

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202100Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 202100

SUPPL #

HFD # 130

Trade Name QUILLIVANT XR

Generic Name methylphenidate extended-release suspension

Applicant Name NextWave Pharmaceuticals, Inc

Approval Date, If Known

### 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 years

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?

Yes, PWR request from FDA dated 6/25/2003, amended 9/2/2003 for Daytrana (NDA 21121). Studies submitted to NDA on 9/5/2003. Pediatric exclusivity granted 12/4/2003.

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#	21514	Daytrana Transdermal Patches
NDA#	21814	Ritalin LA Capsules
NDA#	21259	Metadate CD Capsules
	21419	Methylin Oral Solution
	21475	Methylin Chewable Tablets
	18029	Ritalin SR Tablets
	21121	Concerta tablets
	10187	Ritalin Tablets

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:

Study NWP06-PPK-101: a single-dose, open-label, pharmacokinetic study in 14 children and adolescent patients with ADHD to study the intended NWP06 (20 mg or 60 mg) commercial formulation.

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  NO

Investigation #2 YES  NO

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"):

Study NWP06-PPK-101

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 # 73856 YES  NO   
! Explain:

On July 21, 2010, TrisPharma, Inc, the IND holder, authorized NextWave Pharmaceuticals, Inc to refer to IND 73856 in support of NDA 202100, including any associated amendments

Investigation #2  
IND # YES  NO   
! Explain:



Date: September 28, 2012

Name of Office/Division Director signing form: Thomas Laughren, MD  
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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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  
09/30/2012

THOMAS P LAUGHREN  
10/01/2012

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 202100 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: QUILLIVANT Established/Proper Name: methylphenidate hydrochloride Dosage Form: extended-release oral suspension		Applicant: NextWave Pharmaceuticals, Inc. Agent for Applicant (if applicable): Mike Burdick
RPM: RPM: Sandy Chang		Division: Division: Psychiatry Products
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>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)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Methylin (methylphenidate HCl) Oral Solution (NDA 21419)</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>Methylin is an immediate-release oral solution. Quilivant is a powder that after reconstitution forms an extended-release oral suspension</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p style="color: red;"><b><u>For ALL (b)(2) applications, two months prior to EVERYEVERY each action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input checked="" type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check: September 27, 2012</p> <p><b>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.</b></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>September 30, 2012</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 type="checkbox"/> None    CR August 30, 2011	

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (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).

<p>❖ 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 _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 3</p> <p> <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       </p> <p>         NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)          Subpart I <input type="checkbox"/> Approval based on animal studies       </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request       </p> <p>         BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)          Subpart H <input type="checkbox"/> Approval based on animal studies       </p> <p>         REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input checked="" type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required       </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<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.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input checked="" type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes     No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes     No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes     No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes     No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input checked="" type="checkbox"/> No</p>
<b>CONTENTS OF ACTION PACKAGE</b>	
<p>❖ Copy of this Action Package Checklist<sup>4</sup></p>	
<b>Officer/Employee List</b>	
<p>❖ 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>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<b>Action Letters</b>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) Review Extension: May 25, 2011; CR Aug 30, 2011, AP September 26, 2012</p>
<b>Labeling</b>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	<p>September 25, 2012</p>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<p>July 29, 2010</p>
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ 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>)</li> </ul>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" 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. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	September 25, 2012
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	July 29, 2010
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ 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>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	September 25, 2012
<ul style="list-style-type: none"> <li>❖ 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> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	September 21, 2012, July 16, 2012, May 13, 2011 September 20, 2012, July 16, 2012, May 12, 2011
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA April 14, 2011 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) September 10, 2012, May 19, 2012 <input checked="" type="checkbox"/> ODPD (DDMAC) May 17, 2011 <input checked="" type="checkbox"/> SEALD September 25, 2012 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews PMHS September 26, 2012
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	RPM filing: October 29, 2011 CMC filing: August 31, 2011  <input type="checkbox"/> Not a (b)(2) July 30, 2012 <input type="checkbox"/> Not a (b)(2) September 27, 2012
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ 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></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<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

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>May 18, 2011</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg EOP3: March 29, 2011
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	P-IND: October 11, 2007, May 18, 2006
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<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 type="checkbox"/> None August 29, 2011
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None September 13, 2012, May 11, 2011
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	
• Clinical review(s) ( <i>indicate date for each review</i> )	September 5, 2012, April 7, 2011
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<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> )	April 7, 2011
❖ 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 type="checkbox"/> Not applicable July 19, 2012, April 8, 2011

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<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 checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested letter: August 12, 2011, February 7, 2011; summary: February 9, 2011
<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"/> None
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"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None April 20, 2011
<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"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None August 29, 2011, March 21, 2011
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None
<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"/> None
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None August 15, 2012, May 9, 2011
❖ 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
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI 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"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None August 16, 2012, August 15, 2012, August 26, 2011, May 5, 2011, March 25, 2011, March 23, 2011, August 9, 2010
❖ Microbiology Reviews <input 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>	<input checked="" type="checkbox"/> Not needed
❖ 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>	August 9, 2010
<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) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup>)</i>	Date completed: June 22, 2012 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (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>7</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.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

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

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

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

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

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/s/  
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SHIN-YE CHANG  
10/01/2012



NDA 202100

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

NextWave Pharmaceuticals, Inc.  
20450 Stevens Creek Boulevard  
Suite 150  
Cupertino, CA 95014

ATTENTION: Michael Burdick  
Vice President, Product Development

Dear Mr. Burdick,

Please refer to your New Drug Application (NDA) dated July 29, 2010, received July 30, 2010, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Hydrochloride for Extended-release Oral Suspension, 25 mg/5 mL.

We also refer to your August 2, 2012, correspondence, received August 3, 2012, requesting review of your proposed proprietary name, Quillivant XR. We have completed our review of the proposed proprietary name, Quillivant XR, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your August 3, 2012, 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 Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Shin-Ye Chang at (301) 796-3971.

Sincerely,  
*{See appended electronic signature page}*  
Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
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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CAROL A HOLQUIST  
09/21/2012



NDA 202100

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

NextWave Pharmaceuticals, Inc.  
20450 Stevens Creek Boulevard, Suite 150  
Cupertino, CA 95014

ATTENTION: Michael Burdick  
Vice President Product Development

Dear Mr. Burdick,

Please refer to your New Drug Application (NDA) dated July 29, 2010, received July 30, 2010, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Hydrochloride Extended-Release Powder for Oral Suspension, 25 mg/5 mL.

We also refer to

- your correspondence, dated and received March 31, 2011, requesting review of your proposed proprietary name, Quillivant
- the correspondence issued by Division of Medication Error Prevention and Analysis on May 13, 2011, conditionally finding the proposed name Quillivant acceptable
- the complete response letter issued by Division of Psychiatry Products on August 30, 2011
- your March 30, 2012, resubmission, received March 30, 2012
- the correspondence issued by Division of Psychiatry Products on April 4, 2012, acknowledging your resubmission as a Complete Response to their August 30, 2011 action letter
- your correspondence, dated and received April 17, 2012, requesting review of your proposed proprietary name, Quillivant

We have completed our review of the proposed proprietary name, Quillivant and have concluded that this name is unacceptable for the following reasons:

We have not identified promotional, sound-alike or look-alike concerns with the root name "Quillivant". However, as proposed, the proprietary name does not include a modifier (e.g., ER, XR, XL) to convey that Quillivant is an extended-release dosage form. There are currently marketed methylphenidate immediate-release oral solutions available in 1 mg/mL and 2 mg/mL strengths marketed by another firm under the proprietary name Methylin, along with generic products marketed under the established name, methylphenidate hydrochloride. Methylin, the branded product, is typically administered two to three times daily, with the

dose individualized to the needs of the patient. We recognize there is no marketed immediate-release product with the root name Quillivant that this product needs to distinguish itself from. However, Quillivant needs to be distinguished from the marketed immediate release oral solutions containing methylphenidate. If a modifier is not added to convey the extended-release properties of this oral solution, we are concerned that wrong frequency errors involving the administration of the extended-release dosage form at intervals more frequent than labeled may occur (e.g. taking Quillivant twice or three times a day).

This recommendation is based on new postmarketing data obtained with other extended-release products (not limited to oral suspensions) approved without a modifier in the proprietary name where wrong frequency of administration errors were documented. Wrong frequency errors involved the administration of the extended-release dosage form at intervals more frequent than labeled, (e.g. taking a once daily drug twice a day). Wrong frequency errors occurred despite the presence of clear labeling directives to administer the products at the approved labeled dosing intervals.

Quillivant does not have direct overlapping strengths with the immediate-release methylphenidate oral solutions (5 mg/mL vs. 1 mg/mL or 2 mg/mL). However, prescriptions for Quillivant will not necessarily include the product concentration or strength since this is a single strength product. Moreover, if Quillivant is ordered in milligrams the dose may then directly overlap with immediate-release methylphenidate oral solutions.

The addition of a modifier to the proprietary name may signal to healthcare practitioners that this product differs in regard to formulation and frequency of administration as compared to the currently marketed immediate-release methylphenidate oral solutions, which may help to minimize errors involving the wrong frequency of administration with this product. A modifier may also communicate that this product is an extended-release dosage form and cannot be interchanged with the immediate-release methylphenidate oral solution products.

We recognize there are limitations to this approach since there is postmarketing evidence that modifiers have been omitted or overlooked; however, given the increased risks associated with wrong frequency of administration errors involving Quillivant, we believe the addition of the modifier could add an incremental measure of safety. Therefore, we request you add a modifier to the proposed name, Quillivant.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Shin-Ye Chang at (301) 796-3971.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
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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CAROL A HOLQUIST  
07/16/2012

**From:** [Chang, ShinYe](#)  
**To:** [Mike Burdick](#);  
**Subject:** RE: NDA 202100 Quillivant - (b) (4)  
**Date:** Wednesday, August 24, 2011 3:43:12 PM

---

Hi Mike,

For the ease of quick review of your sample reanalysis submission, please do the following:

1. please report the data in the following format in excel for both study reanalysis sets (study s09-0238 and study NWP06-ppk-101):

Patient ID	time	Original conc.(ng/mL)	Reassayed conc. (ng/mL)	% deviation
------------	------	-----------------------	-------------------------	-------------

2. Perform a linear regression analysis of the above datasets for study NWP06-PPK-01 as well.

3. Perform Incurred Sample Reanalysis using correction factors from both QC sample degradation and linear correlation analysis, respectively, for study NWP06-PPK-101.

4. Provide number of samples that pass the acceptance criteria for study NWP06-PPK-101 using the above correction factors separately.

5. Provide explanation why QC samples stored in human plasma degraded more compared with the real study samples.

We ask for a written response by noon, Thursday, August 25, 2011, followed by a formal submission to the NDA.

Thanks,

Sandy

---

From: Mike Burdick [mburdick@nextwavepharma.com]  
Sent: Wednesday, August 24, 2011 11:03 AM  
To: Chang, ShinYe  
Subject: RE: NDA 202100 Quillivant (b) (4)

Sandy

Thanks for acknowledging receipt. I hope the review goes well. Please let me know if there are any questions or concerns.

Thanks,

Mike

From: Chang, ShinYe [<mailto:ShinYe.Chang@fda.hhs.gov>]  
Sent: Wednesday, August 24, 2011 3:52 AM  
To: Mike Burdick  
Subject: RE: NDA 202100 Quillivant - [REDACTED] (b) (4)

Hi Mike,

The official submission has been received and distributed to the review team. I will let you know if we have any additional questions.

