the same as the reference listed drug. Highlight difference in a concentration will be important to ensure doses are calculated correctly.

To ensure the accurate delivery of Methylphenidate HCl Extended-release Powder for Oral Suspension, the presence of a dosing device is important. In this case, the Applicant appropriately proposed to enclose an oral syringe with each bottle. The proposed oral syringe contains

one milliliter graduation marks, which in this case is a suitable dosing device to help with accurate dosing of the product. However, the applicant has not provided adequate instructions for patients for administration of this product.

Based on a variety of errors seen with other oral powders for suspension that may occur with the reconstitution step of this product, appropriate product labeling is important. Specifically, the strength of the product when reconstituted in milligrams per five milliliters and in milligrams per milliliter, as well as the total drug content in milligrams per milliliters should be presented on the principle display panel to ensure that this information can be easily seen and understood by the practitioners. Additionally, information regarding diluent's name and amount required for reconstitution, as well as the storage of the product should also be prominent on the side panels, since product required different amount of diluent for different strengths and room temperature storage.

What safety risks are there to pharmacy staff in reconstituting this product (i.e., inhalation of powder while reconstituting?)

DMEPA has limited data regarding this issue. The outcome of the physical contact with the powder (whether topical or inhalation) may be related to the safety profile of the product (i.e., adverse reaction); and thus, it may be appropriate for the Applicant to evaluate these safety risks prior to approval.

5 CONCLUSIONS AND RECOMMENDATIONS

The proposed dosage form of powder for suspension of Methylphenidate HCl Extended-release may lead to a number of medication errors related to the reconstitution and administration of the product. Therefore, in order to help minimize the potential for the errors, the labels and labeling should contain prominent and clear information regarding reconstitution instructions, the name and the amount of diluent required, strength of the product when reconstituted expressed in milligrams per milliliter, and the total drug content expressed in milligrams and milliliters. Additionally, clear patient's instructions for use explaining how to correctly administer the product should also be included. Thus, our evaluation of the proposed container labels, carton, prescribing information, and oral syringe labeling noted areas of needed improvements in order to minimize the potential for medication errors. Section 5.1 *Comments to the Division* contains our recommendations regarding prescribing information labeling. Section 5.2 *Comments to the Applicant* contains our recommendations for the container labels, the carton labeling, and dosing device. We request the recommendations in Section 5.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Sandra Griffith at 301-796-2445.

5.1 COMMENTS TO THE DIVISION

A. General Comments for the Container Closure System

There are three different container closure systems that have six different strengths of Methylphenidate HCl Extended-release requiring six different amounts of diluent for product reconstitution. This amount of differences increases the potential for medication errors such as selection errors and using the wrong amount of diluent to reconstitute this product. We recommend, eliminating two container closure systems that contain 1200 mg and 1800 mg of Methylphenidate HCl Extended-release. Two bottles of 600 mg strength can be combined to achieve 1200 mg strength and two bottles of 900 mg can be combined to achieve 1800 mg strength.

Eliminating these two strengths and bottles will help decrease the number of different strengths and amount of diluent to choose from. Additionally, of the remaining four strengths, only the 600 mg strength and 900 mg strength would share the same bottle sizes. Thus, reducing the number of bottles of the same size may help minimize the risk of selecting the wrong strength.

B. Prescribing Information Labeling and Instructions for Use Labeling

1. Include a separate Patient's Instructions for Use, which will include detailed step-by-step instructions in lay-person terms related to the correct administration of the product. We suggest that you include definitions of the product components and illustrations to aid consumer understanding.
2. Include the unit of measurements with each notation of strength throughout the insert labeling. Additionally, use the word 'to' instead of hyphen when referencing a range of values, such as dose range. The hyphen may be misinterpreted as a decimal point. For example, revise the phrase "10-20 mg/day at weekly intervals" to read as "10 mg/day to 20 mg/day at weekly intervals".

C. Highlights of Prescribing Information, *Dosage and Administration*

The presentation of the dosing information in children, adolescents, and adults is repetitive. Additionally, the wording related to weekly titration is different from the *Dosage and Administration* Section in Full Prescribing Information. Thus, revise the dosing information, so it is consistent and not repetitive in the following manner:

(b) (4)

D. Section 2, *Dosage and Administration*

1. The prescribing information labeling does not contain a section for product reconstitution in accordance with CFR 201.57 (c)(3)(iv). This section should include directions for reconstitution including the appropriate diluent, the amount of diluent that should be added to yield the correct product's strength, strength of the final dosage solution, storage conditions, and stability of the drug or the reconstituted product. Revise prescribing information labeling accordingly.
2. The presentation of the dosing information in children, adolescents, and adults is repetitive. Thus, revise the dosing information, so it is consistent and not repetitive in the following manner:

(b) (4)

E. Section 3, *Dosage Forms and Strengths*

The sentence

(b) (4)

Thus, revise this statement to read, "Extended-release Powder for Oral Suspension: 25 mg/5 mL when reconstituted".

