

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205831Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 205831

SUPPL #

HFD # 130

Trade Name Aptensio XR

Generic Name methylphenidate HCL extended-release capsules

Applicant Name Rhodes Pharmaceuticals, LP

Approval Date, If Known April 17, 2015

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request? No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	21259	Metadate CD Capsules
NDA#	21419	Methylin Oral Solution

NDA#	21475	Methylin Chewable Tablets
NDA#	18029	Ritalin SR Tablets
NDA#	21121	Concerta tablets
NDA#	10187	Ritalin Tablets
NDA#	21514	Daytrana Transdermal Patches
NDA#	21814	Ritalin LA Capsules
NDA#	202100	Quillivant XR for extended-release oral suspension

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

**RP-BP-EF001:** A randomized, double-blind study of the time course of response to [Biphentin] methylphenidate hydrochloride extended-release capsules as compared to placebo in children 6 to 12 years with Attention Deficit Hyperactivity Disorder (ADHD) in an analog classroom setting" (note, the approved trade name is Aptensio XR and not Biphentin)

**RP-BP-EF002:** A randomized, parallel, double-blind efficacy and safety study of [Biphentin] methylphenidate hydrochloride extended release capsules compared to placebo in children and adolescents 6 to 18 years with Attention Deficit Hyperactivity Disorder" (note, the approved trade name is Aptensio XR and not Biphentin)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

**RP-BP-EF001**  
**RP-BP-EF002**

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 104624	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND # 104624	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====  
Name of person completing form: Shin-Ye Sandy Chang, Pharm.D.  
Title: Regulatory Project Manager  
Date: April 17, 2015

Name of Office/Division Director signing form: Mitchell Mathis, M.D.

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHIN-YE CHANG  
04/17/2015

MITCHELL V Mathis  
04/17/2015

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 205831 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Aptensio XR Established/Proper Name: methylphenidate HCL Dosage Form: extended-release capsule		Applicant: Rhodes Pharmaceuticals, LP Agent for Applicant (if applicable):
RPM: Shin-Ye Sandy Chang, Pharm.D.		Division: Psychiatry Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="margin: 0;"><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p style="margin: 5px 0 0 20px;"> <input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check: April 8, 2015         </p> <p style="margin: 5px 0 0 20px;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>April 18, 2015</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): 3  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) AP 4/17/2015
Labeling	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	11/26/2014 11/24/2014
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: <input checked="" type="checkbox"/> None DMEPA: <input type="checkbox"/> None 1/27/2015 DMPP/PLT (DRISK): <input type="checkbox"/> None 3/27/2015 OPDP: <input type="checkbox"/> None 3/30/2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )	8/26/2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 3/31/2015
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>3/11/2015</u> If PeRC review not necessary, explain: _____</li> </ul>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings <ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 2/8/2013 <input checked="" type="checkbox"/> No mtg <input type="checkbox"/> N/A <input type="checkbox"/> N/A Pre-IND: 5/19/2009
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	<input checked="" type="checkbox"/> No AC meeting
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/16/2015
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews <ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review 3/20/2015 <input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	3/20/2015
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 3/4/2015
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/1/2015, 3/19/2015
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/27/2015
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/18/2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None Product Quality review: 2/17/2015 Biopharmaceutics review: 3/2/2015
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 1/20/2015
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	2/17/2015
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: 1/22/2015 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
• Finalize 505(b)(2) assessment	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy(BT) Designated drugs: • Notify the CDER BT Program Manager	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): • Notify the Division of Online Communications, Office of Communications	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

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SHIN-YE CHANG  
04/21/2015

**From:** [Delehant, Todd](#)  
**To:** [Chang, ShinYe](#)  
**Subject:** RE: NDA 205831 - Aptensio XR container label  
**Date:** Thursday, April 16, 2015 3:35:55 PM

---

Sandy,

Rhodes Pharma agrees with this change to the Aptensio XR bottle labels.

In order to comply with the United States Pharmacopeia (USP) policy entitled, Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations (the USP Salt Policy), Rhodes commits to updating the Aptensio XR container labels to include the free base equivalent information.

Rhodes will include the following text on the side panel: Each capsule contains xx mg of methylphenidate hydrochloride (equivalent to xx mg of methylphenidate free base)

Rhodes proposes to implement this change as part of the final carton/container/labeling submission post approval.

Best Regards,  
Todd

Todd M. Delehant, Ph.D., RAC  
Director Regulatory Affairs  
Rhodes Pharmaceuticals L.P.  
Ph: (401) 262-9425

---

**From:** Chang, ShinYe [<mailto:ShinYe.Chang@fda.hhs.gov>]  
**Sent:** Thursday, April 16, 2015 3:29 PM  
**To:** Delehant, Todd  
**Subject:** RE: NDA 205831 - Aptensio XR container label

Hi Todd,

In order to comply with the United States Pharmacopeia (USP) policy entitled, Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations (the USP Salt Policy), your container label needs to include the free base equivalent information.

We suggest the following text on the side panel: Each capsule contains xx mg of methylphenidate hydrochloride (equivalent to xx mg of methylphenidate free base)

Please let me know if you have already printed your container labels. If so, we will need your agreement to implement this change as part of the final carton/container/labeling submission post approval.

An agreement to make these changes is requested by COB, today.

Thanks,

Sandy

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/s/  
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SHIN-YE CHANG  
04/17/2015

**PeRC Meeting Minutes  
March 11, 2015**

**PeRC Members Attending:**

Lynne Yao

Rosemary Addy (only reviewed [REDACTED] (b) (4), Neupro, and Linzess)

Jane Inglese

Hari Cheryl Sachs

Wiley Chambers

Tom Smith

Karen Davis-Bruno

Peter Starke

Andrew Mulberg

Gregory Reaman

Daiva Shetty

Julia Pinto

Freda Cooner

Lily Mulugeta

Nisha Jain (only reviewed [REDACTED] (b) (4))