Regards,

Sandy

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From: Mike Burdick [<mailto:mburdick@nextwavepharma.com>]  
Sent: Wednesday, August 24, 2011 4:52 AM  
To: Chang, ShinYe  
Subject: RE: NDA 202100 Quillivant [REDACTED] (b) (4)  
Dear Sandy

Please see attached an email copy of our response to the Information Request letter regarding [REDACTED] (b) (4) bioanalytical data. This was submitted via ESG just a few minutes ago.

As agreed, we have reanalyzed samples from the S09-0238 and NWP-PPK-101 studies. Copies of the submission cover letter and the 2 reanalysis reports are attached for info.

We hope this information addresses the Division's request for confirmatory data to support the reliability of the original data from these 2 studies. Please let me know if you or Division reviewers have any questions, or wish to discuss further.

Thanks,  
Mike

From: Chang, ShinYe [<mailto:ShinYe.Chang@fda.hhs.gov>]  
Sent: Wednesday, August 10, 2011 2:18 PM  
To: Mike Burdick  
Subject: RE: NDA 202100 Quillivant - [REDACTED] (b) (4)

Hi Mike,

We agree with your sample reanalysis plan and acceptance criteria for study S09-0238. We would also like you to reanalyze samples from the pediatric PK study (NWP06-PPK-101). Two time points (4hr and 14hr postdose) each subject (n=14) would be acceptable. The same acceptance criteria can be applied

It is acceptable to conduct the plasma sample reanalysis at (b) (4). We have also forwarded your August 4, 2011 draft response which argues that (b) (4) confirmed that corrected actions were implemented by (b) (4), to CDER Regulatory Affairs for consideration. We've been notified that Compliance should make a decision regarding your proposal during the week of August 15, 2011.

Regards,

Sandy

---

From: Mike Burdick [<mailto:mburdick@nextwavepharma.com>]

Sent: Monday, August 08, 2011 8:23 PM

To: Chang, ShinYe

Subject: RE: NDA 202100 Quillivant - (b) (4)

Dear Sandy,

NextWave wishes to thank you and the Division for talking with us today to address issues related to (b) (4) bioanalytical data in NDA 202100.

As discussed during today's teleconference, NextWave is proposing to conduct an Incurred Sample Reanalysis on retained plasma samples from the S09-0238 relative bioavailability study. The intent of this reanalysis is to provide FDA with assurance that bioanalytical data generated by (b) (4) and included in NDA 202100 is reliable.

Per our discussion, the following is a brief summary of the sampling plan and proposed acceptance criteria:

- ISR will be conducted on Study S09-0238, a 3-way crossover relative bioavailability study, conducted in 28 healthy volunteers. As described in Fast et al 2009, samples from approximate C<sub>max</sub> (4 hrs) and another specified time point (14 hrs) during the elimination phase of the PK curve will be selected. Samples from all 28 subjects, and all 3 treatment arms of the study (approximately 168 samples total) will be reanalyzed.
- Acceptance Criteria: as described in Fast et al 2009, 67% of the

reanalyzed samples should agree within 20% of the initial assay values.

A detailed sample selection and analysis plan will be developed prior to conducting the ISR.

Please let me know if you have any questions.

Best regards,  
Mike

#### Reference

Fast DM, Kelley M, Viswanathan CT, O'Shaughnessy J, King SP, Chaudhary A, Weiner R, DeStefano AJ, Tang D. Workshop Report and Follow-Up—AAPS Workshop on Current Topics in GLP Bioanalysis: Assay Reproducibility for Incurred Samples—Implications of Crystal City Recommendations. AAPS Journal. 2009;11(2):238-241.

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/s/  
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SHIN-YE CHANG  
08/26/2011



NDA 202100

**INFORMATION REQUEST**

NextWave Pharmaceuticals, Inc.  
Attention: Michael Burdick  
VP, Product Development  
20450 Stevens Creek Blvd, Suite 150  
Cupertino, CA 95014

Dear Mr. Burdick:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for QUILLIVANT (methylphenidate hydrochloride) for extended-release oral suspension.

(b) (4)

(b) (4)

**Please respond to this query within 14 days from the date of this letter.**

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Room 6300  
Silver Spring, MD 20993-0002

Once we have made an assessment regarding the potential impact of these data, we will contact you regarding the steps that need to be taken, if any, to assure the accuracy of the data submitted to your application.

If you have any questions, call Shin-Ye Sandy Chang, Regulatory Project Manager, at (301)796-3971.

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

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/s/  
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THOMAS P LAUGHREN  
08/02/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 202100

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

NextWave Pharmaceuticals, Inc.  
Attention: Michael Burdick  
VP, Product Development  
20450 Stevens Creek Blvd, Suite 150  
Cupertino, CA 95014

Dear Mr. Burdick:

Please refer to your July 29, 2010 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for QUILLIVANT (methylphenidate hydrochloride) for extended-release oral suspension.

On May 19, 2011, we received your May 19, 2011, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 30, 2011.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 9, 2011.

If you have any questions, call Shin-Ye Sandy Chang, Regulatory Project Manager, at (301) 796-3971.

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

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/s/  
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THOMAS P LAUGHREN  
05/25/2011



NDA 202100

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

NextWave Pharmaceuticals, Inc.  
20450 Stevens Creek Boulevard, Suite 150  
Cupertino, California 95014

ATTENTION: Michael Burdick  
Vice President Product Development

Dear Mr. Burdick,

Please refer to your New Drug Application (NDA) dated July 29, 2010, received July 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate HCl Extended-Release Powder for Oral Suspension, 25 mg/5 mL.

We also refer to your March 31, 2011, correspondence, received March 31, 2011, requesting review of your proposed proprietary name, Quillivant. We have completed our review of the proposed proprietary name, Quillivant, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your March 31, 2011 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 Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Shin-Ye Chang at (301) 796-3971.

Sincerely,  
*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
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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CAROL A HOLQUIST  
05/13/2011

**From:** [Chang, ShinYe](#)  
**To:** ["Mike Burdick";](#)  
**cc:** [Chang, ShinYe;](#)  
**Subject:** NDA 202100; Nextwave; QUILLIVANT; labeling  
**Date:** Tuesday, May 10, 2011 1:09:22 PM  
**Attachments:** [202100 QUILLIVANT FDA Label 05-10-11.doc](#)

---

Hi Mike,

Please refer to your new drug application submitted to NDA 202100, dated July 29, 2010, and received July 30, 2010. In an effort to take a final action on this NDA, the Agency is seeking your concurrence on the changes denoted in the attached Word document.

We ask that you use this exact document for making any revisions and use 'track changes' to indicate any edits. Please respond with any comments/revisions by COB Monday, May 16, 2011.

Regards,

Sandy

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/s/  
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SHIN-YE CHANG  
05/19/2011



NDA 202100

**GENERAL ADVICE**

NextWave Pharmaceuticals, Inc.  
Attention: Mike Burdick  
VP, Product Development  
20450 Stevens Creek Blvd, Suite 150  
Cupertino, CA 95014

Dear Mr. Burdick:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for methylphenidate extended-release powder for oral suspension 25 mg/5 mL.

We also refer to your April 22, 2011, submission, containing your response to our March 10, 2011 letter containing the Agency's recommendations for the container labels, the carton labeling, and dosing device:

**A. All Container Labels and Carton Labeling**

1. We acknowledge your statement that the presentation of strength in milligrams per milliliter (i.e., 5 mg/mL) will minimize prescription and dosing errors because the calculation for dosing will be easier than presenting the strength as 25 mg/5 mL. We also agree that having the concentration of this product listed per milliliter is important. However, this product is five times as concentrated as the reference listed drug, Methylin Oral Solution and Methylin strength is expressed as 5 mg/5 mL. Labeling the proposed Methylphenidate HCl Extended-release Powder for Suspension with only "5 mg/mL" increases the similarity to the current Methylin presentation of strength. The first four characters of each strength "5 mg/" overlap and the last two characters of each strength "mL" overlap. Because patients and healthcare practitioners may already be familiar with Methylin and the concentration of 5 mg/mL we are concerned that patients and healthcare practitioners may see the same first four characters of the proposed strength and misinterpret the strength of the proposed product as 5 mg/5 mL. As a result of this confusion, dosing errors may occur.

Highlighting the strength of Methylphenidate HCl Extended-release Powder for Suspension as "25 mg/5 mL" and having a numerical difference as the first character of each strength (i.e. 2 vs. 5) would help differentiate the concentration between this product and reference listed drug is important to ensure the doses are calculated correctly.

Thus, we recommend revising the strength of the product to state the strength in milligrams per 5 milliliters and concentration in parentheses in milligrams per milliliter immediately underneath the strength. The strength and concentration of the product should appear as follows:

25 mg/5 mL  
(5 mg/mL)  
When reconstituted

2. Increase the prominence of the dosage form to be as prominent as the established name by increasing the font size

**B. Dosing Device**

3. We recommend that you replace the manufacturer name with the proprietary and established names and dosage form on the dosing device prior to approval. As currently presented, the name of the manufacturer may be misinterpreted as the product's proprietary name, which is confusing and misleading and may cause medication errors. If not feasible at this time, provide a time frame of when the change will be implemented. Additionally, provide information regarding how many units will be sent out using the syringes' current presentation and how long you expect these syringes remain on the market.

Please incorporate the above revisions and submit revised labeling as a MS Word document using track changes delineating the revisions when compared to the labeling submitted on April 22, 2011.

We request that your response be submitted by May 12, 2011.

If you have any questions, call Shin-Ye Sandy Chang, Regulatory Project Manager, at (301) 796-3971.

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

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/s/  
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THOMAS P LAUGHREN  
05/08/2011



NDA 202100

**GENERAL ADVICE**

NextWave Pharmaceuticals, Inc.  
Attention: Mike Burdick  
VP, Product Development  
20450 Stevens Creek Blvd, Suite 150  
Cupertino, CA 95014

Dear Mr. Burdick:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for methylphenidate extended-release powder for oral suspension 25 mg/5 mL.

With the help of the Division of Medication Error Prevention and Analysis (DMEPA) within the Office of Surveillance and Epidemiology (OSE), we have reviewed your submission and have the following recommendations for the container labels, the carton labeling, and dosing device:

**A. All Container Labels and Carton Labeling**

**Principal Display Panel**

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

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

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

25 mg/5 mL  
(5 mg/mL)  
When reconstituted

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

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

### **Side Panel**

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

### **B. Carton Labeling**

#### **Principal Display Panel**

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

#### **Side Panels**

11. Revise all instances of the term [REDACTED] (b) (4) to read “oral syringe”. [REDACTED] (b) (4) [REDACTED].
12. Revise the word [REDACTED] (b) (4) to state ‘bottle adapter’ to enhance clarity of the term.
13. Add the sentence “Use only with the oral syringe provided with this product” immediately underneath the bolded sentence “Instructions for Using Enclosed Dosing Device”. We recommend this change to emphasize consumers understanding that only the enclosed oral syringe is appropriate for administration of this product.

14. Revise the sentence [REDACTED] <sup>(b) (4)</sup> to state “insert tip of oral syringe provided with this product into adapter” to emphasize the use of the oral syringe enclosed with this product.
15. Add the statement “Dispense with enclosed oral syringe” to the Pharmacist Information to emphasize that the product must be dispensed with the oral syringe provided by the manufacturer.

**C. Dosing Device**

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

Please incorporate the above revisions and submit revised labeling as a MS Word document using track changes delineating the revisions when compared to the labeling submitted on February 7, 2011.

We request that your response be submitted by April 22, 2011.

If you have any questions, call Shin-Ye Sandy Chang, Regulatory Project Manager, at (301) 796-3971.