F. Section 16, *How Supplied/Storage and Handling*

1. Revise the second statement in this section

(b) (4)

to read "After reconstitution, the product is a light beige to tan viscous

suspension containing 25 mg per 5 mL of methylphenidate hydrochloride” to ensure consistency in strength expression throughout labels and labeling.

2. *How Supplied* Section does not state that the product is supplied in a carton and each carton contains one bottle. Additionally, the Section does not state that the dosing device (oral syringe) and bottle adapter are included in a carton. Thus, ensure that this information is included in this Section and revise accordingly.

G. Section 17.2, *Instructions for Using the Enclosed Dosing Device* Section

Revise the instructions for use to include detailed step-by-step instructions in lay-person terms related to the correct administration of the product. We suggest that you include definitions of the product components and illustrations to aid consumer understanding during counseling.

5.2 COMMENTS TO THE APPLICANT

A. All Container Labels and Carton Labeling

Principle Display Panel

1. Ensure the location and size of ‘CII’ symbol on the label is clear and large enough to afford prompt identification that this product is a controlled substance in accordance with 21 CFR 1302.04.

Additionally, this symbol should appear away from the proprietary name so that it does not get misinterpreted as a part of the proprietary name.

2. Relocate the Medication Guide Statement to the principle display panel, so that the statement appears in a prominent and conspicuous manner in order to comply with 21CFR 208.24(d). Additionally, revise this statement to read “Pharmacist: Dispense the enclosed Medication guide to each patient.”
3. Increase the prominence of the proprietary name by using a single bright-colored font without italics. As currently presented the differently colored letters of the name blend with the background and decrease the readability of the proprietary name.
4. Revise the strength of the product to state the strength in milligrams per 5 milliliters and concentration in parentheses in milligrams per milliliter immediately underneath the strength. Additionally, add the statement that this strength is achieved when the product is reconstituted. You may present the strength and concentration of the product in the following manner:

25 mg/5 mL

(5 mg/ml)

When reconstituted

We recommend this change to emphasize that this product is 5 times as concentrated as the reference listed drug and to ensure that this information can be easily seen and understood by the practitioners.

5. Revise the net quantity statement to state the net quantity in milligrams followed by milliliters when reconstituted [i.e., xxx mg (xxx mL when reconstituted)]. Additionally, place the net quantity away from the strength and concentration of the product such as at the top of the principle display panel.
6. Decrease the prominence of the “Rx Only” statement by unbolding it. As currently presented, it is as prominent as the product’s net quantity.

Side Panel

1. Add “Usual Dosage” statement to the side panel in accordance with 21 CFR 201.55
2. Increase the prominence of the reconstitution statement “Add xxx mL of water for reconstitution” by using bold, bigger font. We recommend this change to help minimize medication errors related to the reconstitution of the product.
3. Increase the prominence of the storage information by using bold font. We recommend this change to help minimize medication errors related to the storage of the product.

B. Carton Labeling

Principle Display Panel

Decrease the prominence of the statement “Keep out of the reach of children” by relocating the statement to the side panel, unbolding it, and using smaller font.

Side Panels

1. Revise all instances of the term (b) (4) to read “oral syringe”. (b) (4)
2. Revise the word (b) (4) to state ‘bottle adapter’ to enhance clarity of the term.
3. Add the sentence “Use only with the oral syringe provided with this product” immediately underneath the bolded sentence “Instructions for Using Enclosed Dosing Device”. We recommend this change to emphasize consumers understanding that only the enclosed oral syringe is appropriate for administration of this product.
4. Revise the sentence (b) (4) to state “insert tip of oral syringe provided with this product into adapter” to emphasize the use of the oral syringe enclosed with this product.
5. Add the statement “Dispense with enclosed oral syringe” to the Pharmacist Information to emphasize that the product must be dispensed with the oral syringe provided by the manufacturer.

D. Dosing Device

Delete the name of the manufacturer and replace it with the proprietary and established names. As currently presented, the name of the manufacturer may be misinterpreted as the product’s proprietary name, which is confusing and misleading and may cause medication errors.