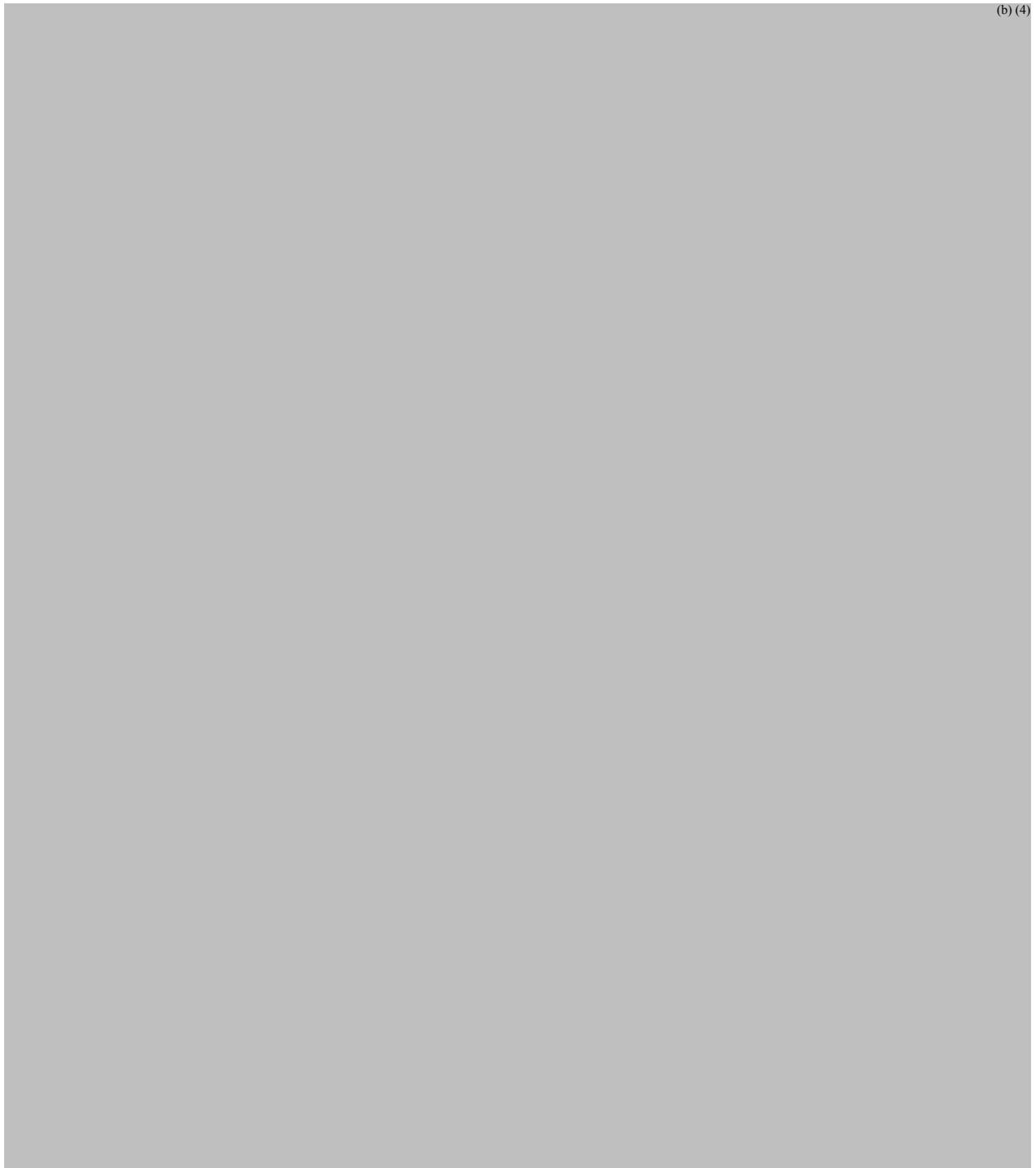
Barbara Buch (only reviewed [REDACTED] (b) (4))

Adrienne Hornatko-Munoz (only reviewed [REDACTED] (b) (4))

Dianne Murphy



	(b) (4)
IND	
IND	



**Avelox (moxifloxacin) Partial Waiver/Deferral/Plan**

- NDAs 021277/056 and 21085/060 seek marketing approval for Avelox (moxifloxacin) for treatment of plague.
- The supplements trigger PREA as directed to new indications.
- The supplements have PDUFA goal dates of May 8, 2015.
- The PeRC noted that information on [REDACTED] (b) (4) [REDACTED] for complicated intra-abdominal infections (cIAI), which will allow the product to be labeled for plague.
- *PeRC Recommendations:*
  - The PeRC agreed with a partial waiver for pediatric patients aged birth to less than 3 months because studies would be impossible or highly impracticable.
  - The PeRC agreed with a deferral for pediatric patients 3 months to less than 17 years of age because adult studies have been completed and the product is ready for approval. The Division clarified that these studies will be due and should be submitted at the end of this year.

#### **Aptensio XR (methylphenidate) Partial Waiver/Deferral/Plan/Assessment**

- NDA 205831 seeks marketing approval for Aptensio XR (methylphenidate) for treatment of attention deficit hyperactivity disorder.
- The application triggers PREA as directed to a new dosage form.
- The application has a PDUFA goal date of April 18, 2015.
- The Division clarified that the sponsor submitted the NDA without an Agreed iPSP. The Division decided to file the application without an Agreed iPSP because the application contained predominately pediatric data, and only data for pediatric patients 4 to less than 6 years of age were not included.
- *PeRC Recommendations:*
  - The PeRC agreed with a partial waiver for pediatric patients less than 4 years of age because studies would be impossible or highly impracticable.
  - The PeRC agreed with a deferral for pediatric patients 4 to less than 6 years of age due to the expected difficulty in enrolling pediatric patients of this age, and the Division's limited experience with the study of ADHD in younger children (4 to less than 6 years old). The PeRC recommended that the Division add a long-term safety study of these patients to the PREA requirement.
  - The PeRC recommended that the PK study be modified by utilizing existing information obtained from older pediatric patients (6-9 year olds) in order to decrease the amount of PK sampling needed.

(b) (4)

### Neupro (rotigotine) PMR change

- NDA 21829/001 was approved April 2, 2011, for Neupro (rotigotine) for treatment of moderate-to-severe primary restless legs syndrome.
- At the time of approval, the following three pediatric postmarketing studies were required under PREA:
  - 1885-1 Conduct a PK/PD study in adolescents ages = 13 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome.
    - Final Protocol Submission: June 2012
    - Study Completion: April 2014
    - Final Report Submission: November 2014
    - Status- Final report submitted November 19, 2014.
  - 1885-2 Conduct a clinical trial to assess the efficacy and safety of rotigotine transdermal (Neupro) in adolescents  $\geq 13$  years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome. Develop age appropriate dose(s) in order to then identify the lowest maximally effective dose in this age group.
    - Final Protocol Submission: September 2015
    - Study Completion: July 2024
    - Final Report Submission: February 2025
    - Status-Pending
  - 1885-3 Conduct a long-term safety study of adolescents ages =13 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome. The study must provide a descriptive analysis of safety data in pediatric patients during at least 12 months of continuous treatment with rotigotine transdermal at individualized doses in association with the trial described in the pediatric efficacy study.
    - Final Protocol Submission: June 2012
    - Study Completion: September 2026
    - Final Report Submission: April 2027

(b) (4)

(b) (4)

**Linzess (linaclotide)**

(b) (4)

- NDA 202811 was approved August 30, 2012, for Linzess (linaclotide) for treatment of chronic idiopathic constipation.

(b) (4)

(b) (4)



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/s/  
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JANE E INGLESE  
03/23/2015



NDA 205831

## LABELING PMR/PMC DISCUSSION COMMENTS

Rhodes Pharmaceuticals, L.P.  
Attention: Todd Delehant, Ph.D.  
Associate Director of Regulatory Affairs  
498 Washington Street  
Coventry, RI 02816

Dear Dr. Delehant:

Please refer to your New Drug Application (NDA) dated June 18, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Aptensio XR (methylphenidate hydrochloride) extended-release capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg,

(b) (4)

We also refer to our August 28, 2014, letter in which we notified you of our target date of March 21, 2015 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On December 19, 2014, we received your December 19, 2014, proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by April 3, 2015. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

We have the following proposed Pediatric Research Equity Act (PREA) Postmarketing Requirements.

1. A deferred pediatric study under PREA for the treatment of Attention Deficit Hyperactivity Disorder in pediatric patients ages 4 to less than 6 years old. A randomized, double-blind, placebo-controlled, flexible-dose titration study of methylphenidate hydrochloride extended-release capsules (Aptensio XR) in children ages 4 to 5 years diagnosed with ADHD.

Final Protocol Submission Date: by December 31, 2015

Study/Trial Completion Date: by March 31, 2019

Final Report Submission: by December 31, 2019

2. A deferred pediatric study under PREA for the treatment of Attention Deficit Hyperactivity Disorder in pediatric patients ages 4 to less than 6 years old. A single-dose, open-label, randomized pharmacokinetic study of Aptensio XR capsules in male or female children (4 to less than 6 years of age) with ADHD in fed condition

Final Protocol Submission Date: by March 31, 2015

Study/Trial Completion Date: by December 31, 2016

Final Report Submission: by June 30, 2017

3. A deferred pediatric study under PREA for the treatment of Attention Deficit Hyperactivity Disorder in pediatric patients ages 4 to less than 6 years old. A one year Pediatric Open-Label Safety Study for patients age 4 to 5 years (at the time of entry into Study 1 or Study 2 or at the time of enrollment if directly enrolled into Study 3) with ADHD.