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

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/s/  
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THOMAS P LAUGHREN  
04/18/2011

**From:** [Chang, ShinYe](#)  
**To:** ["Mike Burdick";](#)  
**Subject:** RE: NDA 202100; information request - instructions for use  
**Date:** Thursday, March 31, 2011 12:57:13 PM  
**Attachments:** [Banzel labeling.pdf](#)

---

Hi Mike,

We would also need an Instruction for Use, either appended to the Med Guide or given as a separate document. The preference is appended to the end of the Med Guide.

A drug product that has a similar dosing device to yours is Banzel (rufinamide) suspension. For your reference, I've attached the labeling to Banzel.

Please let me know if you have any other questions.

Regards,

Sandy

---

**From:** Mike Burdick [mailto:[mburdick@nextwavepharma.com](mailto:mburdick@nextwavepharma.com)]  
**Sent:** Wednesday, March 30, 2011 1:50 PM  
**To:** Chang, ShinYe  
**Subject:** RE: NDA 202100; information request - instructions for use

Hi Sandy

In the proposed prescribing information (Section 17.2), we have included the following text:

(b) (4)



On the proposed carton labeling, we have included the following text:

(b) (4)

We think the above labeling text provides adequate instructions for use to patients/caregivers. We can develop some graphic images to show details about some of the critical steps (I have highlighted in yellow what I think are critical steps). Is this approach acceptable?

Thanks,  
Mike

---

**From:** Chang, ShinYe [mailto:ShinYe.Chang@fda.hhs.gov]  
**Sent:** Wednesday, March 30, 2011 10:19 AM  
**To:** Mike Burdick  
**Subject:** NDA 202100; information request - instructions for use

Hi Mike,

In reviewing the labeling for methylphenidate ER powder for suspension, we notice there is a lack of instructions for use for the caregiver/patient. We ask that you submit a proposed instructions for use for patients. You should develop useful, clearly labeled diagrams that address each step of the process for using the product.

Please provide this information in writing at your earliest convenience, but no later than COB Monday, April 18, 2011.

Let me know if you have any additional questions.

Regards,

Sandy

**From:** [Chang, ShinYe](#)  
**To:** ["Mike Burdick";](#)  
**Subject:** RE: NDA 202100;Nextwave; CMC information request  
**Date:** Tuesday, February 15, 2011 4:21:33 PM

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**From:** Mike Burdick [mailto:mburdick@nextwavepharma.com]  
**Sent:** Tuesday, February 15, 2011 3:54 PM  
**To:** Chang, ShinYe  
**Subject:** RE: NDA 202100;Nextwave; CMC information request

Dear Sandy

Please note that Tris Pharma responded to this question in a 02/14/2011 submission to DMF 023870. A copy of the cover letter for this DMF submission is attached for information.

Please let me know if there are any further questions regarding this topic.

Best regards,  
Mike

---

**From:** Chang, ShinYe [mailto:ShinYe.Chang@fda.hhs.gov]  
**Sent:** Wednesday, February 09, 2011 11:13 AM  
**To:** Mike Burdick  
**Subject:** RE: NDA 202100;Nextwave; CMC information request

Hi Mike,

To clarify, the information request from 2/7/2011 is a follow-up to the previous requests.

In the Formulation Development Report found in the original IND submission dated 11/20/2008 (paragraph below), there was discussion of the (b) (4)

(b) (4)

(b) (4)

Our request is for the stability data for this pre-IND (b) (4) that is currently proposed.

Let me know if you have any additional questions.

**From:** [Chang, ShinYe](#)  
**To:** ["Mike Burdick";](#)  
**Subject:** RE: Request for alternative delivery method for a Paragraph IV certification notice  
**Date:** Thursday, September 30, 2010 2:55:26 PM

---

Hi Mike,

As long as you can provide documentation that the company holding the patent received the Paragraph IV certification notice, you can use FedEx.

Regards,

Sandy

---

**From:** Mike Burdick [mailto:mburdick@nextwavepharma.com]  
**Sent:** Wednesday, September 29, 2010 1:44 PM  
**To:** Chang, ShinYe  
**Subject:** Request for alternative delivery method for a Paragraph IV certification notice

Dear Sandy,

Reference is made to NextWave Pharmaceuticals' recently filed 505(b)(2) application for Methylphenidate HCl Extended-Release Powder for Oral Suspension (NDA 202100). Module 1.3.5.2 of our NDA 202100 contained a Patent Certification Statement that NextWave will serve a Paragraph IV certification notice to the NDA and patent holder for the reference listed drug, Methylin Oral Solution (NDA 21-419).

**The purpose of this email is to request allowance to use an alternative delivery service for the Paragraph IV certification notice. Instead of using registered or certified mail as described in 21 CFR 314.95(a) and (e), we intend to use FedEx overnight delivery.**

Thank you for considering our request to use an alternative delivery service for a Paragraph IV certification notice.

Please let me know if you have any questions regarding this request.

Best regards,  
Mike

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Michael Burdick  
VP, Product Development  
NextWave Pharmaceuticals, Inc  
20450 Stevens Creek Blvd, Suite 150

Cupertino, CA 95014  
T 650.248.9205 | [mburdick@nextwavepharma.com](mailto:mburdick@nextwavepharma.com) | [www.nextwavepharma.com](http://www.nextwavepharma.com)

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/s/  
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SHIN-YE CHANG  
05/16/2011



NDA 202100

**PROPRIETARY NAME REQUEST  
WITHDRAWN**

NextWave Pharmaceuticals Inc.  
20450 Stevens Creek Blvd, Suite 150  
Cupertino, California 95014

ATTENTION: Michael Burdick  
Vice President, Product Development

Dear Mr. Burdick:

Please refer to your New Drug Application (NDA) dated July 29, 2010, received July 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate HCl Extended-release Powder for Oral Suspension, 25 mg per 5 mL.

We acknowledge receipt of your March 8, 2011 correspondence, received March 8, 2011, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b)(4). This proposed proprietary name request for (b)(4) is considered withdrawn as of March 8, 2011.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sandra Griffith, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Shin-Ye Chang at (301) 796-3971.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
03/09/2011

**From:** [Chang, ShinYe](#)  
**To:** ["Mike Burdick";](#)  
**Subject:** NDA 202100; Nextwave; methylphenidate ER powder for susp; information request  
**Date:** Wednesday, March 09, 2011 11:09:43 AM

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Hi Mike,

In your February 7, 2011 response to our January 13, 2011 CMC information request for data to support the "shake vigorously" statement, you stated that full potency was obtained (b) (4) minutes.

We have concerns regarding the potency of the suspension if shaken for less than (b) (4) minute, and ask that you provide the potency data of the suspension from 0 to 1 min, in 10 second increments.

Please provide this information to me as well as officially to the NDA by COB Wednesday, March 23, 2011.

Regards,

Sandy

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/s/  
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SHIN-YE CHANG  
03/10/2011

**MEMORANDUM**

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

**Time/Date:** 1530-1600 EST - March 2011

**To:** Carol Holquist

**CC:** Chris Wheeler

**From:** Sandra J. Griffith

**Application:** NDA 202100 (b)(4) (Methylphenidate Hydrochloride) Extended-release Powder for Oral Suspension, RCM 2011-77.

**OSE Goal Date:** 4/11/2011

**FDA Participants: OSE**

Carol Holquist, R.Ph., DMEPA Director

Yelena Maslov, Pharm.D., DMEPA Primary Reviewer,

Sandra J. Griffith, BSN, RN, OSE Safety Regulatory Project Manager

**FDA Participants: OND**

Thomas Laughren, M.D., DPP Division Director

Mitchell Mathis, M.D., DPP Deputy Division Director

Robert Levin, M.D., DPP Clinical Team Leader

**Sponsor/Applicant:** Next Wave Pharmaceuticals

Michael Burdick: Vice President Product Development, and POC

Craig Chambliss, SVP and Chief Business Officer

Tracy Woody, VP Sales and Marketing

Nora Roselle, Managing Director US Regulatory Affairs, Drug Safety Institute

**Background:**

A request for review of the proposed proprietary name (b)(4) was submitted to the FDA on 1/11/2011.

During the review DMEPA became concerned regarding the safety issues found with the proposed proprietary name, (b)(4). The name was found to be vulnerable to confusion with the name (b)(4) due to the name pair's phonetic similarity and overlapping product characteristics.

**Discussion**

DMEPA communicated the following concerns to the Applicant regarding potential confusion:

(b)(4)

(b)(4)

**Steps Forward**

DMEPA informed the Applicant of the following options to be taken as steps forward:

1. Withdraw the proposed proprietary name (b) (4) and submit a new proprietary name for review within a week. This will allow DMEPA to complete a proprietary name review by the OND PDUFA date. DMEPA also suggested that by Friday (03/04/2011) or Monday (03/07/2011) the Applicant emails a list of 3 to 4 proposed proprietary names to screen prior to official submission.
2. Wait for the official completed results of our review, which DMEPA will finalize on or before 4/11/2011. However, if the alternate name is submitted after the denial letter, DMEPA may not be able to complete the proprietary name review by the OND PDUFA goal date of May 30, 2011. Thus, the product may need a post-approval supplement for the proprietary name.

**Decision:**

The Applicant verbalized understanding of their options and stated they wish to market the product with a proprietary name. They agreed to withdraw the proposed proprietary name (b) (4). They plan to send a few proposed names to DMEPA by Friday March 4, 2011 for screening prior to formally submitting a new proprietary name for review. DMEPA agreed to a cursory review of a list of proposed names from the Applicant prior to official submission since the application is close to the PDUFA review goal date. The Applicant was referred to the Draft Guidance for Industry for complete submission for the Evaluation of Proprietary Names at the FDA web site to aid in their re-submission process.

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/s/  
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SANDRA J GRIFFITH  
03/04/2011

**From:** Chang, ShinYe  
**To:** "Mike Burdick";  
**Subject:** RE: NDA 202100;Nextwave; CMC information request  
**Date:** Tuesday, February 15, 2011 4:21:33 PM

---

**From:** Mike Burdick [mailto:mburdick@nextwavepharma.com]  
**Sent:** Tuesday, February 15, 2011 3:54 PM  
**To:** Chang, ShinYe  
**Subject:** RE: NDA 202100;Nextwave; CMC information request

Dear Sandy

Please note that Tris Pharma responded to this question in a 02/14/2011 submission to DMF 023870. A copy of the cover letter for this DMF submission is attached for information.

Please let me know if there are any further questions regarding this topic.

Best regards,  
Mike

---

**From:** Chang, ShinYe [mailto:ShinYe.Chang@fda.hhs.gov]  
**Sent:** Wednesday, February 09, 2011 11:13 AM  
**To:** Mike Burdick  
**Subject:** RE: NDA 202100;Nextwave; CMC information request

Hi Mike,

To clarify, the information request from 2/7/2011 is a follow-up to the previous requests.

In the Formulation Development Report found in the original IND submission dated 11/20/2008 (paragraph below), there was discussion of the (b) (4)

(b) (4)



(b) (4)

Our request is for the stability data (b) (4) that is currently proposed.

Let me know if you have any additional questions.

Regards,

Sandy

---

**From:** Chang, ShinYe  
**Sent:** Monday, February 07, 2011 3:12 PM  
**To:** 'Mike Burdick'  
**Subject:** RE: NDA 202100;Nextwave; CMC information request

Hi Mike,

Please provide all available stability data

(b) (4)

(b) (4)

Regards,

Sandy

---

**From:** Mike Burdick [mailto:mburdick@nextwavepharma.com]  
**Sent:** Monday, January 31, 2011 11:51 AM  
**To:** Chang, ShinYe  
**Subject:** RE: NDA 202100;Nextwave; CMC information request

Hi Sandy

If necessary, Tris could retain reconstituted samples that have already reached the 4-month storage point, and assay them at month 5, month 6, etc. This would be informal data, gathered outside of the stability protocol.