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

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

/s/

YELENA L MASLOV
04/14/2011

ZACHARY A OLESZCZUK
04/14/2011

CAROL A HOLQUIST on behalf of KELLIE A TAYLOR
04/14/2011

CAROL A HOLQUIST
04/14/2011



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

Date: April 8, 2011

To: Thomas Laughren, MD, Director
Division of Psychiatry Products (DPP)

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

From: Stephen Sun, MD, Medical Officer
Controlled Substance Staff

Subject: Methylphenidate HCl Extended-Release Powder for Oral Suspension
NDA-202100
Indication: Attention Deficit and Hyperactivity Disorder
Dosages: 300mg, 600mg, 900mg, 1200mg, 1500mg, 1800mg strength bottles containing powder to be reconstituted with water by a pharmacist administered at 25mg/5mL
Sponsor: NextWave Pharmaceuticals

Materials reviewed: Mid-Cycle Meeting

I. Summary

A. Background

This memorandum is in response to a consult request dated December 15, 2011, from the Division of Psychiatry Products (DPP) pertaining to NDA202100 for Methylphenidate HCl ER Powder for Oral Solution under development by NextWave Pharmaceuticals. In addition to requesting CSS participation in the internal meeting and industry meeting, the consult requested CSS to provide input to the following questions that are relevant:

NDA 202-100 (Methylphenidate HCl Extended-Release Powder for Oral Suspension) was submitted on 29 July 2010, as a 505(b)(2) NDA application with Methylin Oral Solution as the reference drug product. The new drug product is proposed to be shipped to pharmacies in the following bottle strengths: 300mg, 600mg, 900mg, 1200mg, 1500mg, and 1800mg strength bottle. Each bottle is to be reconstituted with water by pharmacy staff (per the sponsor's directions) in order to yield a final concentration of

25mg/5mL suspension (5mg/mL) that is apparently stable for up to 120 days after reconstitution. We would like your input on the following questions:

1. Are there any additional concerns regarding overdose, abuse and diversion of this orally administered powder and reconstituted oral suspension preparation, beyond those that exist for other methylphenidate preparations?
2. We would appreciate any other comments or recommendations.

B. Conclusions:

1. Methylphenidate is a Schedule II substance that requires management and handling according to present regulations or the Controlled Substances Act (CSA). Therefore, all respective institutional and legal requirements for schedule II substance management pertain. All pharmacy-level and patient-level safeguards against misuse, abuse, and diversion are also required.
2. The proposed product in a large quantity suspension bottle is distributed as a powder from the manufacturer to the pharmacy, followed by reconstitution by a pharmacist and dispensing to the patient (and/or caregiver) for oral administration. Therefore, there are specific safety concerns in both the powder and the liquid form.
 - (a) Powder –
 - (i) The powder formulation is likely similar to a crushed solid oral formulation, e.g. tablet.
 - (ii) In the event of attempted abuse by the intranasal or sublingual routes, the effect of powder on nasal mucosa or sublingual contact has not been defined in any clinical venue.
 - (iii) Safeguards to prevent the possibility of the pharmacy directly providing the patient the “powder” formulation to reconstitute at home, after dispensing, have not been described sufficiently.
 - (b) Liquid –
 - (i) Once reconstituted, the ability for the liquid to be easily dehydrated back into powdered form was not described. Once powdered, the risk profile is as previously described.
 - (ii) Present immediate-release formulations are 1 to 2 mg/mL while the proposed extended-release concentration is 5 mg/mL. The high potency of this extended-release liquid has a narrower margin of safety than the presently approved immediate-release formulations. Thus, the operator-dependent step of administering the correct dose is more concerning for safety issues, including those related

to unintentional misuse and abuse. Inaccurate patient or provider dispensing of this formulation could be hazardous to the patient and abuser. Formulation strength differentiation needs to be an essential component of the communication plan.

- (iii) Disposal of existing immediate release liquid formulation should be part of the instructions for safe use. See FDA website at: <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalofMedicines/ucm186187.htm#MEDICINES>
- (iv) The proposed high dosage strength containers are likely to have high street value if diverted.
- (v) Use of an alternative dosing device that does not function as a syringe or have an “incompatible-to-needle” tip would minimize intentional misuse via parenteral route.
- (vi) Misuse of the formulation via parenteral routes has not been examined in any clinical venue; therefore, the effect of (b) (4) that enters the bloodstream directly is unknown.
- (vii) Extraction of methylphenidate from (b) (4) was not assessed by the Sponsor. Other (b) (4) products have shown the feasibility of extraction of the “active” component.

- 3. The proposed high dosage strength containers of 1200mg, 1500mg, and 1800mg quantity containers, as proposed by the Sponsor, are greater than previously approved amounts of immediate-release liquids. There are no federal limits for the quantity of drug allowed to be dispensed from this regard, but states and insurance companies may impose stricter limits and all may vary. As an example, the Utah CSA specifies only a 30-day supply as the maximum quantity of CII to be dispensed at any one time. Prescribers and pharmacists will need to consult the provisions of their individual state CSA’s.