Final Protocol Submission Date: by December 31, 2015

Study/Trial Completion Date: by March 31, 2019

Final Report Submission: by December 31, 2019

If you have any questions, contact me at [shinye.chang@fda.hhs.gov](mailto:shinye.chang@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

LCDR Shin-Ye Sandy Chang, Pharm.D.  
Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE: Draft Labeling

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

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/s/  
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SHIN-YE CHANG  
03/20/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration  
Silver Spring, MD 20993

NDA 205831

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Rhodes Pharmaceuticals L.P.  
498 Washington Street  
Coventry, RI 02816

ATTENTION: Todd M. Delehant, Ph.D.  
Associate Director Regulatory

Dear Dr. Delehant:

Please refer to your New Drug Application (NDA) dated and received June 18, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Hydrochloride Extended Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, (b) (4)

We also refer to your correspondence, dated and received September 5, 2014, requesting review of your proposed proprietary name, Aptensio XR.

We have completed our review of the proposed proprietary name, Aptensio XR and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your September 5, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Vasantha Ayalasomayajula, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-5035. For any other information regarding this application, contact Shin-Ye Chang, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3971.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES on behalf of KELLIE A TAYLOR  
11/26/2014



NDA 205831

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

Rhodes Pharmaceuticals, L.P.  
Attention: Todd Delehant, Ph.D.  
Associate Director of Regulatory Affairs  
498 Washington Street  
Coventry, RI 02816

Dear Dr. Delehant:

Please refer to your New Drug Application (NDA) dated June 18, 2014, received June 18, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Aptensio XR (methylphenidate hydrochloride) extended-release capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (b)(4)

We also refer to your amendment dated August 13, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is April 18, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 21, 2015. In addition, the planned date for our internal mid-cycle review meeting is November 11, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

**Clinical**

Subject 2-18-13-342 experienced the serious adverse event “injury-induced migraine headache”. The narrative states that the subject experienced a head injury, but no other details are provided. Please provide further details regarding the head injury.

**Chemistry, Manufacturing, and Controls/Nonclinical**

1. Provide justification for the (b) (4) testing at drug product release and stability with regard to its potential impact on drug product quality (b) (4)
2. Include a second, orthogonal identification test to the drug substance and drug product specifications as the current tests are nonspecific.
3. We request that you lower the drug product acceptance criterion for the (b) (4) to (b) (4)% or provide justification based on the risk to the patient for the proposed (b) (4)% level.

**Product Microbiology**

(b) (4)  
More

information on your process is needed. Address the following points.

1. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.
  - a. Define the maximum processing time for the (b) (4)
  - b. Define the maximum holding time for the (b) (4)
2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
3. Describe activities taken when microbiological acceptance criteria are not met at control points.

In addition to these points, address the following:

1. Provide the results of microbial limits testing performed on exhibit or stability batches of the drug product.
2. You should minimally perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule to reflect this testing.
3. In the absence of historical data, you should perform quarterly microbial limits testing on stability batches for the first year of stability. Following the first year, testing may be performed annually.

In lieu of the above information, provide updated drug product release and stability specifications that include testing for microbial enumeration (USP<61>) and specified organisms (USP<62>) with acceptance criteria consistent with USP<111>. Include data summaries demonstrating method suitability of the microbiological test methods with the drug product.

### **ONDQA-Biopharmaceutics**

1. The data supporting the proposed dissolution acceptance criteria of your product are insufficient. Therefore, submit the following information/data:
  - a. Dissolution profiles (individual and mean values) in tabular and graphical form from all pivotal clinical and PK studies.
  - b. In general, the selection of the dissolution acceptance criteria limits is based on the mean target value  $\pm 10\%$  and NLT<sup>(b)(4)</sup> % for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model or in vivo BE study.
  - c. Implement a dissolution acceptance criterion for the immediate release portion of your proposed product [*sampling time point (e.g., 30 min) and limit*].
2. Provide the following in support of the extended release designation claim (refer also to CFR 320.25f):
  - a. The BA profile established for the drug product rules out the occurrence of any dose dumping;
  - b. The drug product's steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed non-controlled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.
  - c. The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units;
  - d. The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.
3. Provide the data generated on the in vitro dose-dumping study in the presence of alcohol.
  - a. The following alcohol concentrations for the in vitro dissolution studies (using 12 units each) are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.
  - b. Generally a range of alcohol concentrations in 0.1 N HCl and the QC dissolution medium is recommended. If the optimal dissolution medium has not been identified, then dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.
  - c. Submit the dissolution profile comparisons with similarity testing (e.g.,  $f_2$  values)
    - i. Compare the shape of the dissolution profile to see if the modified release characteristics are maintained, especially in the first 2 hours.
    - ii. The report should include the complete data (i.e., individual, mean, SD, comparison plots, statistical testing for similarity, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study.
4. Provide Dissolution profile comparisons with similarity testing (e.g.,  $f_2$  testing) between the highest and lower strengths of your proposed product in three different media.
5. Provide dissolution profile comparisons with similarity testing between the US clinical trial formulation and the commercial (Canadian) formulation; in addition provide a side-by-side table comparing their manufacturing processes.

### **Office of Surveillance and Epidemiology, Division of Risk Management (DRISK)**

Your original submission dated June 18, 2014 included a draft risk evaluation and mitigation strategy (REMS) and the Office of Surveillance and Epidemiology/Division of Risk Management have the following comments:

1. We note that although other approved methylphenidate products (oral, transdermal and injection) include Medication Guides (MG) as part of their approved labeling, no other approved methylphenidate product has a REMS. FDA Guidance [Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies \(REMS\)](#) states that “...the Agency has the authority to determine, based on the risks of a drug and public health concern, whether a Medication Guide should be required as part of a REMS when the standard in part 208 is met, and may decide the Medication Guide should be required as labeling but not part of REMS if FDA determines that a REMS is not necessary to ensure the benefits of the drug outweigh its risk.”
  - a. Given the information provided above, if it is Rhodes Pharmaceuticals’ intent to propose a REMS for their NDA 205831, the following is required:
    - Submit an **Amendment to your original application** to include the addition of a REMS Supporting Document. A REMS Supporting document is required as part of a REMS submission, as outlined in FDA’s **Guidance for Industry – Format and content of Proposed Risk Evaluation and Mitigation Strategies (REMS) REMS Assessments, and Proposed REMS Modifications**. Please refer to this guidance for details including content of the REMS Supporting Document at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf> including Background, Goals Section, Supporting Information About Proposed REMS Elements (***including rationale for the proposed REMS***), REMS Assessment Plan and Other Relevant Information. Specifically include your rationale about why you are proposing the need for a REMS for NDA 205831 Methylphenidate ER to ensure the benefit outweighs the risk for this product. Including what aspects of the application are unique to this methylphenidate product to require additional mitigation beyond a Medication Guide in labeling.
  - b. Given the information provided above, if Rhodes Pharmaceuticals chooses to withdraw the REMS as part of your application (i.e. your intent is to have a Medication Guide as part of labeling only), the following is required:
    - Submit a **REMS Correspondence** submission stating you did not plan to provide a REMS as part of your application along with your rationale why a REMS is not needed.

## **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

### **HIGHLIGHTS: GENERAL FORMAT**

The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by September 19, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver and a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver and deferral requests are denied.