The available stability data supports storing the product for at least 4 months after reconstitution, which is well beyond the expected usage interval. Please note that the packaging configurations are intended to provide a 30-day supply of product (due to DEA/pharmacy dispensing restrictions for controlled substances). We therefore thought that 4 months expiration dating on the reconstituted product would be more than sufficient.

I hope this answers the questions, but let me know if further information or discussion is needed.

Best regards,  
Mike

---

**From:** Chang, ShinYe [mailto:ShinYe.Chang@fda.hhs.gov]

**Sent:** Monday, January 31, 2011 8:39 AM  
**To:** Mike Burdick  
**Subject:** RE: NDA 202100;Nextwave; CMC information request

Hi Mike,

Can you provide more information as to how you would generate data from existing samples, and what the periods of time would be?

Thanks,

Sandy

---

**From:** Mike Burdick [mailto:mburdick@nextwavepharma.com]  
**Sent:** Sunday, January 30, 2011 2:46 PM  
**To:** Chang, ShinYe  
**Subject:** RE: NDA 202100;Nextwave; CMC information request

Dear Sandy,

The manufacturer (Tris Pharma), who is also conducting the stability studies, has replied to me that they do not have any existing stability data for periods greater than 4 months for the reconstituted drug product in suspension. Some data can be generated from existing samples if needed.

Please let me know if you or the CMC reviewers have further questions. Please also let me know if this email response is sufficient, or if you want the response to be formally submitted to the NDA.

Best regards,  
Mike

---

**From:** Chang, ShinYe [mailto:ShinYe.Chang@fda.hhs.gov]  
**Sent:** Sunday, January 30, 2011 5:51 AM  
**To:** Mike Burdick  
**Subject:** RE: NDA 202100;Nextwave; CMC information request

Hi Mike,

Can you tell me when we can expect a response on this information request?

Thanks,

Sandy

---

**From:** Mike Burdick [mailto:mburdick@nextwavepharma.com]  
**Sent:** Friday, January 21, 2011 6:03 PM  
**To:** Chang, ShinYe  
**Subject:** RE: NDA 202100;Nextwave; CMC information request

Dear Sandy

Acknowledging receipt of this latest question – I'm checking into it, should have a response soon.

Best regards,  
Mike

---

**From:** Chang, ShinYe [mailto:ShinYe.Chang@fda.hhs.gov]  
**Sent:** Friday, January 21, 2011 1:20 PM  
**To:** Mike Burdick  
**Subject:** NDA 202100;Nextwave; CMC information request

Hi Mike,

We'd like to obtain any existing stability data for periods greater than 4 months for the reconstituted drug product in suspension. The reason for the request is to address the potential concern about cases in which a patient might keep unused drug product in suspension for periods greater than 4 months and then use the product subsequently.

We request a written response by COB Friday, January 28, 2011. Please let me know if more time will be needed.

Regards,

Sandy

**From:** [Chang, ShinYe](#)  
**To:** ["Mike Burdick"](#);  
**Subject:** RE: NDA 202100;Nextwave; stat information request  
**Date:** Tuesday, January 25, 2011 3:34:59 PM

---

**From:** Mike Burdick [mailto:mburdick@nextwavepharma.com]  
**Sent:** Tuesday, January 25, 2011 3:34 PM  
**To:** Chang, ShinYe  
**Subject:** RE: NDA 202100;Nextwave; stat information request

Hi Sandy

I'm working on it right now. We'll either have it in by COB (Pacific time) today, or tomorrow.

Best regards,  
Mike

**From:** Chang, ShinYe [mailto:ShinYe.Chang@fda.hhs.gov]  
**Sent:** Tuesday, January 25, 2011 12:30 PM  
**To:** Mike Burdick  
**Subject:** RE: NDA 202100;Nextwave; stat information request

Hi Mike,

Please let me know if we can still expect your response to this information request by COB today.

Regards,

Sandy

---

**From:** Mike Burdick [mailto:mburdick@nextwavepharma.com]  
**Sent:** Wednesday, January 19, 2011 11:54 PM  
**To:** Chang, ShinYe  
**Subject:** RE: NDA 202100;Nextwave; stat information request

Dear Sandy

Just wanted to confirm that I have received this request, and am checking into.

We should have a response soon.

Best regards,  
Mike

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**From:** Chang, ShinYe [mailto:ShinYe.Chang@fda.hhs.gov]  
**Sent:** Tuesday, January 18, 2011 7:02 AM  
**To:** Mike Burdick  
**Subject:** NDA 202100;Nextwave; stat information request

Hi Mike,

We would like to request the following information to aid the review of NDA 202100, MPH extended release powder for oral suspension:

- 1) Please submit the body weight, height and BMI for subjects in adult PK study S09-0238. Data should be submitted in .xpt format.
- 2) Please clarify whether the pediatric patient PK study (PPK-101) was done under fed condition or not.

Please send this information to me via email, as well as submit it officially to the NDA.

We request a written response by COB Tuesday, January 25, 2011.

Regards,

Sandy



NDA 202100

**INFORMATION REQUEST**

NextWave Pharmaceuticals, Inc.  
Attention: Michael Burdick  
Vice President Product Development  
20450 Stevens Creek Blvd., Suite 150  
Cupertino, CA 95014

Dear Mr. Burdick:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Hydrochloride Extended-Release Powder for Oral Suspension.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- 1) Your proposed chemical name of the drug substance [REDACTED] (b) (4) [REDACTED] is not consistent with the USP chemical name (methyl  $\alpha$ -phenyl-2-piperidineacetate hydrochloride). Include chemical name of the drug substance in labeling consistent with the USP (methyl  $\alpha$ -phenyl-2-piperidineacetate hydrochloride).
- 2) Since the drug product is a suspension dosage form it is possible that sedimentation would take place. Define “shake vigorously” with time and type of shaking along with test data to support your statement.
- 3) In draft carton and container labels you stated that “Shake well before using. Keep bottle tightly closed. Discard and unused portion of the reconstituted suspension after 120 days”. Change this statement as “Shake well before using. Keep bottle tightly closed. Discard any unused portion of the reconstituted suspension after 120 days”( replace **and** with **any**).

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.

Branch Chief  
Branch I, Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAMESH K SOOD  
01/13/2011



NDA 202100

**FILING COMMUNICATION**

NextWave Pharmaceuticals, Inc.  
Attention: Michael Burdick  
VP, Product Development  
20450 Stevens Creek Blvd, Suite 150  
Cupertino, CA 95014

Dear Mr. Burdick

Please refer to your new drug application (NDA) dated July 29, 2010, received July 30, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for methylphenidate extended-release powder for oral suspension 25 mg/ 5 ml.

We also refer to your submission dated August 18, 2010.

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 May 30, 2011.

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, midcycle, 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 May 9, 2011.

We acknowledge your request for consideration for 6 months of additional exclusivity for this product related to pediatric exclusivity. Please refer to the July 12, 2010 email communication between yourself and Project Manager Shin-Ye Sandy Chang of the Division of Psychiatry Products, in which you were notified that "you would be eligible for a Written Request, as long as you do not submit the completed studies to the NDA for 505(b)(2). You would be ineligible if any study reports are submitted to the NDA. In order to qualify for a Written Request, you will need to submit a Proposed Pediatric Study Request (PPSR) for review." Because you have submitted to the Agency results of the studies that would be included in the Written Request, you are not eligible to receive a Written Request for these studies.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

If you have any questions, call Shin-Ye Sandy Chang, Regulatory Project Manager, at (301) 796-796-3971.

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

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/s/

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THOMAS P LAUGHREN  
09/27/2010



NDA 202100

**NDA ACKNOWLEDGMENT**

NextWave Pharmaceuticals, Inc.  
Attention: Michael Burdick  
VP, Product Development  
20450 Stevens Creek Blvd  
Suite 150  
Cupertino, CA 95014

Dear Mr. Burdick:

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: Methylphenidate HCl Extended-Release Powder for Oral Suspension  
25 mg/5 ml

Date of Application: July 29, 2010

Date of Receipt: July 30, 2010

Our Reference Number: NDA 202100

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 September 28, 2010 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.

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>

If you have any questions, call me, at (301) 796-3971.

Sincerely,

*{See appended electronic signature page}*

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-202100	ORIG-1	NextWave Pharmaceuticals, Inc. 20450 Stevens Creek Blvd, Suite 150, Cupertino, CA 95014	METHYLPHENIDATE HCL ER

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/s/

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SHIN-YE CHANG  
08/05/2010



IND 73856

**MEETING MINUTES**

TrisPharma, Inc.  
Attention: W. Scott Groner  
Director Regulatory Affairs and Compliance  
2033 Route 130, Suite D  
Monmouth Junction, NJ 08852

Dear Mr. Groner:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate (b)(4) ER Powder for Oral Suspension.

We also refer to the meeting between representatives of your firm and the FDA on March 22, 2010. The purpose of the meeting was to review the results of the Phase 3 trial, and to discuss plans for addressing outstanding concerns from the pre-IND meetings and IND submissions before NDA submission.

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, call Shin-Ye Sandy Chang, Regulatory Project Manager at (301) 796-3971.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure – meeting minutes

**MEMORANDUM OF MEETING MINUTES**

IND 73856 – Methylphenidate (b) (4) ER Powder for Oral Suspension  
Tris Pharma, Inc.  
Type B meeting/ End of Phase 3  
Face to Face

Tris Pharma, Inc. requested this End of Phase 3 meeting in a submission dated November 24, 2009, received November 25, 2009. This is an End of Phase 3 meeting held on March 22, 2010. The purpose of this meeting is to review the results of the Phase 3 trial, and to discuss the sponsor's plans for addressing outstanding concerns from the pre-IND meetings and IND submissions before NDA submission.

**FDA Participants:** (Title and Office/Division)

Thomas Laughren, M.D.	Division Director
Mitchell Mathis, M.D.	Deputy Division Director
Robert Levin, M.D.	Medical Team Leader
Francis Becker, M.D.	Medical Reviewer
Thomas Oliver, Ph.D.	Pharmaceutical Assessment Lead
Raman Baweja, Ph.D.	Clinical Pharmacology Team Leader
Andre Jackson, Ph.D.	Clinical Pharmacology Reviewer
Linda Fossom, Ph.D.	Pharmacology/Toxicology Team Leader
Ikram Elayan, Ph.D.	Pharmacology/Toxicology Reviewer
Yang, Peiling Ph.D.	Statistical Team Leader
Chen, Yeh-Fong Ph.D.	Mathematical Statistician
Shin-Ye Sandy Chang, Pharm.D.	Regulatory Project Manager

**Anticipated Sponsor Attendee List:**

Scott Groner	Director, Reg. Affairs & Compliance, Tris Pharma, Inc.
Yu-Hsing Tu, Ph.D.	Vice President of R&D, Tris Pharma, Inc.
Ashok Peruma	Manager, Product Development, Tris Pharma, Inc
Michael Burdick	Vice President, Product Development, NextWave Pharmaceuticals
Sally Berry, M.D., Ph.D.	Vice President of Clinical Affairs, NextWave Pharmaceuticals

(b) (4)

**Background:**

IND 73,856 was submitted on November 20, 2008 to support the development of NWP06 (Methylphenidate (b)(4) Extended Release Powder for Oral Suspension) for the treatment of children with Attention Deficit Hyperactivity Disorder (ADHD). The drug product contains the equivalent of 25 mg methylphenidate HCl per 5 mL of oral suspension. The sponsor plans to submit an NDA application, utilizing the 505(b)(2) regulatory pathway for the approval of NWP06, using Methylin® Oral Solution as the Reference Listed Drug (RLD). The purpose of this meeting shall be to review the results of the Phase 3 trial, NWP06-ADD-100, and to discuss the sponsor's plans for addressing outstanding concerns from the pre-IND meetings and IND submission, as well as any other issues that need to be addressed before NDA submission. Topics to be discussed shall be CMC, Pharmacology/Toxicology, Clinical Pharmacology, Clinical, and Labeling.