C. Recommendations (to be conveyed to the Sponsor via Division):

- 1. Sponsor should provide additional monitoring of selected postmarketing adverse events in addition to current, mandatory pharmacovigilance requirements. The proposed plan should include maintenance of all adverse events in a centralized safety database with expedited reporting of the following “Events of Interest”. Individual case safety reports (ICSRs) that include these events should be submitted to the Agency as expedited reports, 15-day reports, for one (1) year unless a renewal is stated. These Events of Interest based on the latest MedDRA terminology are:

Specific Preferred Terms:

- Drug administered at inappropriate site
- Drug administration error

- Incorrect dose administered
 - Incorrect route of drug administration
 - Wrong technique in drug usage process
 - Intentional drug misuse
 - Accidental exposure
 - Accidental overdose
 - Intentional overdose
 - Multiple drug overdose
 - Multiple drug overdose accidental
 - Multiple drug overdose intentional
 - Overdose
 - Drug abuser
 - Substance abuser
 - Dependence
 - Drug dependence
 - Drug tolerance
 - Drug tolerance decreased
 - Drug tolerance increased
2. In addition to expedited reporting of the above events, a discussion in the quarterly periodic report should provide numbers and trends based upon MSSO's Standardized MedDRA Query (SMQ): "Drug Abuse, Dependence and Withdrawal" for the entire period the drug is marketed.
 3. Sponsor should also follow and report relevant data from national abuse databases: Drug Abuse Warning Network (DAWN), and the Toxic Exposure Surveillance System (TESS) report prepared by the American Association of Poison Control Centers (AAPCC), currently the National Poison Data System (NPDS), and any additional product-specific databases that are helpful to understand the use in real-world conditions. However, the Office of Surveillance and Epidemiology should be able to provide the final determination on the adequacy of the proposed, post-marketing plan and that of the reporting frequency.
 4. Sponsor should highlight all precautions against misuse, abuse, and diversion for any materials seen by patients and healthcare professionals.
 5. Sponsor should highlight instructions to the pharmacists that the drug should be reconstituted only by the pharmacist and not to permit distribution of the product in powder form to allow patient- or caregiver self-reconstitution.

D. Recommendations to Division:

1. The company should be aware of and monitor for diversion and possible abuse of methylphenidate and provide reports of such cases to the FDA. Labeling should have appropriate warnings to the prescribing physician and the pharmacist should instruct the patient on proper secure storage and handling in the home.
2. Lower thresholds of safety should be considered since the proposed formulation is more potent than currently-approved immediate-release formulations and may affect both the patient and the abuser population.
3. OSE/Division of Risk Management may be consulted for evaluation of a Risk Evaluation and Mitigation Strategy (REMS) for recommending needed risk management safeguards, particularly with healthcare training and patient counseling for this novel formulation of an existing controlled substance.
4. OSE/Division of Medication Error Prevention and Analysis may be consulted to advise on designing and/or implementing fixed risk management systems directly into the product and/or packaging to minimize overdose risk and parenteral injection risk. Product and package safety warnings about the high potency product and dosing directions should be prominently displayed.

II. Review

A. Background

Methylphenidate HCl ER powder is a Schedule II methylphenidate product proposed for attention deficit disorder (ADD) that is manufactured and formulated as a powder and distributed to pharmacies. At the pharmacy, the powder is reconstituted with distilled water by the pharmacist and dispensed to the patient according to the prescription. The containers vary in size depending on the quantity (powder plus water volume) of substance; the concentration of drug remains constant. Medicines are to be dispensed with a syringe-like dosing device for oral ingestion.

B. Integrated abuse potential assessment

1. Intentional Misuse, Abuse, and Diversion of Methylphenidate

Methylphenidate is well-characterized as an abusable stimulant as cited by SAMHSA and DEA and already approved methylphenidate drug products. Therefore, appropriate precautions and handling should be similar to other methylphenidate products in the handling of this product. Some recent relevant statistics include:

- Drug Abuse Warning Network (DAWN).¹ National Estimates document 4,782 emergency department (ED) visits for methylphenidate (26% of all CNS stimulant ED visits) in 2007. This number is second only to amphetamine substances in the CNS stimulant class: 6,372 ED visits (34.3% of all CNS stimulant ED visits) in 2007. From 2004 to 2007, CNS stimulant ED visits increased by 89%.
- According to DEA's recent National Drug Intelligence Report, the street value of methylphenidate was \$5.00 per tablet as identified in 5 states.²
- Of 1,047 surveyed individuals ≥ 12 year olds reporting nonmedical stimulant use in the National Survey on Drug use and Health (NSDUH), 19% had stimulant dependence³
- Of 10,904 randomly selected students surveyed from 119 four-year colleges, stimulant misuse was noted as 6.9% lifetime, 4.1% past-year, 2.1% in past-month⁴
- Oral administration of abuse was preferred route. Approximately 40% also used intranasal administration in 2 studies.^{5,6}

Therefore, methylphenidate has inherent abuse and diversion risks within the indicated population. There are two potential scenarios of misuse, abuse, and diversion based upon this product formulation.