If you have any questions, contact Shin-Ye Sandy Chang, Regulatory Project Manager, at [shinye.chang@fda.hhs.gov](mailto:shinye.chang@fda.hhs.gov)

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D  
CAPT, USPHS  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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MITCHELL V Mathis  
08/28/2014



NDA 205831

**NDA ACKNOWLEDGMENT**

Rhodes Pharmaceuticals L.P.  
Attention: Todd M. Delehant, Ph.D.  
Associate Director of Regulatory Affairs  
498 Washington Street  
Coventry, RI 02816

Dear Dr. Delehant:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Aptensio XR (methylphenidate hydrochloride) extended-release capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (b)(4)

Date of Application: June 18, 2014

Date of Receipt: June 18, 2014

Our Reference Number: NDA 205831

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 17, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Psychiatry Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications. If you have any questions, contact me, at [shinye.chang@fda.hhs.gov](mailto:shinye.chang@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

LCDR Shin-Ye Sandy Chang, Pharm.D.  
Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHIN-YE CHANG  
07/14/2014



IND (b) (4)

**MEETING PRELIMINARY COMMENTS**

Rhodes Pharmaceuticals L.P.  
Attention: Todd Delehant, Ph.D.  
Associate Director of Regulatory Affairs  
498 Washington Street  
Coventry, RI 02816

Dear Dr. Delehant:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Hydrochloride Extended-Release 10mg, 15mg, 20mg, 30mg, 40mg, 50mg, 60mg (b) (4) Capsules.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the teleconference scheduled for Monday, February 11, 2013, from 10-11AM EST (Teleconference number: (b) (4); participant code (b) (4)) between Rhodes Pharmaceuticals, L.P. and Division of Psychiatry Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting via an email me at [Juliette.Toure@fda.hhs.gov](mailto:Juliette.Toure@fda.hhs.gov). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, email me to discuss the possibility of including these items for discussion at the meeting.

IND 104624  
Rhodes Pharmaceuticals, L.P.  
Type B meeting  
Pre-NDA Teleconference

This is a Pre-NDA meeting for IND 104624, methylphenidate HCl extended release capsules for the treatment of ADHD (b) (4).

**Contributors/Participants:**

***FDA***

Mitchell Mathis, M.D.	Division Director (acting)
Bob Levin, M.D.	Clinical Team Leader
Chhagan Tele, Ph.D.	Chemistry Review Team Leader
Pei-I Chu, Ph.D.	Chemistry Reviewer
Linda Fossom, Ph.D.	Pharmacology/Toxicology Supervisor
Ikram Elayan, Ph.D.	Pharmacology/Toxicology Reviewer
Hao Zhu, Ph.D.	Clinical Pharmacology Team Leader
Andre Jackson, Ph.D.	Clinical Pharmacology Reviewer
Peiling Yang, Ph.D.	Statistics Team Leader
Jinglin Zhong, Ph.D.	Statistics Reviewer
Doug Warfield	Regulatory Information Specialist, Office of Business Informatics, CDER Data
Valerie Gooding	Regulatory Information Specialist, Office of Business Informatics, ESUB
Ida-Lina Diak, PharmD	Safety Evaluator Team Leader, Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilance (DPV)
Vicky Huang, PharmD	Safety Evaluator, OSE/DPV
Irene Chan, PharmD, BCPS	Safety Evaluator Team Leader, OSE, Division of Medication Error Prevention and Analysis (DMEPA)
Loretta Holmes, BSN, PharmD	Safety Evaluator, OSE/DMEPA
Sandra Rimmel, BSN, RN	Safety Regulatory Project Manager, OSE
Colleen Locicero	Associate Director for Regulatory Affairs, ODE 1
Juliette Touré, Pharm.D.	Senior Regulatory Project Manager

**Background:**

Rhodes Pharmaceuticals, LP has developed a formulation of methylphenidate hydrochloride extended-release capsules. It is intended to be taken as a single daily dose, with a biphasic plasma profile. It distinguishes itself from similar extended-release products on the market by achieving a first  $C_{max}$  more similar to immediate-release methylphenidate, which may offer clinical advantages. It also is available (b) (4) strengths (10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (b) (4) that allow individualized dosing.

The ratio of immediate-release content to controlled-release content (approximately 40% / 60%) in the formulation is unique among the available controlled release methylphenidate products. This ratio was designed to optimize the balance between the magnitude of a rapidly attained initial post-dose peak concentration in the morning and a subsequent more prolonged peak later in the day. In contrast, the other controlled release formulations use the following ratios of immediate to controlled release methylphenidate, e.g.: Concerta (22% / (b) (4)); Metadate CD (30% / 70%); and Ritalin LA ((b) (4) (b) (4)).

This drug was approved by Health Canada on March 2006 and launched in Canada on August 2006, marketed as Biphentin®. The sponsor submitted two requests to the FDA for review of a proposed proprietary name, the first for (b) (4) (dated September 1, 2011) and the second for (b) (4) (dated April 19, 2012). Both names were denied and the reasons for denial were communicated to the sponsor on February 29, 2012 and October 16, 2012, respectively.

### **Questions:**

#### **Clinical**

Question 1. Demographic data for the two clinical efficacy studies are provided in Attachments 2 and 3 of the briefing package. The 80 mg Biphentin strength was used in the adult PK studies but was not required for any of the subjects in the two efficacy and safety studies. (b) (4)

**Preliminary Comments:** *We will need to discuss this with you further.* (b) (4)

(b) (4)

#### **Discussion at Meeting:**

Question 2. We have used MedDRA terms for documenting adverse events (AE) in both clinical efficacy studies (protocols RP-BP-EF001 and RP-BP-EF002). A record of early terminations from each of the two clinical studies is provided in Attachments 5 and 6 of the briefing package. Does the Agency agree the summary of early terminations and AEs is satisfactory?

**Preliminary Comments:** *We agree. Generally, we ask sponsors to provide more specific reasons for discontinuations than Withdrew Consent, if possible. For example, it would be helpful to know if any of these discontinuations were related to adverse events or lack of efficacy.*

#### **Discussion at Meeting:**

Question 3. Listings of SAEs, TEAEs, and non-TEAEs for both studies are provided in Attachments 7, 8 and 9 of the briefing package, respectively. We have not seen any serious adverse events in ongoing studies that have never been associated with other methylphenidate dosage forms on the US market. There were no serious adverse events related to study drug for either study. Four serious adverse events not related to study drug that required hospitalization were reported for Study EF002. Does the Agency agree that the summary data are satisfactory in the submission? We will of course be submitting all raw data.

**Preliminary Comments:** *The presentation of serious adverse reactions is acceptable.*

*For the presentation of treatment-emergent and non-treatment adverse events, what were the criteria determining whether an event was treatment-emergent or not? For EF002, please provide separate AE tables for the placebo-controlled study and the long-term, open-label study, and include the AEs in the placebo group. Also, provide an additional table presenting the AE data by fixed doses. In addition, list the AEs by organ system instead of in decreasing order of frequency. Combine the terms insomnia, initial insomnia, and middle insomnia under the term Insomnia. Combine the terms sedation, somnolence, and any related terms under Sedation. Combine the terms abdominal pain and abdominal pain upper under the term Abdominal Pain. Provide more specific terms for change in sustained attention and sensory motor disorder. Define weight loss poor.*

**Discussion at Meeting:**

Question 4. Listings of the Subject Disposition, Demographics, and Analysis of Populations from Study EF001 are provided in Attachments 10, 11 and 12 of the briefing package, respectively. These are consistent with the table formats presented in the Statistical Analysis Plan. Does the Agency agree that the summary data in these attachments are satisfactory as constructed for the submission?

**Preliminary Comments:** *We agree.*

**Discussion at Meeting:**

Question 5. Listings of the Subject Disposition, Demographics, and Analysis of Populations from Study EF002 are provided in Attachments 13, 14, and 15 of the briefing package, respectively. These are consistent with the table formats presented in the Statistical Analysis Plan. Does the Agency agree that the summary data in these attachments are satisfactory as constructed for the submission?