In support of the NDA, the sponsor plans to submit data from the following studies:

1. Study S09-0238 – will be a single-dose, 3-way, bioavailability and PK study in healthy adult subjects (n = 30) with the Tris product versus Methylin® Oral Solution under fasting conditions. This study shall also include a food-effect arm for the Tris product.
2. NWP06-PedPK-101 – will be a single-dose bioavailability and PK study to be conducted in pediatric patients 6 to 17 years of age (n = 12) with the Tris product.
3. NWP06-ADD-100 – The study was completed in August 2009. This was a Phase 3, randomized, double-blind, placebo-controlled, crossover, laboratory classroom study assessing the efficacy and safety of Methylphenidate (b)(4) Extended-Release Oral Suspension in 45 pediatric patients (ages 6 to 12 years) with ADHD. In the open-label dose-optimization phase (4-6 weeks), subjects were treated with flexible doses ranging from 20 to 60 mg/day. After dose-optimization, subjects were randomized to one of two double-blind treatment sequences. In Sequence A, subjects were treated with active methylphenidate for one week, followed by placebo for one week. In Sequence B, the order of study drug treatments was reversed. At the end of each week, subjects had ADHD assessments in a laboratory classroom. There was a practice laboratory classroom session before the randomized, controlled phase. The initial methylphenidate dose for all subjects was 20 mg once daily in the morning. The dose could be titrated weekly in increments of 10 or 20 mg until an optimal dose or maximum dose (60 mg/day) was reached. During the controlled phase, subjects were treated with the optimal dose that was established in the open-label, optimization phase.

The sponsor states that NWP06-ADD-100 demonstrated the efficacy of the Tris methylphenidate product, compared to placebo, as measured by the difference in SKAMP-Combined scores at 4 hours post-dosing between treatment groups. The sponsor also reports that the study was positive for the key secondary efficacy endpoints: difference between treatments in the SKAMP-combined scores at each post-dose time point. Reportedly, the onset of efficacy was demonstrated at 0.75 hours post-dose, which was the first assessment

time point. Efficacy was demonstrated at all time points including 12 hours post-dose, which was the last assessment. The assessment time points included: baseline and 0.75, 2, 4, 8, 10, and 12 hours after dosing. The sponsor used a closed-testing procedure when analyzing data for the multiple time points.

4. Study S07-0443 – This study was a single-dose, open-label, 2-way cross-over, pharmacokinetic study in healthy adult subjects (n = 11) who received Tris Methylphenidate (b) (4) extended-release liquid in a 72 mg single dose, compared to Concerta 72 mg. The two formulations were not demonstrated to be bioequivalent. Data from this single-dose study were used in a model simulation to predict steady state methylphenidate plasma levels. The sponsor concludes that the analysis predicts a negligible potential for accumulation of methylphenidate for both the Tris product (72 mg) and Concerta 72 mg.

Data modeling was conducted using trough plasma levels obtained at steady state in children in the NWP06-ADD-100 trial as well as the levels observed in adult subjects dosed with Tris Methylphenidate (b) (4) product in Study S07-0443. The sponsor states that when the plasma level data was normalized for dose and body weight, very similar plasma concentrations at 24 hours (Conc<sub>24hr</sub>) values were observed in the pediatric subjects as compared to the adult subjects.

#### **Questions from the sponsor:**

#### **CMC**

#### **Stability Studies**

***Question 1a: Based on the information provided in section 10.1, is the amount of stability proposed at the time of filing acceptable for submission?***

***Question 1b: Based on the information provided in section 10.1, would the FDA grant a 24-month room temperature expiration date for all proposed fill sizes of the drug product?***

***Question 1c: Based on the information provided in section 10.1, would the FDA grant (b) (4) ?***

***Question 1d: Will adequate data be generated to support a 4-month post-reconstitution expiration date for all proposed fill sizes of the drug product?***

#### **Preliminary Comments:**

*We recommend that you submit 12 months of long term and 6 months of accelerated stability data at the time of NDA submission. It is unknown whether you propose to have the post-reconstitution expiry added to the drug product expiry or whether the post-reconstitution expiry will be included within the drug product expiry. Ultimately, your NDA will need to delineate how these expiries will be stated in labeling. The assigned expiry and the post-reconstitution expiry will be determined as part of the NDA review and will be based on the “quantity” and “quality” of the submitted data. Properly aged*

product (i.e., newly prepared and aged Methylphenidate (b) (4) ER Powder) will need to be evaluated as part of your reconstitution stability program (refer to ICH Q1A, Section 2.2.7). These recommendations are for the drug product outlined in the briefing package and may change if another packaging form (b) (4) is ultimately chosen.

**Discussion at Meeting:**

The sponsor stated that stability data from 3 batches of Methylphenidate (b) (4) ER Powder (b) (4) will be submitted in the original NDA. In addition to this proposed commercial packaging size, additional proposed commercial sizes (b) (4)

(b) (4)

(b) (4)

**Question 2:** Based on information provided in section 10.1.4, has Tris adequately addressed FDA concerns regarding the potential for the formation of (b) (4)

**Preliminary Comments:**

It is still not clear whether any (b) (4) and you will need to include information on this issue in your NDA. Otherwise, the general approach you have taken appears reasonable. The ultimate decision on whether there is adequate control of potential (b) (4) will be determined as part of the NDA review. The data package generated by your approach will need to be included as part of your NDA submission.

**Discussion at Meeting:**

There was no further discussion.

**Oral Dispenser**

**Question 3:** Tris proposes that the packaging system contains a 12 mL syringe with the following markings: (b) (4) Are the proposed markings in the oral syringe acceptable for commercial labeling?

**Preliminary Comments:**

We will require considerably more detail about the proposed product system, in order to make this determination. Ultimately, these issues will be a matter of review. You will have to demonstrate that the overall product system is usable by caregivers and health care professionals. In addition, you must provide information about how the drug

*product would be managed at the pharmacy level. You will be required to provide relevant data to support your specific proposals regarding the syringe, volume markings, instructions for use, etc. We strongly recommend that you conduct a usability study with the final product system to be marketed. We will discuss this with you. It is possible that a usability study would be a requirement.*

*The demarcations on the syringe must be clear and easily readable. Since the drug product would likely be dosed for some patients in multiples of 5 mg, you should consider including additional demarcations on the syringe for 1, 3, 5, 7, 9, and 11 mL, to allow for precise dosing of the corresponding 5, 15, 25, 35, 45, and 55 mg doses.*

*Generally, you must address these types of issues in detail, for all components of the product system. Do you propose a specific kit for the drug product system?*

**Discussion at Meeting:**

*The sponsor stated that the materials used in the manufacture of the proposed commercial syringe are found in another commercially approved syringe; however, the proposed syringe is not approved for commercial use. As a result, the sponsor will ultimately need to highlight the differences between their proposed syringe and the related commercially approved syringe. Appropriate information will need to be submitted to support the approval of the new syringe. The sponsor indicated that the proposed commercial syringe will not be used as part of the upcoming clinical trials. CDRH will be consulted as part of our review of your NDA.*

*It was noted that the bottom of the plunger is both white and convex. It will need to be demonstrated that patients and caregivers can withdraw and administer the correct amount of drug product (white) per instruction. Labeling will need to be clear so that patients can withdraw the correct amount of drug product in a reproducible manner. Our assessment of the proposed syringe will be a matter of review. We recommended that the sponsor provide as much data as possible regarding the usability of the proposed syringe to be marketed.*

**Dissolution Studies**

**Question 4:** *Based on information provided in section 10.1.5, are the proposed in vitro alcohol and pH dissolution studies acceptable to FDA?*

**Preliminary Comments:**

***In vitro Dissolution Test:*** *No, the dissolution study “as proposed” is not acceptable. We have the following comments:*

- 1. Please provide the solubility data for your drug across the complete pH range.*

2. *To support the selection of the dissolution medium and paddle speed, you should collect dissolution data using the proposed dissolution media (i.e., pH 1.2, 4.5, and 6.8) at different rotations of paddle speed (i.e., 50, 75, 100 rpm).*
3. *We recommend that you collect complete profile data for each variable that is tested at the following times; 30 min, 1 hr, 2, hr, and every 2 hrs thereafter until at least (b) (4) of the labeled content is dissolved.*
4. *After your dissolution testing is completed, please provide the dissolution method report including the complete dissolution data generated during the development and validation of the dissolution methodology (i.e., individual, mean, and plots). The dissolution testing conditions and lot number for each test should be specified.*
5. *We advise you to submit the dissolution report as soon as possible for review and comments, as an acceptable dissolution method should be used for the stability studies.*
6. *Additionally, we consider that the dissolution data presented in the stability tables included in Appendix A, are less than adequate due to the following reasons:*
  - *A non-approved method was used for the stability testing.*
  - *The details for the dissolution testing were not included (i.e., apparatus, speed, media, volume, assay, number of units tested, etc.).*
  - *The proposed sampling scheme is not acceptable. Sampling does not cover at least (b) (4) of label content.*
  - *The proposed dissolution specifications are very wide and are not acceptable.*

***In Vitro Alcohol Induced Dose Dumping Study:*** *No, the in vitro alcohol study “as proposed”, is not acceptable. We have the following comments:*

1. *Your proposal of using USP Apparatus 2 (paddle) at 50 rpm, 900 ml of media at 37°C, and sampling every 15 minutes for 2 hrs to evaluate if alcohol induces dose dumping of your formulation is acceptable.*
2. *Because you have not identified an optimal dissolution medium for the dissolution of your product, the in vitro testing should be conducted using a range of alcohol concentrations in different pH media e.g. pH 1.2, 4.5 and 6.8. The same dissolution apparatus, agitation speed and medium’s volume & temperature should be used during the testing.*
3. *If your formulation is characterized as susceptible for dose dumping, a full design (assessment of in vitro dissolution profiles at 0%, 5%, 15 %, 20%, and 40% alcohol using 12 units each) will be required. However, if your formulation is categorized as rugged, you can adopt a reduced design (assessment of in vitro dissolution profiles at 0 %, 5%, and 40 % alcohol).*

**Discussion at Meeting:**

*There was no further discussion.*

## Extraction Studies for Container/Closure

**Question 5:** *As the proposed container is glass extraction studies shall not be performed for the container itself; however, extraction studies shall be performed for the adapter and closure liner since they will be in contact with the suspension. The adapter and closure liner contact surfaces are (b) (4) therefore Buffering Capacity analysis as per USP <661> shall be performed. Are the proposed extraction studies acceptable to FDA? Does FDA agree that these studies are only required for the reconstituted product, and not the dry powder? Does FDA agree that these studies are only required for the adapter and closure liner, and not the oral dispenser since the suspension product will not be in constant contact with the oral dispenser?*

### **Preliminary Comments:**

Very few details were provided in the briefing package. As a result, it is unknown even what type of glass (b) (4) will be used for the container closure. As part of the NDA review, we will be evaluating the materials that will be in contact with the aqueous drug product. As an (b) (4) will be employed, we will be interested in what information you have about the migration of compounds (b) (4) (b) (4) from the glass, adapter/closure liner and the syringe surfaces into the drug product).