¹ SAMHSA. Drug Abuse Warning Network. National estimates of drug-related emergency department visits. 2007. Accessed: Jan 5, 2011. Link: <https://dawninfo.samhsa.gov/files/ED2007/DAWN2k7ED.pdf>.

² DEA. National Drug Intelligence Center. National prescription drug threat assessment. April 2009. Product No. 2009-L0487-001.

³ Wu LT, Schlenger WE. Psychostimulant dependence in a community sample. *Subst Use Misuse*. 2003. 38: 221-248.

⁴ McCabe SE, Knight JR, Teter CJ et al. Non-medical use of prescription stimulants among US college students: prevalence and correlates from a national survey. *Addiction*. 2005. 99: 96-106.

⁵ White BP, Becker-Blease KA, Grace-Bishop K. Stimulant medication use, misuse, and abuse in an undergraduate and graduate student sample. *J Am Coll Health*. 2006. 54: 261-68.

⁶ Teter CJ, McCabe SE, LaGrange K, et al. Illicit use of specific prescription stimulants among college students: prevalence, motives and routes of administration. *Pharmacotherapy*. 2006. 26: 1501-10.

(a) Powder (pre-reconstitution) Access from manufacturer-to-pharmacy

- (i) Powdered version of methylphenidate would be, at a minimum, similar to crushing currently available solid, oral tablet formulations. Therefore, the general medical risks of orally ingested stimulant abuse are expected to be similar.
- (ii) The effect on nasal mucosa from intentional intranasal abuse has not been described or provided.
- (iii) The effect on sublingual mucosa from intentional sublingual abuse has not been described or provided.
- (iv) The dispensing unit quantities, as proposed by the Sponsor, of 1200mg, 1500mg, and 1800mg are larger than presently approved quantities of available liquid-equivalent units (Tables 1 and 2).

(b) Liquid (post-reconstitution) Access from pharmacy-to-patient

- (i) Availability of large volume bottles of methylphenidate and higher potent liquid would raise the concern of accidental overdose and death even with small quantities of liquid, e.g. abuser assuming this is equivalent to an immediate-release concentration of methylphenidate. The specific unit-dosing “syringe” may provide more accuracy and precision in dosing but its critical differences in potency, compared to immediate-release formulations, must be highlighted. Households may have both immediate-release liquid formulations and extended-release formulation at any one time due to titration, conversion, or multiple-patient scenarios. Therefore, disposal of immediate-release formulations or separate handling instructions should be stressed.
- (ii) The ease by which the liquid can easily be dehydrated to powder has not been described. If it can be easily rehydrated, large quantities of drug may be consumed or diverted with a minimal amount of volume. The drug may also be re-processed easily for administration via non-oral routes.
- (iii) Management on the appropriate disposal of unused liquids needs to be clarified. The proposed higher strength containers is likely of higher street value and of greater interest as a source of diversion to an abuser due to its large quantities of potent methylphenidate per diverted dispensed unit. Based upon Table 2, the 1800mg container for a patient who is prescribed at the common daily dose of 20mg per day has 90 days of supply. Although the maximum number of supply days per prescription is not defined by the Controlled Substances Act for Schedule II drugs, currently approved 1000mg Methylin container at a daily dose of 60mg/day has 16.7-day supply and at 20mg/day has a 50-

day supply. Given the concerns of community-based misuse, abuse, and diversion, the 1200mg, 1500mg and 1800mg quantity containers (Table 2), as proposed by the Sponsor exceeds the previously approved amounts, and would not be permissible without justification as it exceeds the supply for a patient who is prescribed 20mg/day of 60, 75, and 90 days, in a single dosing unit, respectively. The Controlled Substances Act does allow refills; multiple prescriptions up to a 90 day supply may be written (21CFR1306.12)⁷.