**Preliminary Comments:** *We agree.*

**Discussion at Meeting:**

Question 6

(b) (4)

**Discussion at Meeting:**

Question 7. We recognize the Agency desires standardization of safety classification that is consistent across product types in similar drug groupings, such as, “Intolerable, Ineffective or Acceptable” conditioning noted for other methylphenidate products. In the current Biphentin studies, a low percentage of the study populations terminated early due to treatment emergent adverse events (TEAE). For the EF001 Classroom study, 1 of 26 subjects (3.8%) terminated early due to TEAE, and for the EF002 study, 7 of 230 subjects (3.0%) terminated early due to TEAE. The TEAE early terminations could be due to forced dosing at higher strengths that we will only know after unblinding. Treatment emergent adverse events occurring at a greater than 5% frequency in the total population of 256 were:

Headaches	21.5%
Decreased appetite	19.5%
Abdominal pain upper	14.5%
Initial insomnia	9.0%
Insomnia	7.0%
Affect lability	6.3%
Irritability	6.3%

Complete summaries of TEAE and non-TEAE are attached. Does the Agency prefer additional or alternate summaries on safety?

**Preliminary Comments:** Refer to the comments under Question 3. It is not necessary to categorize adverse events or responses as intolerable, ineffective, or acceptable for the purposes of safety analyses or labeling. Are you referring to the use of these categories for making decisions about dose titration during the dose optimization phase?

For all safety analyses, please provide separate analyses for 1) EF001 data combined with the data from the placebo-controlled phase of EF002 (including the placebo data); and 2) safety data from the longer-term extension phase of EF002.

Please provide exposure analyses. These should include: the overall total Biphentin exposure in patient-years in the clinical studies, as well as the total Biphentin exposure in EF001, the placebo-controlled phase of EF002, and the extension phase of EF002. In addition, provide the mean and median doses in each study and the mean and median durations of exposure in each of the studies. Provide mean and outlier analyses for relevant safety parameters (e.g., blood pressure, heart rate, weight, ECG, and clinical laboratory assessments). Please describe in more detail the safety analyses that you plan to provide.

**Discussion at Meeting:**

## Chemistry Manufacturing and Controls

**Question 1. Known Degradation Products:** The potential degradation products and byproducts from the drug substance manufacturing process are (b) (4). The maximum level of (b) (4) observed in Biphentin from 12 months long-term stability conditions is (b) (4)%. The maximum level observed from accelerated stability is (b) (4)%, and since (b) (4) is the major metabolite of methylphenidate, the specification for this has been reset at NMT (b) (4)% based on the maximum levels observed in stability batches kept under accelerated and long-term stability conditions. Does the Agency agree that the revised specification of (b) (4)% would be acceptable?

**Preliminary Comments:** Yes, we agree with the proposed acceptance criteria.

**Discussion at Meeting:**

## Structural

**Question 1.** Does the agency agree that the proposed presentation format for the draft content of labeling (package insert labeling) is acceptable?

**Preliminary Comments:** From a technical standpoint (not content related), the proposed format for the draft content of labeling is acceptable. Please see additional comments below.

- When submitting word documents, remember to include "word" in the leaf title, so reviewers can quickly identify the word version of the document.

- *SPL files should be included in their own unique folder marked spl within the labeling folder in m1 of your submission and referenced in m1.14.1.3 Draft labeling text*
- *Please include technical point of contact in your cover letter.*
- *Providing a linked reviewer's aid/ reviewer's guide in module m1.2, as a separate document from the cover letter, to briefly describe where information can be found throughout the application, would be helpful to reviewers*

**Discussion at Meeting:**

Question 2. Does the agency agree that the format for the proposed presentation of the clinical efficacy data is acceptable?

**Preliminary Comments:** *Yes, we agree.*

**Discussion at Meeting:**

**ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS**

- We request that you conduct simulations using the adult PK data and the PD SKAMP score data in children to establish the optimal time intervals that coincide with the maximum SKAMP scores. This information will be important for any future formulation changes.
- Based upon this informative time interval, determine the sensitivity and power of the partial AUCs (PAUC) that corresponds to this interval (Pharm Res 30, 192-202, 2013).
- Data for all simulations should be submitted as SAS transfer files with a separate file defining all variables.
- Supply all control streams and SAS codes used in the simulations.

**ADDITIONAL BIostatISTICS COMMENTS**

When you submit the supplemental NDA, please include as part of the original submission:

- all raw as well as derived efficacy variables in .xpt format,
- the SAS programs that produced all efficacy results,
- the SAS programs by which the derived variables were produced from the raw variables, and
- a list of IND number with serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings.

**INFORMATION ON SUBMITTING AN APPLICATION THROUGH THE 505(B)(2) PATHWAY**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval (this includes reliance on language/information for the labeling) on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described (e.g., by trade name(s)) in the published literature.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies. We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

Please note that a 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug may rely only on that finding as is reflected in the approved labeling for the listed drug.

Please further note that foreign labeling or assessment reports may not be relied upon as these are neither reliance on FDA's findings related to a listed drug, nor are they reliance on literature. If the studies upon which the foreign conclusions are based have been published, you may be able to rely upon that literature.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

## **DATA SPECIFICATIONS**

Research study designs should define the protocol for data collection. The Agency's methodology and submission structure supports research study design, as indicated in the *Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* and the *Study Data Specifications*. The Agency's methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. The Agency prefers implementation of analyses datasets to tabulations datasets traceability. In addition, the Agency prefers each study submitted to be complete and evaluated on its own merits.

The Agency prefers sponsors submit datasets based on the Study Data Specifications version published at the time of submission (currently 2.0). However, in general, the Agency accepts datasets, which comply, within a reasonable timeframe, with previous versions of the Study Data Specifications and other related guidance; based on the timing of protocol design, protocol initiation, and data collection.

The Agency expects sponsors to evaluate the risk involved converting study data collected to standardized data, if applicable. The Agency prefers sponsors to submit study data conversion explanation and rationale. The study data conversion rationale and explanation should address either scenario; decision rationale for not converting or decision rationale for converting. The Agency expects the sponsor's evaluation and rationale includes study data scientifically relevant to the application's safety and efficacy representation. As such, the evaluation and explanation may include rationale based on the pooling/integrating of data from multiple studies.

The Agency also prefers studies be maintained independently in the SEND datasets, SDTM datasets, and that analyses (ADaM) datasets provide traceability to the study's SDTM, including analyses that combine multiple studies (e.g. Safety and/or Efficacy analyses) (See *SEND*, *SDTM* and *ADaM* as referenced in *Study Data Specifications*).

In addition, please reference the *CDER Common Data Standards Issues Document* for further information on data standardization in submissions.

If you have any further questions, please feel free to send an email to [cdcr-edata@fda.hhs.gov](mailto:cdcr-edata@fda.hhs.gov).

Additional Links:

*[Electronic Regulatory Submissions and Review Helpful Links](#)*  
*[Electronic Common Technical Document \(eCTD\)](#)*  
*[Study Data Standards Resources](#)*

## **PREA PEDIATRIC STUDY PLAN**

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at [Ped drugs@fda.hhs.gov](mailto:Ped drugs@fda.hhs.gov).