### **Discussion at Meeting:**

The sponsor clarified the bottles will be constructed of USP Type 3 class. USP testing may not be specific for the types of compounds that could leach out. As a result, we recommended the sponsor work with their suppliers to determine what types of compounds (b) (4) they should analyze for with their testing. The sponsor was also encouraged to include literature information on the ability of these types of (b) (4) to absorb charged compounds from the surfaces of materials.

## USAN

**Question 6:** *Tris has recently begun the process of applying for a USAN for “methylphenidate (b) (4) as previously requested by the FDA. Does FDA agree that the NDA may be filed before the USAN has been granted?*

### **Preliminary Comments:**

The drug will be referenced by the drug substance (e.g., methylphenidate or methylphenidate HCl) but not as “methylphenidate (b) (4)

### **Discussion at Meeting:**

There was no further discussion.

**Pharmacology/Toxicology**

***Question 7: Based on the information submitted in section 10.2 and Appendix B, Tris proposes that no non-clinical studies are required for product approval. Does FDA agree that no non-clinical studies are required to support the NDA?***

**Preliminary Comments:**

*On face, the non-clinical and clinical information that you have provided regarding the excipient polystyrene sulfonate appears adequate to support its use in your drug product.*

**Discussion at Meeting:** *We clarified that there are no non-clinical concerns for methylphenidate, since under 505(b)(2) we will rely on our previous findings of safety for the RLD. However, we reminded the sponsor that new impurities or degradants might require qualification. [For CTD format issues, see discussion under Question 23.]*

**Clinical Pharmacology**

**Single-Dose PK Study (S09-0238)**

***Question 8: Does FDA have any further feedback on the study design for the adult PK study provided in Appendix C?***

**Preliminary Comments:**

*In the protocol you propose to study 12ml(60mg) of Tris Pharma (b) (4) vs. 15ml(30mg) of the reference Methylin IR oral solution (10mg/5ml) given at 0 hrs and at 6 hrs. We have the following comments:*

- 1. The design of the protocol is acceptable.*
- 2. You have stated on page 26 of 41 of the revised protocol, "As per the (b) (4) (b) (4) SOP entitled (b) (4) samples from subjects who experience emesis within 12 hours after the Hour 0 drug administration will be analyzed for d- and l- methylphenidate and PPAA plasma concentrations, but data from the period in which these subjects vomited will not be included in the pharmacokinetic and statistical analysis."*

*You need to submit the analysis including and excluding those subjects with the information on the exact time of emesis.*

- 3. You have stated, "Data from the period in which subjects withdraw due to adverse events will not be included in the pharmacokinetic and statistical analyses, but their samples will be analyzed by the bioanalytical laboratory. Samples from the other two completed periods will be analyzed and included in the pharmacokinetic and statistical analysis if Treatment B was administered in one of the completed periods.*

*Data from subjects with missing concentration values (missed blood draws, lost samples, samples unable to be quantitated) may be used if pharmacokinetic parameters can be estimated using the remaining data points. Otherwise, concentration data from these subjects will be excluded from the final analysis.”*

*You need to submit the analysis including and excluding those subjects with adverse events. The amount of data lost and the time frame of the missing samples will be the major determinant of the utility of the data. Therefore a separate analysis should be done including those subjects designated as having missing values and submitted to OCP.*

- 4. You have proposed to exclude data for subjects who discontinued due to an adverse event. Please clarify whether that is the case. We request that you provide all PK and safety data for all subjects treated.*

**Discussion at Meeting:**

*The sponsor has incorporated the requested changes in their revised protocol. This study is already underway.*

**Single-Dose Pediatric PK Study (NWP06-PedPK-101):**

***Question 9: Does FDA have any further feedback on the study design for the pediatric PK study provided in Appendix D?***

**Preliminary Comments:**

- 1. What is the proposed Clinical dose for your Tris Pharma (b) (4) used in efficacy study NWP06-ADD-100? What is the highest proposed Clinical dose you plan to use? (b) (4)*

*However, if higher doses will be used then your study should be done at the highest proposed clinical dose.*

- 2. In module 1.13.9 based upon the December 18, 2009 letter a general investigation plan was provided. In that plan you stated, “The second study is a single-dose, open-label study to evaluate the bioavailability of the test extended release oral suspension when given in pediatric patients from 6 to 17years of age. Twelve (12) pediatric patients in 2 main age groups; 6 to 12 years and 13 to 17 years of age, shall receive the test product. Drug administration consists of a single 4 mL (20 mg) dose of the test extended-release oral suspension at 8 am (Time 0).”*

*You need to clarify your dose, is it (b) (4) per your protocol NWP06-PEDPK-101 or is it 20 mg as in module 1.13.9?*

3. *You propose to collect blood samples at time [REDACTED] (b) (4). These times are inadequate. You need to collect more times between 0-6 hrs to better define the absorption as presented in Appendix E for subjects 2-11. In addition you need to collect samples until at least 24 to 36 hrs to adequately define elimination.*

**Discussion at Meeting:**

*The sponsor agreed to study 3 children (ages 6-12) treated with 20 mg and 3 adolescents (ages 13-17) treated with 20 mg. In addition, they agreed to study 3 children (ages 6-12) and 3 adolescents (ages 13-17) treated with 60 mg. The Division encouraged the sponsor to study an intermediate dose (i.e., 40 mg), in order to better define the pharmacokinetic profile. However, the sponsor predicted that the pharmacokinetics would be linear and saw no need for studying the 40 mg dose. The sponsor agreed to change the sampling times to 0, 30 min, 1 hr, 2hr, 4hr, 6 hr, 8 hr, 12 hr, and 24 hr to better define the plasma concentration profile over time.*

**Additional Analysis of Methylphenidate Plasma Level Sampling:**

***Question 10a: Based on information provided in Appendices E and F, does the Division agree that the results of the steady state trough PK sampling collected in study NWP06-ADD-100 shall address concerns about accumulation of our product?***

**Preliminary Comments:**

*Study NWP06-ADD-100 was designed using 20 to 60 mg doses administered as the Tris formulation. A single concentration was collected on day 20. The firm then did a multiple linear regression analysis including dose, gender and weight in the analysis. A traditional approach would be to compare kinetic parameters such as Cmax or AUC for the first dose vs. steady-state at comparable doses. Data is needed following a single dose and at steady-state to determine accumulation. The data which the firm shows for steady-state is all predicted data not observed.*

*Please explain why you used this non-standard analysis?*

**Discussion at Meeting:**

*The sponsor clarified that they plan to determine the degree of accumulation by comparing the steady-state Cmin values obtained in the clinical study to the 24-hour single-dose samples collected in study PED-101. They were not using simulated data.*

***Question 10b: Is submitting a summary table of the trough levels (such as in Appendix E) in the study report (trough PK data is not planned to be submitted in the SAS datasets), with an excel spreadsheet with individual data in an appendix, acceptable to the Division?***

**Preliminary Comments:**

*In the perusal of the information in Appendix E the aforementioned excel spreadsheet could not be readily identified. Please give the exact Table number to which you refer in Appendix E. The data can be submitted as a \*.csv file or as a SAS transfer file.*

*The firm needs to clarify what was done in study NWP06-ADD-100 by answering the following questions:*

*In volume 2 of 2 in your synopsis of study NWP06-ADD-100 on page 9 of 52 you list two blood draws/subject and the N=40. However, in volume 1 of 2 page 1 of 29 in a description of project NWP06-ADD-100 (N=36) you state, "A single plasma sample was obtained on Day 20 steady-state and assayed for methylphenidate." Are these the same studies? If these studies are the same why was there no mention of the sample analysis in the volume 2 of 2 protocol write-up that the reviewer could identify?*

**Discussion at Meeting:**

*The sponsor agreed to submit the PK data as SAS transfer or \*.csv files.*

*The sponsor clarified that Day 20 of Study ADD-100 preceded the controlled, crossover phase of the efficacy trial. Sampling for Cmin was conducted on Day 20 at steady state on the optimized dose.*

**Multi-dose (sparse sampling) PK in Pediatrics**

***Question 11: Based on information provided in Appendices E and F, does the Division agree that no further pharmacokinetic studies (other than S09-0238 and NWP06-PedPK-101) will be required to support the NDA?***

**Preliminary Comments:**

*No.*

- 1. S09-0238 is to determine the relative bioavailability vs. Methylin Oral solution in adults.*
- 2. NWP06-PedPK-101 is designed to evaluate the pharmacokinetics of Tris (b) (4) ER powder in children and adolescents. This study is not properly designed see OCP comments to question #9.*

*These studies do not address questions related to exposure response which can only be addressed during the planned/completed efficacy study in children. However, it is not clear if samples were collected during the efficacy study, NWP06-ADD-100 (please see OCP reply to question #10).*

*You must collect plasma samples and efficacy data within the same trial.*

**Discussion at Meeting:**

*The sponsor explained the design of efficacy study ADD-100 and clarified when PK samples were collected. If the PK results turn out as the sponsor predicts, and the exposure-response relationship can be characterized based on a PK model using results of other studies (adult study 0238, Ped-PK-101, and ADD-100), then no further PK would be required to support the NDA. However, this would be a matter of review upon submission of the NDA.*

**Clinical**

**Efficacy Study**

***Question 12: Does FDA concur that study NWP06-ADD-100 (Section 10.4 and Appendix H) confirms the efficacy of our methylphenidate formulation and is adequate to support the planned NDA from an efficacy perspective?***

**Preliminary Comments:**

*On face, it appears that the study demonstrated efficacy; however, this would be a matter of review. The efficacy data would probably support the filing of an NDA.*

**Discussion at Meeting:**

*There was no further discussion.*

**SAP**

***Question 13: Does FDA concur that our modified Statistical Analysis Plan for study NWP06-ADD-100 (Appendix I) and the subsequent results (Section 10.4) meet Agency expectations to demonstrate efficacy, and to support onset of effect and duration of effect claims?***

**Preliminary Comments:**

*You have made suitable changes in the Statistical Analysis Plan per FDA's earlier comments. Thus, the modified SAP appears acceptable. However, whether your efficacy analysis results meet the onset and duration of efficacy claim would be a matter of review.*

**Discussion at Meeting:**

*There was no further comment on this point.*

**General Comments Regarding the NDA Submission:**

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

- a) *All raw as well as derived variables in SAS transport (.xpt) format. We strongly encourage you to submit future NDA data (efficacy and safety) using the CDISC (Clinical Data Interchange Standards Consortium) and ADaM (Analysis Data Model) standards. Standardization of data structures and terminology will facilitate a more efficient and comprehensive data review. Please refer to the following link from FDA web site for more information:*  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>
- b) *The SAS programs that produced all efficacy results,*
- c) *The SAS programs by means of which the derived variables were produced from the raw variables, and*
- d) *A list of serial numbers and submission dates for all protocols, all protocol amendments, and any statistical amendments [including Statistical Analysis Plans] submitted to all relevant INDs.*

## **ECGs**

***Question 14a: Does the Division agree that a summarized table shall be adequate for the ECG data, as only pre-dosing ECG data were collected?***

**Preliminary Comments:**

*Yes, this would be adequate for baseline ECGs. If there were any subsequent ECGs performed (for safety follow up or other reasons), we request that you submit data for these as well.*

**Discussion at Meeting:**

*There was no further discussion.*

***Question 14b: Also, for the same reason, Tris does not plan to load this pre-dosing ECG data to the [REDACTED] (b) (4). Does the Division agree with this approach?***