- (iv) The method for disposal of unused liquids may also be subject to unintended ingestion and overdose by young children and infants in the household. Information noted on the label states “Keep out of the reach of children” but it is unclear on what fixed safeguards to the bottle itself will be child-proof or -resistant. The typical family profile of patients who are prescribed stimulants for ADD is likely to be a younger family with multiple children in the household. Therefore, prevention of access of these medicines to young children is a priority.
- (v) The dosing device appears to be “syringe-like” (Figure 1). The impression of a “syringe” like device is of concern since “orally” administered drugs are typically provided dosing spoons and syringes are typically provided and perceived for injection purposes. Since methylphenidate is a known drug of abuse, a syringe-like device may give a false impression of safety in intentional misuse via injection administration.
- (vi) The parenteral injection of methylphenidate (b)(4) has not been studied; therefore, it is unknown what the effects of (b)(4) administered directly into the bloodstream may be.
- (vii) Extractability of an active ingredient from a (b)(4) containing formulation is achievable. No data was provided to determine if methylphenidate can be extracted from the (b)(4)

2. Unintentional Misuse of Methylphenidate (b)(4)

(a) Need for Product Distinction and User Instruction to Minimize Misuse

- (i) Some 19 different formulations of stimulants presently exist, which include: methylphenidate, dexamethylphenidate, amphetamine, dextroamphetamine, and lisdexamfetamine for the treatment of ADD.

⁷ 21CFR1306.12. Refilling prescriptions; issuance of multiple prescriptions. (a) The refilling of a prescription for a controlled substance listed in Schedule II is prohibited; (b)(1) An individual practitioner may issue multiple prescriptions authorizing the patient to receive a total of up to a 90-day supply of a Schedule II controlled substance provided the following conditions are met; (2) Nothing in this paragraph (b) shall be construed as mandating or encouraging individual practitioners to issue multiple prescriptions or to see their patients only once every 90 days when prescribing Schedule II controlled substances. Rather, individual practitioners must determine on their own, based on sound medical judgment, and in accordance with established medical standards, whether it is appropriate to issue multiple prescriptions and how often to see their patients when doing so.

Importantly, a professionals' knowledge and understanding of the advantages and disadvantages of the different formulations exist, the multitude of options carries a safety concern of prescribing and dispensing confusion and medication errors.

- (ii) Appropriate failure mode and effects analyses should be considered due to two important roles for the appropriate administration of this drug. A trained pharmacist is required to appropriately reconstitute to the labeled concentration for proper drug dispensing. The RLD, Methylin[®] is an immediate-release liquid that is administered TID with a concentration of 1 to 2 mg/mL (depending on package) that is already in liquid form. In contrast, the potency of the proposed product is 2.5x more than currently approved dosage at 5 mg/mL and includes 2x more doses than currently approved packages (Tables 1 and 2). This is likely the first time a pharmacist is involved in the preparation of a methylphenidate liquid
- (iii) The narrow margin of safety or likelihood for dispensing error by patient or caregiver is cause for concern. Both lower potency immediate-release formulations and higher-potency extended-release formulations may be found in the household at one time (particularly during titration or additional patients in the household).
- (iv) Given the narrow margin of safety, a lower threshold of medication error should be considered given its operator-dependent dispensing. Therefore, a usability of the present dosing device would be recommended to ensure individuals are able to dose the accurate amount of substance.

3. **Appropriate Labeling**

- (a) The relevant sections on abuse in the label will need to be tailored to reflect a stronger boxed warning and information on misuse, abuse and diversion given the unique powder and liquid formulations.
- (b) Appropriate failure mode and effect analysis should be considered due to the important role of a trained pharmacist to appropriately reconstitute to the labeled volume and the need for the patient and/or provider to accurately dispense the appropriate dose.

Figure 1. Dosing device.

(b) (4)

Table 1. Approved labeling of immediate-release liquid, e.g. Methylin and maximum daily dosing⁸

Marketed Strength	Product Volume	Quantity	Concentration	Dosing Volume (60mg/day)	# of dosing days (60mg/day)	Dosing Volume (20mg/day)	# of dosing days (20mg/day)
5 mg/5mL	500 mL	500 mg	1 mg/mL	20 mL TID	8.3 days	10 mL BID	25.0 days
10 mg/5mL	500 mL	1000 mg	2 mg/mL	10 mL TID	16.7 days	5 mL BID	50.0 days

Table 2. Based on proposed submission of NextWave's extended-release liquid and maximum daily dosing

Marketed Strength	Product Volume (water)	Quantity	Concentration	Dosing Volume (60mg/day)	# of dosing days (60mg/day)	Dosing Volume (20mg/day)	# of dosing days (20mg/day)
25 mg/5mL	(b) (4)	300 mg	5 mg/mL	12 mL QD	5 days	4 mL QD	15 days
25 mg/5mL	(b) (4)	600 mg	5 mg/mL	12 mL QD	10 days	4 mL QD	30 days
25 mg/5mL	(b) (4)	900 mg	5 mg/mL	12 mL QD	15 days	4 mL QD	45 days
25 mg/5mL	(b) (4)	1200 mg	5 mg/mL	12 mL QD	20 days	4 mL QD	60 days
25 mg/5mL	(b) (4)	1500 mg	5 mg/mL	12 mL QD	25 days	4 mL QD	75 days
25 mg/5mL	(b) (4)	1800 mg	5 mg/mL	12 mL QD	30 days	4 mL QD	90 days

⁸ Methylin Oral Solution (methylphenidate HCl). Prescribing information. Shionogi Pharma (Atlanta, GA). Rev. 10/2010.