## **PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

## **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

## **MANUFACTURING FACILITIES**

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

### CLINICAL SITE INSPECTION

#### **NDA Information and Format: OSI Request to Sponsor**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate clinical investigator and sponsor/monitor/CRO inspections. The dataset requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

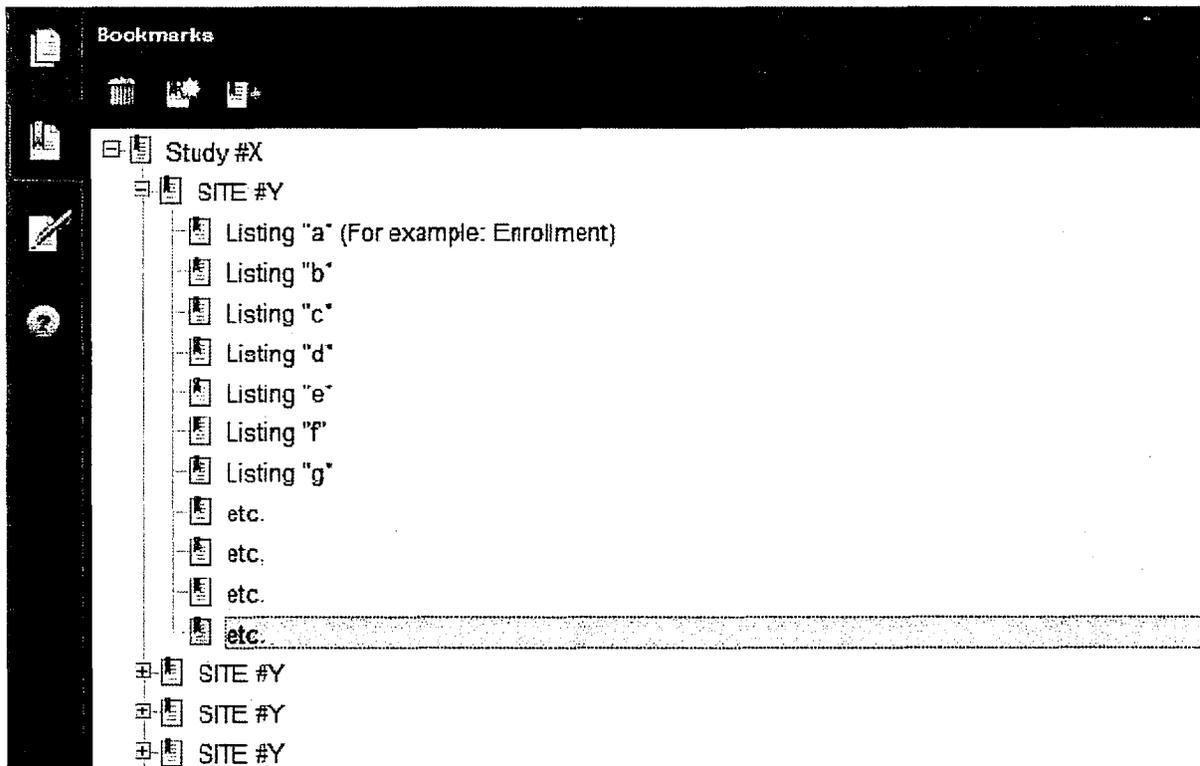
#### **I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
  - a. Site number and principal investigator name
  - b. Site location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - c. Current location of principal investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
  - a. Number of subjects screened for each site by site

- b. Number of subjects randomized for each site by site
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
    - a. Name, address and contact information of all CROs in the clinical trials
    - b. Physical location of study documents (location of inspection): (1) trial master file; (2) source documents generated by CROs; (3) sponsor/monitor files (e.g., monitoring master file, files for drug accountability, SAE, etc.)
  4. For each pivotal trial provide a sample annotated Case Report Form (if provided elsewhere in submission, please provide a link to the requested information).
  5. For each pivotal trial provide original protocol and all amendments (if provided elsewhere in submission, please provide a link to requested information).

## **II. Request for Subject Level Data Listings by Site**

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
  - a. Listing of subject screened and reason for subjects not meeting eligibility requirements
  - b. Subject listing for treatment assignment (randomization)
  - c. Subject listing of drop-outs and subjects that discontinued with date and reason
  - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal trials)
  - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the format shown below:



### III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, email me at [Juliette.Toure@fda.hhs.gov](mailto:Juliette.Toure@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Juliette Touré, PharmD  
 CDR, United States Public Health Service  
 Senior Regulatory Project Manager  
 Division of Psychiatry Products  
 Office of Drug Evaluation 1  
 Center for Drug Evaluation and Research

**Enclosures:**

- Attachment 1 (Summary Level Clinical Site Data for Inspection Planning in NDA Submissions)
- Attachment 2 (Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format)

## Attachment 1

### Summary Level Clinical Site Data for Inspection Planning in NDA Submissions

#### Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

#### Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

#### Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy:

- Treatment Efficacy Result (TRTEFFR) – efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on result reporting)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies with a time-to-event primary endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.

- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (\*.xpt).

**Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)**

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

**Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)**

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.



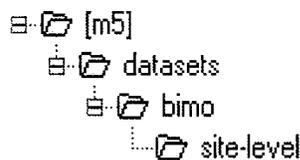
**Attachment 2**

**Technical Instructions:  
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

OSI Pre-NDA Request Item <sup>1</sup>	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

**References:**

eCTD Backbone Specification for Study Tagging Files v. 2.6.1  
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

<sup>1</sup> Please see the OSI Pre-NDA Request document for a full description of requested data files

IND 104624

Page 2

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JULIETTE T TOURE  
02/08/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 104,624

Rhodes Pharmaceuticals, L.L.C.  
Attention: Robert J. Kupper, Ph.D.  
Vice President & CTO  
498 Washington Street  
Coventry, RI 02816  
USA

Dear Dr. Kupper:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Hydrochloride Extended-Release Capsules, (b) (4)

We also refer to the meeting between representatives of your firm and the FDA on May 19, 2009. The purpose of the meeting was to discuss with the Division of Psychiatry Products whether the existing information, especially the clinical study information, would be satisfactory for filing an NDA in the U.S.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, you may email LCDR Juliette Touré, Senior Regulatory Project Manager, at [Juliette.Toure@fda.hhs.gov](mailto:Juliette.Toure@fda.hhs.gov).

Sincerely,  
*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Cc: (b) (4) Consultant to Rhodes Pharmaceuticals, L.L.C.

Enclosure – Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** Tuesday, May 19, 2009  
**TIME:** 3:00 to 4:00 PM EST  
**LOCATION:** FDA White Oak Building 22, Rm 1315  
**APPLICATION:** IND 104,624  
**DRUG NAME:** Methylphenidate Hydrochloride Extended-Release Capsules  
**TYPE OF MEETING:** Type B, Pre-IND Meeting  
**MEETING CHAIR:** Thomas Laughren, M.D.  
**MEETING RECORDER:** Juliette Touré, Pharm.D.

**FDA ATTENDEES/CONTRIBUTORS:** (Title and Office/Division)

Thomas Laughren, M.D.	Division Director, Division of Psychiatry Products (DPP)
Mitchell Mathis, M.D.	Deputy Director, DPP
Robert Levin, M.D.	Clinical Team Leader, DPP
Cheri Lindberg, M.D.	Clinical Reviewer, DPP
Laurie Duncan, M.D., F.A.C.P., M.S.	Safety Reviewer, DPP
Barry Rosloff, Ph.D.	Pharmacology/Toxicology Supervisor, DPP
Linda Fossom, Ph.D.	Pharmacology/Toxicology Team Leader, DPP
Ikram Elayan, Ph.D.	Pharmacology/Toxicology Reviewer, DPP
Thomas Oliver, Ph.D.	Pharmaceutical Assessment Lead, DPP
Phillip Dinh, Ph.D.	Statistical Reviewer
Yang Yang, Ph.D.	Statistical Reviewer
Raman Baweja, Ph.D.	Clinical Pharmacology Team Leader
Bei Yu, Ph.D.	Clinical Pharmacology Reviewer
Hiren Patel, Pharm.D.	Regulatory Project Manager, DPP
Juliette Touré, Pharm.D.	Senior Regulatory Project Manager, DPP

**EXTERNAL CONSTITUENT ATTENDEES:**

Robert Kupper, Ph.D. Vice President and CTO, Rhodes Pharmaceuticals

(b) (4)

**BACKGROUND:**

Rhodes Pharmaceuticals plans to file a 505(b)(2) NDA to obtain approval of (b) (4) (methylphenidate extended release capsules), a once-daily dose product. Biphentin<sup>®</sup> was approved by Health Canada on March 2006 and launched in Canada on August 2006. Rhodes Pharmaceuticals has obtained the rights to incorporate all data for the new drug filing in the U.S. as well as access to the data sources. At the time the clinical studies were conducted, there was no U.S. sponsor for a U.S. based IND.