**Preliminary Comments:**

*Yes, we agree.*

**Discussion at Meeting:**

*There was no further discussion.*

## **Labeling**

***Question 15: Study NWP06-ADD-100 was conducted in 6 to 12 year old children. Tris is seeking an indicated population from ages 6 [REDACTED] (b) (4) for treatment of ADHD. Based on the white paper provided in Appendix G which would support that the kinetics of methylphenidate does***

*not differ significantly in adults as compared to children, does the Division agree with this age group as appropriate? If not, what further information would the Division require?*

**Preliminary Comments:**

*The standard claim in the indications section would be: “for the treatment of Attention-Deficit Hyperactivity Disorder.” The indications section would then mention that this claim was based on a study in patients ages 6-12. In the Clinical Studies section, you would describe the precise population in which the study demonstrated efficacy: ages 6 to 12.*

**Discussion at Meeting:**

*There was no further discussion.*

**Question 16:**

(b) (4)

***Does the Division concur?***

**Preliminary Comments:**

*In the Dosing and Administration section of labeling, you would be required to use language reflecting only the actual dosing and administration used and studied in the pivotal trial that established efficacy. As you note, the dosing would be once daily in the morning.*

(b) (4)

*However, in the Clinical Studies section, you may describe the actual duration of efficacy measured and the specific time points at which you demonstrated efficacy. In addition, the Clinical Pharmacology section would describe the pharmacokinetic findings.*

**Discussion at Meeting:**

*There was no further discussion.*

**Question 17:**

(b) (4)

**Preliminary Comments:**

*Such an approach is possible, depending on the PK data. However, we can't make a determination at this point. Upon submission of the NDA, we will consider your specific labeling proposal and supporting data regarding (b) (4)*

**Discussion at Meeting:**

*We recommended that the sponsor propose a specific (b) (4) strategy, based on available PK data. This would be a review issue.*

**Question 18:** *Tris plans to include in the dosing recommendations section language such as: (b) (4). Tris also plans to recommend a starting dose of (b) (4) 20 mg per day. The 20 mg starting dose was tested in our efficacy study in children ages 6 to 12 years. (b) (4)*

**Does the Division agree that there is adequate support for this approach based on our Study NWP06-ADD-100 and generally accepted clinical practice of methylphenidate starting doses?**

**Preliminary Comments:**

*We acknowledge that (b) (4) of a methylphenidate immediate-release formulation may be a reasonable starting dose for some patients. Generally, however, the information in the dosing and administration section would be consistent with that used in pivotal efficacy study. We had recommended that you establish a minimum effective dose as part of an efficacy trial. We can't make a conclusion at this point, but you may submit a detailed rationale regarding this proposal in the NDA.*

**Discussion at Meeting:**

*There was no further discussion.*

**Question 19:** *Tris plans to compile methylphenidate adverse events from the clinical literature, as well as noting those seen in the clinical trial NWP06-ADD-100, and this would be the basis for the safety section of the proposed product labeling. Does the Division agree that this safety data shall adequately support the NDA when filed for Methylphenidate (b) (4)*

**Preliminary Comments:**

*The safety data that you propose is acceptable. In addition, the label for your drug product would include all relevant safety data that is included in labeling for other methylphenidate products. This would include specific warnings and precautions, and other adverse reactions data from these labels. Labeling for your product must also include safety data regarding the (b) (4) and other relevant excipient components.*

**Discussion at Meeting:**

*There was no further discussion.*

**Other**

***Question 20: Tris believes that this product is eligible for receiving 3 years of regulatory exclusivity upon approval of a 505(b)(2) NDA since a clinical efficacy study was performed at the request of the FDA to confirm the efficacy of our product. Does the Division agree with this, even if the Tris formulation patent is not issued at the time of approval?***

**Preliminary Comments:**

*This determination will be made at the time of review.*

**Discussion at Meeting:**

*There was no further discussion.*

***Question 21: Tris assumes that since other forms, including other long-acting forms of methylphenidate, have been approved by FDA, no risk management program shall be required. Does the Division agree with this?***

**Preliminary Comments:**

*No. As with all other stimulant products, your product will require a Medication Guide. Because the product must have a Med Guide, you will also be required to have a risk evaluation and mitigation strategy (REMS) in place. We can discuss this with you in more detail.*

**Discussion at Meeting:**

*We clarified that the Tris methylphenidate product would have the standard Med Guide for stimulants. The REMS would be a Med Guide only REMS. The sponsor asked whether there were any new developments related to med guides for stimulants, and we reassured the sponsor that there are no new safety concerns or policies regarding Med Guides.*

***Question 22: Tris shall request a partial waiver for the conduct of pediatric studies in children 0 to < 6 years of age because it is difficult to accurately diagnose and treat children in this age range. Tris shall request a partial waiver for the conduct of pediatric studies in children 13 to 17 years of age because methylphenidate indicated for the treatment of ADHD has been studied extensively in adolescents 13 to 17 years of age and is labeled for the treatment of this population (section 505B(a)(4)(B)(iii) of the Act). Moreover, Tris has proposed to conduct a single dose PK study in children ages 6 to 17 which shall provide pertinent information for adolescent children. Does the Division agree with this?***

**Preliminary Comments:**

*To answer these questions definitively, we would be required to present your proposals to the Pediatric Equity in Research Committee (PeRC). This would occur at some point after the NDA submission. It is likely that you would be granted a waiver for studying subjects younger than 6 years of age. You would be required to conduct an adequate pharmacokinetic study in adolescents (ages 13 to 17). We will discuss the details of your proposed PK studies. It is unlikely that you would be required to conduct an efficacy study in adolescents.*

**Discussion at Meeting:**

*There was no further discussion.*

**Question 23: Are there other areas/questions/issues that the Division believes Tris must address as it moves from this End of Phase 3 meeting in order to have a complete and adequate NDA filing?**

**Preliminary Comments:**

*No*

**Discussion at Meeting:**

*The sponsor had questions regarding the CTD format, and we came to the following agreements:*

- *Module 2 – Organization and Content of the Clinical Summary*
  - *2.4 Nonclinical Overview*
    - *We agreed that a written summary is acceptable for this section.*
  - *2.5 Clinical Overview/2.7 Clinical Summary*
    - *We agreed that an ISS/ISE will not be required.*
  - *2.6 Nonclinical Written and Tabulated Summary*
    - *We agreed that this section may be omitted, and confirmed that it will not be a filing issue since the 5050(b)(2) application will rely on the safety of the RLD.*
  - *2.7.4.5.6 Summary of Clinical Safety/ Drug Abuse*
    - *We agreed that a summary of abuse potential will not be required.*
- *Module 5 – Clinical Study Reports*
  - *5.3.7 Case Report Forms and Individual Patient Listings*
    - *The sponsor will submit case report forms for efficacy and PK studies.*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-73856	GI-1	TRIS PHARMA INC	Methylphenidate (b) (4) ER Powder for Oral Suspension

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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  
03/29/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 73,856

Tris Pharma, Inc.  
Attention: Cynthia Katsempris, Manager  
Regulatory Affairs & Compliance  
2033 Route 130  
Monmouth Junction, NJ 08852

Dear Ms. Katsempris:

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

We also refer to the teleconference meeting between representatives of your firm and the FDA on October 1, 2007. The purpose of the meeting was to discuss the product development for this drug to treat attention deficit hyperactivity disorder.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call LCDR Janet Cliatt, Regulatory Project Manager, at (301) 301-796-0240.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** October 1, 2007  
**TIME:** 1:15 – 1:35 PM  
**LOCATION:** WO 22; Room 1419  
**APPLICATION:** 73,856  
**DRUG NAME :** Methylphenidate (b) (4) Extended Release Oral Suspension (CII)  
**TYPE OF MEETING:** Pre-IND Meeting (#2)  
**MEETING FORMAT:** Conference Call  
  
**MEETING CHAIR:** Thomas Laughren, M.D.

**MEETING RECORDER:** Janet Cliatt

Meeting Request: July 27, 20007  
Meeting Package: August 22, 2007  
Teleconference Meeting: October 1, 2007

### **FDA Attendees:**

Thomas Laughren, M.D. - DPP Division Director  
Mitchell Mathis, M.D. - DPP Deputy Division Director  
Ni Khin, M.D. - Clinical Team Leader  
Michelle Chuen, M.D. - Medical Reviewer  
Gwen Zornberg, MD. – Medical Reviewer/Acting Clinical Team Leader  
Ramen Baweja, Ph.D. – OCP Team Leader  
Andre Jackson, Ph.D. – OCP Reviewer  
Barry Rosloff, Ph.D. – Pharmacology Team Leader  
Ikram Elayan, Ph.D. – Pharmacology Reviewer  
Thomas Oliver, Ph.D. – ONDQA Team Leader  
Paul David, DPP CPMS  
Janet Cliatt, DPP Project Manager

### **EXTERNAL CONSTITUENT ATTENDEES:**

Yu Hsing Tu, PhD, Vice President, R&D, Tris Pharma  
Alivia Chaudhuri, Research Scientist, R&D, Tris Pharma  
Scott Groner, Director, Regulatory Affairs and Compliance, Tris Pharma  
Cynthia Katsempris, Manager, Regulatory Affairs and Compliance, Tris Pharma  
Mahendra Shah, Chairman and CEO, NextWave Pharmaceuticals (client/partner)

(b) (4)

**BACKGROUND:**

The sponsor plans to develop an extended release oral suspension of methylphenidate that it intends to show is bioequivalent (rate and extent of absorption) to an immediate release oral methylphenidate product. They seek approval for once-a-day administration of this product for ADHD. The Agency previously had a Pre-IND conference call with Tris Pharma on May 8, 2006, to discuss their development plan.

Tris intends to reference the preclinical studies for previously approved methylphenidate products. Therefore, no new pre-clinical studies are being proposed by Tris.

Tris has revised the original clinical plan in the following manner:

- Tris has changed the reference drug from an immediate release formulation to a Methylphenidate extended release oral formulation at the highest dose. The proposed reference drug will be Concerta<sup>®</sup> (methylphenidate hydrochloride) Extended-Release Tablets and the comparator dose in the study will be the highest approved dose of 72 mg.
- Tris has also changed the strength of the test drug from (b) (4) to (b) (4) to be consistent with the Concerta<sup>®</sup> dosing regimen.
- Tris has revised the clinical study plan from (b) (4) (b) (4), to a single-dose, three-way cross-over, bioequivalence study comparing Test Methylphenidate (b) (4) Extended Release Oral Suspension under fasting conditions vs. Test Methylphenidate (b) (4) Extended Release Oral Suspension under fed conditions (to demonstrate food-effect of test formulation against itself) vs. Concerta<sup>®</sup> extended release tablets under fasting conditions in healthy adult volunteers. Bioequivalence determination and bioavailability comparisons will be based on AUC, AUCpR, and Cmax, between test and reference shall be made.
- Tris proposes that if bioequivalence is established using the above criteria, then no further clinical efficacy studies will be conducted.

Tris is seeking the following feedback from the Agency:

1. To obtain the Agency's agreement for the proposed BA/BE study and the proposed plan for BE determination required for product approval.
2. Assuming BE is established between our product and the reference drug, to obtain the Agency's agreement that the proposed BA/BE study is sufficient for NDA 505(b)(2) filing and no additional clinical efficacy studies will be required for product approval.
3. To obtain the Agency's agreement that the proposed data needed for an alternate source of the active is sufficient.

**Questions:**

**Question 1** - Does the Agency agree with the proposed reference product Concerta<sup>®</sup>, test product strength, and dose for our revised three-way pk study?

**Preliminary Comments**

The proposed reference product Concerta, test product strength, and dose for your revised three-way pk study is acceptable to OCP. [See additional comments also]

**Discussion at Meeting:**

No further discussion.