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/s/

STEPHEN W SUN
04/08/2011

MICHAEL KLEIN
04/08/2011

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: February 7, 2011

TO: Shin-Ye (Sandy) Chang, Regulatory Project Manager
Mark A. Ritter, MD, Medical Officer
Robert L. Levin, MD, Medical Officer Team Leader
Division of Psychiatry Products, HFD-130

THROUGH: Tejashri Purohit-Sheth, MD
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Anthony Orenca, MD, FACP
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202100

APPLICANT: NextWave Pharmaceuticals, Inc.

DRUG: methylphenidate (b)(4) extended release for oral suspension (NWP06)

THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review

INDICATIONS: Treatment of Attention Deficit Hyperactivity Disorder
in patients six years and older

CONSULTATION REQUEST DATE: October 6, 2010

DIVISION ACTION GOAL DATE: April 25, 2011

PDUFA DATE: May 30, 2011

I. BACKGROUND:

Psychostimulants, including methylphenidate, dextroamphetamine, dextromethylphenidate, and nonstimulants such as atomoxetine are approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). No methylphenidate extended release or sustained release liquid formulations are currently approved for this indication.

The sponsor submitted this application in support of the use of methylphenidate (b) (4) (NWP06) for the treatment of ADHD in patients 6 to 12 years. A single adequate and well-controlled study was submitted in support of the pediatric indication as summarized below.

STUDY Protocol NWP06-100

The study was designed to demonstrate the efficacy and safety of NWP06 in pediatric subjects with ADHD. This study utilized a randomized, double blind, placebo-controlled, crossover design in a laboratory classroom setting to evaluate the effect of NWP06 over placebo on the signs and symptoms of ADHD in children 6 to 12 years. Subjects were randomized to a treatment sequence in this crossover design study. The study consisted of the following phases:

- (1) Screening period. A four week screening period and baseline evaluation were to be conducted.
- (2) Open label phase. Open label treatment with study drug for four weeks for dose optimization, and an additional two weeks double-blind treatment (one week of NWP06 with no dose adjustments and one week of placebo).
- (3) Double blind phase. Double blind study medication was dispensed beginning on the first practice Laboratory Classroom Day (end of Week 4). Daily dosing of double blind study medication was to be at home for the following 6 days, Sunday, Monday, Tuesday, Wednesday, Thursday and Friday. The final dose of the first double blind study medication was to be administered by study staff on the first test laboratory classroom day, Saturday, end of Week 5. All subjects were then to receive a new bottle of double blind medication at the end of the first Laboratory Classroom test day of the opposite treatment. The following day (Sunday), subjects began the second bottle of double blind study medication at home for 6 days, Sunday through Friday. The final dose of the second double blind study medication was administered by study staff on the second Laboratory Classroom test day, Saturday, end of Week 6.

The primary efficacy endpoint was the mean change from pre-dose Swanson, Kotin, Agler, M-Flynn, and Pelham rating scale (SKAMP)-Combined scores at 4 hours post-dose between NWP06 and Placebo. The Phase III study was conducted at 2 study centers, in Las Vegas (NV) and Irvine (CA), with a combined total of 45 enrolled patients and 39 subjects completing the study.

Although not a new molecular entity, field inspections of this new methylphenidate formulation as potential alternative drug therapy in pediatric patients ages six and older with ADHD are important. Verification of data for safety and efficacy, and evaluation of the conduct of this study is important. Two domestic clinical investigator sites were selected for inspection due to high enrollment.

II. RESULTS (by protocol/site):

Name of CI	City, State	Protocol /Study Site	Insp. Date	Final Classification
Ann Childress, MD	Las Vegas, NV	Study Protocol NWP06 -ADD-100 Site #1	January 10-14, 2011	Preliminary: NAI
Sharon B. Wigal, MD	Irvine, CA	Study Protocol NWP06 -ADD-100 Site #2	November 16-18, 2010	NAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Preliminary= The EIR has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATOR

1. Ann Childress, M.D./Site #1

Center for Psychiatry and Behavioral Medicine, Inc.
7351 Prairie Falcon Road Suite 150
Las Vegas, NV 89128

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from January 10-14, 2011.