(b) (4) was designed to be a single, once-daily dose alternative to separate doses of immediate-release methylphenidate by providing a biphasic plasma profile. The sponsor claims that it distinguishes itself from similar extended release products on the market by achieving a first C<sub>max</sub>, more similar to immediate-release methylphenidate.

The ratio of immediate release content to controlled release content (40% / 60%) in the (b) (4) formulation was designed to optimize the balance between the magnitude of a rapidly attained initial post-dose peak concentration in the morning and a subsequent more prolonged peak later in the day. Other controlled-release formulations use the following ratios of immediate to controlled release methylphenidate: Concerta (22% / (b) (4)); Metadate CD (30% / 70%); and Ritalin LA ((b) (4)).

**Clinical Studies with Biphentin<sup>®</sup>**Efficacy Studies

Study 022-005 was a single-center, randomized, double-blind, placebo controlled, 3-way, 3-period crossover study comparing Biphentin, Ritalin, and placebo in 17 children (7-15 years of age) with a diagnosis of ADHD, combined type. Patients were given methylphenidate doses of 1.2 mg/kg. The outcome measures included the IOWA Connors Rating Scale and the CGI-I. There was significant improvement in ADHD symptoms in the Biphentin and Ritalin groups, without significant differences in efficacy between the two treatments.

Study 022-004 was a multicenter (7), randomized, double-blind, non-placebo-controlled, crossover study comparing Biphentin and Ritalin in 79 children (6-18 years of age) with a diagnosis of ADHD. Subjects were evaluated for two weeks on each treatment. The outcome measures were the Connors Parent and Teacher Rating Scales and the CGI-I. Both treatments demonstrated efficacy, and there was no significant difference in efficacy between the Biphentin and Ritalin treatment groups.

Study 022-008 was a multicenter (4), randomized, double-blind, placebo-controlled, crossover study comparing Biphentin, Ritalin and placebo in 50 adults (aged 18-57 years) with a diagnosis of ADHD. The dose range was 10-80 mg/d. Patients were titrated to their optimal dose during the first 3 weeks of treatment. The outcome measures were the CGI, the CAARS-Self, and the CAARS-Observer (spouses, peers, coworkers). Treatment with Biphentin demonstrated efficacy, as measured by the CGI and CAARS-

Self scale, but the changes in CAARS-Observer scores were not statistically significant ( $p=0.14$ ).

### Bioavailability Studies

Study 022-001 was a pilot single-dose, relative bioavailability study in 12 healthy subjects, comparing the pharmacokinetics of Biphentin® 20mg and Ritalin® 10mg at 0 and 4 hours in the fed and fasting states.

Study 022-006 was a relative bioavailability study comparing the pharmacokinetics of Biphentin® 20mg to Ritalin® 10 mg BID (at 0 and 4 hours) in the fed and fasting states in 24 healthy subjects. The bioavailability was similar between the two formulations. The  $T_{max}$  0-4 was shorter for Biphentin® than for Ritalin®. There appeared to be a second rise in the methylphenidate concentration with Biphentin® which resulted in higher concentrations than the immediate release reference product at 10-12 hours post dose.

Study 022-010 was a relative bioavailability study comparing U.S. and German manufacturers of Biphentin®. This was a randomized, double-blind, 2-way crossover study in the fasting state comparing the bioavailability of two batches of Biphentin®.

Study 022-011 was a single center, randomized, open-label, two-way crossover study comparing the PK profile of Biphentin® 10, 15 20, 30, and 40 mg and Ritalin® IR 10 and 20 mg in children with ADHD. Eighteen children between the ages of 6 and 12 years were enrolled. The sponsor states that the PK profile in children was similar to that in adults. The study demonstrated a biphasic concentration/time profile.

Study 022-013 was a single-dose, comparative bioavailability study of Biphentin 20 mg and Concerta® 18mg. This was a randomized, open-label, two-way crossover study in healthy young adults ( $n=24$ ). The sponsor reports that there was a significant difference between Biphentin and Concerta treatment in the methylphenidate concentrations achieved in the early post-dose period. Biphentin administration resulted in comparable plasma concentrations to Concerta over the remainder of the dosing interval and an overall bioavailability equivalent to Concerta.

### **DISCUSSION POINTS:**

DPP sent Preliminary Comments to the Sponsor on Monday, May 18, 2009.

### **Clinical Pharmacology and Biopharmaceutics**

**Question 1.** Are the studies that have been conducted sufficient? Refer to Section 7, pages 13-19 and Attachments 2 and 3.

***Preliminary Comments:** Additional studies will likely be needed. The Office of Clinical Pharmacology (OCP) refers you to 21 CFR 320.25 (f). Furthermore, since you are planning to develop an extended release dosage form, OCP recommends conducting the following studies:*

- *A single dose fasting study comparing the ER product at the highest strength to the IR reference when the drug shows linear PK and the ER strengths are compositionally proportional*
- *A single dose fasting dosage strength proportionality study for the ER product when the ER strengths are not compositionally proportional.*
- *A single dose, food-effect study on the highest ER strength.*
- *A steady state study on the highest strength of the ER product versus an approved IR reference.*
- *For Drugs Showing Non-Linear Kinetics – Comparison of ER to IR reference*
  - *A single dose fasting study for every strength of the ER product compared to the IR reference, or, a single dose study each comparing the highest strength of the ER product to the corresponding IR reference and the lowest strength of the ER product to the corresponding IR reference.*

**Discussion at Meeting:** *The sponsor mentioned that all strengths of the formulation are compositionally proportional and that the drug shows linear PK. Therefore, they feel that the second and fifth items mentioned above may not be relevant.* (b) (4)

Furthermore, in order to characterize the pharmacokinetics of the drug as per its proposed labeling in the ADHD children population, they may need to administer a lower strength to children for safety reasons. OCP suggested that the sponsor provide both an outline of their drug development program as well as study protocol(s) when they open their IND.

## Clinical and Statistics

**Question 2.** Are the studies that have been conducted sufficient? Refer to Section 8, pages 20-25, and Attachments 4, 5 and 6.