**Question 2** – Does the Agency agree that no other BA/BE Studies are required for NDA submission and subsequent product approval?

**Preliminary Comments**

Yes, the Agency agrees that no other BA/BE studies will be required.

**Discussion at Meeting:**

No further discussion.

**Question 3** - If our proposed product is BE to Concerta<sup>®</sup> based on AUC, AUCpR, and Cmax, does the Agency agree that additional efficacy studies are required for NDA submission and subsequent product approval?

**Preliminary Comments**

We assume you meant to say “additional efficacy studies are not required.” If you have a strong case for demonstrating bioequivalence, additional efficacy studies would not be required. However, besides AUC, Cmax and your suggested AUCpR, comparable curve shape will also be evaluated in making a decision on the comparability of the two products. Although it is possible you will be able to meet this higher standard for bioequivalence, it seems unlikely.

**Discussion at Meeting:**

We emphasized to the sponsor that, while we are investing considerable resources into trying to establish a standard for making a bioequivalence determination for comparisons of various controlled release methylphenidate formulations with Concerta, we have not yet made a final judgment on this matter. Thus, we were not able to state precisely what standard would be used in making this determination. We did agree to provide feedback to the sponsor on their proposals and preliminary data, and would of course provide them more definitive advice on this matter when a standard is established.

**Question 4** - If our proposed product is **not** BE to Concerta® based on AUC, AUCpR, and Cmax, Tris shall propose to conduct **one** short-term, placebo-controlled efficacy trial. Will this plan be satisfactory for NDA submission and subsequent product approval?

**Preliminary Comments**

One short-term, placebo-controlled efficacy study should be sufficient to provide clinical data to support efficacy.

**Sponsor's response to preliminary comments:**

On 9/28/2007, the sponsor submitted in a brief outline of clinical study (protocol # (b) (4))  
entitled (b) (4)

**Discussion at Meeting:**

Based on the brief protocol outline, we noted that there were inconsistencies in the proposed study population (b) (4). The sponsor clarified (b) (4).

We noted that we would likely have additional comments when the full protocol is submitted. The sponsor agreed to collect plasma samples for pharmacokinetic analyses during the conduct of the efficacy study.

**Question 5** - Does the Agency agree that the information proposed to support an alternate source is sufficient?

**Preliminary Comments**

We believe that the question is premature at this time and that it would be more appropriate at a Pre-NDA meeting or after NDA submission.

**Discussion at Meeting:**

No further discussion.

**Additional Preliminary Comments:**

**Chemistry**

- A complete description of the drug product manufacturing process should be included in your IND submission. Since you plan to utilize sodium polystyrene sulfonate, the

possibility exists for the formation of [REDACTED] (b) (4)  
[REDACTED] As a result, the potential presence of these genotoxic compounds will be evaluated based upon your proposed plan and any appropriate testing that is in place.

- Describe how the exposure of sodium polystyrene sulfonate to patients in your proposed clinical study compares to other approved products.
- Discuss how [REDACTED] (b) (4) sodium polystyrene sulfonate was chosen, and how it is controlled in your proposed drug product.

**Discussion at Meeting:**

As sodium polystyrene sulfonate [REDACTED] (b) (4)  
[REDACTED]. A complete description of your manufacturing process will need to be provided. The acceptance specification of sodium polystyrene sulfonate should also be submitted.

**Pharmacology/Toxicology**

- Data from animals and/or human studies should be provided to support the use of the inactive ingredient sodium polystyrene sulfonate. In addition, you should provide data to demonstrate that the formulation of the proposed product falls within the acceptable ranges for impurities and degradants.

**Clinical Pharmacology**

- There is an error in the drug concentration presented as [REDACTED] (b) (4) by the sponsor. 5 ml is a “teaspoonful” and abbreviation as “tsp.” You have used the incorrect abbreviation [REDACTED] (b) (4)  
[REDACTED] (b) (4).

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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 Laughren  
10/11/2007 08:06:47 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

PIND 73856

Tris Pharma, Inc.  
Attention: Imtiyaz Ubharay  
Team Leader, QA/RA  
2033 Route 130, Suite D  
Monmouth Junction, NJ 08852

Dear Mr. Ubharay:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Methylphenidate (b)(4) Extended Release Suspension.

We also refer to the teleconference between representatives of your firm and the FDA on May 8, 2006. The purpose of the meeting was to obtain the Agency's feedback and concurrence on the proposed development plan.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Susan Player, M.S., Regulatory Project Manager, at (301) 796-1074.

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

Enclosure(s)

TELECONFERENCE MINUTES  
IND 73856

Date: May 8, 2006  
Location: CDER Conference Room 4396  
Time: 1:00 – 2:00 PM  
Firm: Tris Pharma  
Type: Teleconference  
Meeting: Type B Pre-IND  
Drug: Methylphenidate (b) (4) Extended Release Oral Solution  
Indication: Attention Deficit Hyperactivity Disorder (ADHD)  
Meeting Chair: Thomas Laughren, M.D., Division Director, DPP  
Meeting Recorder: Susan Player, M.S., Regulatory Project Manager

Participants:

**FDA:**

Dr. Thomas Laughren	Division Director, DPP
Dr. Ni Aye Khin	Clinical Team Leader, DPP
Dr. Michelle Chuen	Clinical Reviewer
Dr. Andre Jackson	OCPB Reviewer
Dr. Raman Baweja	OCPB Team Leader
Dr. Barry Rosloff	Pharmacology/Toxicology Team Leader, DPP
Dr. Ikram Elayan	Pharmacology/Toxicology Reviewer, DPP
Dr. Thomas Oliver	ONDQA Team Leader
Ms. Susan Player	Regulatory Project Manager
Mr. Ketan Mehta	President and CEO, Tris Pharma Inc.
Dr. Yu Hsing Tu	Vice President, Tris Pharma Inc.
Mr. Imtiyaz Ubharay	Team Leader QA/RA, Tris Pharma Inc.

(b) (4)

**Meeting Objective**

To obtain the Agency's feedback and concurrence on the proposed development plan.

**Background:**

The sponsor plans to develop an extended release oral suspension of methylphenidate (b) (4) that it intends to show is bioequivalent (rate and extent of absorption) to an immediate release oral methylphenidate solution (Methylin; 10 mg/5 mL). They seek approval for once-a-day administration of this product for ADHD. The sponsor does not plan to conduct efficacy and safety studies and intends to submit this as a 505(b)(2) application. They seek a waiver for the PREA requirement. The purpose of the meeting is to seek FDA concurrence on their planned program.

The planned bioequivalence study would be a comparison of single doses of their extended release product (b) (4) with Methylin (b) (4). This would be a crossover study under fasting conditions in n=24 normal volunteers. The primary comparisons would be for Cmax and AUC.

-Sponsor Questions:

1. Does the Agency agree that the planned PK studies will be sufficient to support approval of the NDA?

FDA Preliminary Comments: Although it is possible that these 2 formulations might be shown to be equivalent with regard to Cmax and AUC, it is highly unlikely that the time/concentration profiles would be superimposable (b) (4)

Furthermore, immediate release methylphenidate would ordinarily be given bid (morning and noon), rather than only in the morning. Thus, the appropriate comparison would be with methylphenidate IR bid, or preferably, with a reference controlled release methylphenidate product. In addition, the comparison should be at the highest dose, i.e., 60 mg/day. These products ordinarily attempt to achieve a profile similar to that seen with immediate release methylphenidate given bid (morning and noon). However, it is also unlikely that the new product would have a time/concentration profile that would be superimposable with another controlled release methylphenidate product. It is current division policy to require a clinical study to show efficacy of a new controlled release product that does not have a superimposable time/concentration profile to a reference controlled release product. There are published studies showing that controlled release methylphenidate products with different time/concentration profiles but similar Cmax and AUC values may have different pharmacodynamic profiles [e.g., see Swanson, et al; Pediatrics; 2004,113(206-216)].

Discussion at Meeting: The sponsor asked for further clarification of the need for a clinical study. We reiterated points made in the preliminary comments, i.e., that for a controlled release product we are reluctant to make assumptions about what differences in a time-concentration profile might have on clinical efficacy. Given the likelihood that the time-concentration profile for their product will likely differ from that seen with other controlled release products and with immediate release methylphenidate, we feel that it is likely that a clinical study will be needed to demonstrate efficacy for this controlled release product. We suggested that they look to the literature and to FDA's website for information on controlled trials that have supported approvals for other controlled release methylphenidate products in recent years. It was noted that a short-term, placebo-controlled outpatient study would be optimal for demonstrating efficacy for their product.

2. Tris believes that no new clinical studies will be required to support approval of the NDA, does the Agency concur?

FDA Preliminary Comments: No (see response to question #1).

Discussion at Meeting: (see Discussion at Meeting response to question #1).

3. Tris believes that no additional non-clinical studies are necessary to support approval of the NDA, does the Agency concur?

FDA Preliminary Comments: The company should provide data from animals and/or humans to support the safety of the excipient used with this product (sodium polystyrene sulfonate). It is important that the existing data be relevant to the proposed use of this product (b) (4)

(b) (4) route of administration, and duration of exposure). In accordance with the Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, "the inclusion of an excipient in a USP/NF monograph or other non-FDA document is not an indication that the substance has been reviewed by the FDA and found safe for use." The company also needs to address any impurities and/or degradants in the drug product which may need to be qualified.

Discussion at Meeting: The sponsor was referred to the Excipient Guidance (see attachment). Current policy is to treat excipients similar to new drugs regarding animal toxicity studies, with allowances made for extensive previous human use, similarity to other excipients, limited systemic exposure, etc. The sponsor should submit all available animal and human data. Regarding previous human use, (b) (4), dose, duration of use, and patient population, in relation to the proposed use, should be taken into account.

4. Does the Agency agree with the proposed dosing regimen of the proposed PK studies support similar rate and extent of absorption as the listed drug?

FDA Preliminary Comments: No (see response to question #1).

Discussion at Meeting: (See Discussion at Meeting response to question #1)

5. Tris believes that the product should be labeled as Methylphenidate (b) (4) ER Suspension (b) (4) does the Agency concur?

FDA Preliminary Comments: Although it is premature to discuss labeling at this point, we remind you that you will need to apply for a USAN with the USAN Council.

Discussion at Meeting: No additional discussion.

6. Are the proposed Quality Control release tests mentioned in the CMC section (Section VII) acceptable to the Agency?

FDA Preliminary Comments: The adequacy of the drug substance testing will be determined as part of the DMF evaluation. A LoA to the methylphenidate DMF will need to be included in the IND submission. The drug product testing appears reasonable. Ultimately, a discussion about (b) (4) will need to be included in any potential NDA (see ICH Q6A). In addition, extraction studies should be performed with the ultimate drug product and the commercial container closure system.

Discussion at Meeting: No additional discussion.

7. What are the Agency's general expectations for in vitro dissolution testing methods?

FDA Preliminary Comments: You should investigate the dissolution of your product at 3 pH values and also in water and then set appropriate dissolution specifications for your product.

Discussion at Meeting: No additional discussion.

8. Does the Agency concur that the proposed application may be filed as a 505 (b)(2) application?

FDA Preliminary Comments: Yes, but as noted, it will likely be necessary to conduct a clinical efficacy study.

Discussion at Meeting: No additional discussion.

9. Tris proposes to submit the 505 (b)(2) application with 6 months of stability data (as per ICH conditions). Does the Agency find this acceptable from a filing standpoint?

FDA Preliminary Comments: Acceptable. The expiration date will be ultimately determined based on the quantity and quality of your data. Stability updates received less than 3 months from the PDUFA due date can't be guaranteed to be reviewed in the first cycle.

Discussion at Meeting: No additional discussion.