A total of 32 subjects were screened, 29 subjects were enrolled, and 26 subjects completed the study. There was no under-reporting of adverse events. An audit of 20 screened study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

The study appears to have been conducted adequately at this site. Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. No significant issues were identified during the inspection, and a Form FDA 483, List of Inspectional Observations, was not issued at the end of the inspection.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data in support of clinical efficacy and safety from this clinical site appear acceptable for this specific indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

2. Sharon B. Wigal, M.D./Site #2

Child Development Center
19722 MacArthur Boulevard
University of California
Irvine, CA 92612-2418

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from November 16-18, 2010.

A total of 21 subjects were screened, 16 patients enrolled, 3 subjects discontinued, and 13 subjects completed the study. There was no under-reporting of adverse events noted. An audit of 21 of enrolled study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

The study appears to have been conducted adequately at this site. Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. No clinically significant findings were observed and a Form FDA 483 was not issued at the end of the inspection.

d. Data acceptability/reliability for consideration in the NDA review decision.

The data, in support of clinical efficacy and safety from this clinical site, appear acceptable for this specific indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As part of the PDUFA-related inspections, two clinical investigator sites were inspected in support of this application. The inspection documented general adherence to Good Clinical Practices regulations governing the conduct of clinical investigations, and the data are considered reliable in support of the application.

Note: Observations noted above for Dr. Childress' clinical site are based on the Form FDA 483 or preliminary communications from field investigator, an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

ANTHONY J ORENCIA
02/09/2011

TEJASHRI S PUROHIT-SHETH
02/09/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 202100 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: N/A (sponsor plans to submit NOV 2010) Established/Proper Name: methylphenidate HCl extended-release Dosage Form: powder for suspension Strengths: 25 mg/ 5 ml		
Applicant: NextWave Pharmaceuticals, Inc. Agent for Applicant (if applicable): Michael Burdick		
Date of Application: July 29, 2010 Date of Receipt: July 30, 2010 Date clock started after UN:		
PDUFA Goal Date: May 30, 2011		Action Goal Date (if different):
Filing Date: September 28, 2010		Date of Filing Meeting: September 7, 2010
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s): treatment of ADHD in patients 6 years and older		
Type of Original NDA: AND (if applicable)	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 73,856				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<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 UN letter and contact user fee staff.</i>	Payment for this application: <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			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X		
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 less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X		
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))?			X		
<i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X			
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
N21514	Daytrana	NPP	Jun 29, 2013		
N21121	Concerta	NPP, M-88	Jun 27, 2011, Nov 4, 2012		
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?			X		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>					
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)					
If yes, # years requested: 3		X			
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>					
Is the proposed product a single enantiomer of a racemic drug			X		

previously approved for a different therapeutic use (<i>NDAs only</i>)?				
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				
Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <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)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance ¹ ? If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial</i>				

<i>disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature? <i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?		X		Per sponsor, patent certification will be submitted with receipt of filing letter
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? <i>Forms must be signed by the APPLICANT, not an Agent.</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	X			
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>) <i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i> <i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: 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>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i></p>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
<p>Check all types of labeling submitted.</p>	<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 checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
<p>Is Electronic Content of Labeling (COL) submitted in SPL format?</p>	X			

<i>If no, request in 74-day letter.</i>				
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?				
<i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
REMS consulted to OSE/DRISK?	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)				
<i>If yes, specify consult(s) and date(s) sent:</i> CSS – AUG 26, 2010 DMEPA – AUG 26, 2010	X			

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):				
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): March 22, 2010	X			EOP3
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):				
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

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

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 27, 2010

BLA/NDA/Supp #: 202100

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: methylphenidate extended-release powder for oral suspension

DOSAGE FORM/STRENGTH: 25 mg/ 5 ml

APPLICANT: NextWave Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of ADHD in patients 6 year and older

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sandy Chang	Y
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)	Mitch Mathis		Y
Clinical	Reviewer:	Mark Ritter	N
	TL:	Bob Levin	Y
Clinical Pharmacology	Reviewer:	Huixia Zhang	Y
	TL:	Ray Baweja	Y
Biostatistics	Reviewer:	Yeh-Fong Chen	Y
	TL:	Peiling Yang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ikram Elayan	Y
	TL:	Linda Fossom	Y

Product Quality (CMC)	Reviewer:	Chhagan Tele	Y
	TL:	Tom Oliver	Y
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? 	<input type="checkbox"/> YES

<p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p>Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p>Reason:</p>
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</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>Comments:</p>	
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Thomas Laughren, M.D., Division Director</p> <p>21st Century Review Milestones (see attached) (optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input 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. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input type="checkbox"/>	
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none">• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)• notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

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

/s/

SHIN-YE CHANG
10/29/2010