**Preliminary Comments:** *The clinical studies conducted with Biphentin may not be sufficient for approval of a 505(b)(2) NDA. We will discuss this with you in more detail at the meeting. Although the publication provided suggests that Study 022-005 demonstrated the efficacy of Biphentin in children with a diagnosis of ADHD, we would need to better understand the details of the design, conduct, and analysis of the study. It appears that the adult ADHD study (022-008) did not demonstrate efficacy as measured by an objective instrument that is specific for ADHD. While the CGI results appear to have been positive, the results of the Connors Adult ADHD Rating Scale-Observer scores did not appear to be statistically significant. Furthermore, the CAARS-Observer was not rated by investigators. Pediatric Study 022-004 was not a placebo-controlled efficacy study; thus, it could not serve as a pivotal efficacy study.*

*Neither placebo-controlled study evaluated dose response which is critical for this class of medications. The outcome measures utilized in these studies were not the standard instruments used in most US studies, and we would need to have more complete information on these instruments before we could reach a judgment about their acceptability. Optimally, you would conduct two adequate and well-controlled trials in subjects with ADHD (one in children and one in adults).*

*Regarding statistics, whether the studies that have been conducted would be sufficient to support an NDA would be a matter of review. We would need to see the study protocols and the statistical analysis plans (SAPs) for potential NDA review. We would also need to see whether each SAP included a detailed description of the primary efficacy analysis. For example, what were the primary efficacy endpoints? What were the variables in the statistical models? Was there any multiplicity adjustment for multiple endpoints? How did you assess the effect of phase and sequence (first-order carryover)? How did you handle the missing data?"*

**Discussion at Meeting:** *The sponsor explained the rationale for selecting the* (b) (4)

*The division recommended using the ADHD-RS as the primary efficacy measure and suggested using the Adler adaptation for the adult population. If the sponsor would like to use instruments other than the ADHD-RS, the division recommends including the justification supporting their use in the IND submission.*

*The sponsor also explained the reasons for proposing a non-inferiority study (Biphentin compared to Ritalin) as opposed a placebo-controlled clinical trial: 1) another placebo-controlled trial would not add value to current efficacy data of stimulants in treating ADHD, 2) Canadian IRB considers withholding treatment for the period of the study unethical, when there is an effective drug available. The division stated that we are not aware of IRBs in the U.S. having an issue with placebo treatment for a short-term ADHD trial. Furthermore, many of the trials have a crossover design, such that all subjects have the potential to receive treatment with the active drug.*

*The division reiterated that a non-inferiority study design would not provide evidence of efficacy. The sponsor would need to conduct adequately designed, placebo-controlled trials to demonstrate efficacy. Furthermore, the sponsor would need to reach prospective agreement with the division regarding the designs and statistical analysis plans for studies. The division recommended conducting a fixed-dose study in order to characterize the dose-response relationships for both efficacy and safety. The sponsor inquired about the number of subjects that would be required for the fixed-dose, dose-response study. The division responded that the numbers would be comparable to those of other trials in the stimulant drug class and that this information can be found in the Clinical Studies section of their labels. For an ADHD study in children, the division also recommended that the sponsor consider conducting a laboratory classroom study in which one could assess efficacy at a number of time points, in order to characterize the pattern of efficacy throughout a single testing day.*

*The sponsor discussed a potential plan to conduct a 3-arm pharmacokinetic study comparing Biphentin with two other modified-release methylphenidate products, in order to bypass the need to conduct efficacy trials. The division stated that this would be theoretically possible; however, it would be challenging. One would have to demonstrate that the concentration/time profile for Biphentin is completely bracketed by those of the other products, without excursions. Another challenging issue would be choosing comparable doses among the different drug products.*

## Pharmacology

**Question 3.** Rhodes Pharmaceuticals will use methylphenidate from a U.S. manufacturer which is already used in commercial product. We expect the submission to be a 505(b)(2) filing. We will submit available information from scientific literature, and have the right to reference other pharmacological data from one or more existing methylphenidate dosage forms. Will this information be sufficient?

**Preliminary Comments:** *Yes; as long as you select a reference listed drug (RLD) that has been approved in the U.S. for the same indication and patient population that you are pursuing, the nonclinical pharmacology and toxicology data that supported approval of the RLD, as part of the total safety and efficacy data, would be expected to support a 505(b)(2) application. However, if clinical systemic exposures to parent drug and/or metabolites are significantly higher than those for the approved RLD, additional nonclinical studies may be needed.*

*It should also be noted that new excipients and/or impurities in the drug product may need to be qualified for safety for the intended route of administration and the daily human dose.*

**Discussion at Meeting:** *The sponsor acknowledged the division's recommendations.*

## Chemistry

**Question 4.** Are there any questions on the CMC summary (Sections 1-6, pages 5-12) from the information package? Are there new CMC issues that need to be addressed in the application?

**Preliminary Comments:** *Your approach seems reasonable. However, it is noted that few details were provided in the briefing package and the ultimate acceptability of the drug substance and drug product specifications will be a review decision. Your drug product identification test will need to be specific (refer to ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances). You are reminded that your drug product will need to be uniquely identified as per 21 CFR 206.10. Stability/photostability data will need to be included in the NDA that evaluates fading of the capsules shell colors as a function of time. The*

[REDACTED] (b) (4).  
[REDACTED] should be incorporated into your drug product specification and the limit justified.

**Discussion at Meeting:** An alternative approach for controlling the [REDACTED] (b) (4)

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED] The sponsor acknowledged the advice and stated that these issues will be addressed in their IND submission.

## General

**Question 5.** Are there other issues (e.g. suicidality assessment) that must be addressed?

**Preliminary Comments:** *There has been much focus on treatment-emergent suicidality (suicidal ideation and behavior) in recent years, including the question of how best to assess for this in future trials. Given this development, the Division of Psychiatry Products (DPP) has developed a policy regarding how we will address this issue.*

*All clinical protocols for products developed in DPP, whatever the indication, must include a prospective assessment for suicidality. These assessments would need to be included in every clinical protocol, at every planned visit, and in every phase of development. An acceptable instrument would be one that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). The Columbia Suicide Severity Rating Scale (C-SSRS) would be an acceptable instrument. You can obtain information about the C-SSRS from Dr. Kelly Posner at Columbia University ([posnerk@childpsych.columbia.edu](mailto:posnerk@childpsych.columbia.edu)).*

*You may propose alternatives, but you would then need to justify that the alternative instrument would meet this need, and you would need to obtain DPP's prior approval of the instrument. There will likely be several different approaches to administering the C-SSRS, including investigator administered or self report (phone, computer, etc). Any approach could be acceptable as long as the method is validated.*

*There are two reasons for implementing this policy. One is to ensure that we collect better data on suicidality than we have up to now, so that in the future we will be able to conduct additional meta-analyses on this matter. A second reason is to ensure that patients in clinical trials who are experiencing suicidality are detected and adequately managed. This is important whether or not a particular drug is associated with treatment-emergent suicidality.*

*This new policy, effective immediately, is applicable to all new protocols submitted to DPP and to ongoing protocols in which you have an IND residing within DPP, i.e., a protocol amendment must be submitted to incorporate this assessment.*

**Discussion at Meeting:** *The sponsor stated that it will incorporate the C-SSRS suicidality assessment into the clinical trial protocols and also mentioned that they have data on suicidality from a naturalistic study. The division explained that C-SSRS is the prospectively used instrument that maps directly to the C-CASA, which is the coding algorithm that will be used for future meta-analyses.*

*The sponsor's consultant, Dr. (b) (4), provided a statement from a clinician's perspective on her experience using Biphentin. She considers Biphentin a first-line drug and finds the beaded formulation particularly useful for rural Canadian residents because it allows some flexibility in dosing and is easy to administer to children. The division advised that, if this information were to be included in labeling, e.g., advice regarding sprinkling over applesauce, then additional PK work would be needed to link the sprinkled contents of the capsule to the intact dosage form. Also, if the sponsor wishes to make a claim for efficacy over a specific interval during the course of the day, the clinical protocol would need to include testing at various time points over this interval, e.g., every hour starting at 1 hour post-dose until 12 hours post-dose.*

**General Comments:**

***These are the official minutes of our May 19, 2009 meeting. If you have any questions or disagree with the content of these minutes in any particular, it is your responsibility to bring these points to our attention.***

Linked Applications

Sponsor Name

Drug Name / Subject

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IND 104624

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RHODES PHARMACAL  
CO

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Methylphenidate Hydrochloride Extended  
Release Capsules

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS P LAUGHREN

05/28/2009