

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205489Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 205489

SUPPL #

HFD # 130

Trade Name Cotempla XR-ODT

Generic Name methylphenidate (b) (4) extended release orally disintegrating tablets

Applicant Name Neos Therapeutics Inc.

Approval Date, If Known June 19, 2017

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)

b) 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:

c) 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

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

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA 21514 (Daytrana)
NDA 205831 (Aptensio XR)
NDA 21259 (Metadate CD)
NDA 21284 (Ritalin LA)
NDA 10187 (Ritalin)
NDA 21121 (Concerta)
NDA 21419 (Methylin Oral Solution)
NDA 18029 (Ritalin SR)
NDA 21475 (Mehylin Chewable Tablets)
NDA 202100 (Quillivant XR)
NDA 21278 (Focalin)
NDA 21802 (Focalin XR)
NDA 207960 (Quillichew ER)

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 NT0102.1004, entitled "A randomized, multicenter, double-blind, placebo-controlled, parallel group, laboratory classroom study of NT0102 Methylphenidate Extended Release Oral Disintegrating Tablets in children ages 6 to 12 years with attention-deficit hyperactivity disorder (ADHD).

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 NT0102.1004, entitled "A randomized, multicenter, double-blind, placebo-controlled, parallel group, laboratory classroom study of NT0102 Methylphenidate Extended Release Oral Disintegrating Tablets in children ages 6 to 12 years with attention-deficit hyperactivity disorder (ADHD).

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 # 109108	YES ☒ ! NO ☐
	! Explain:

!

YES ☐

!

! NO ☐

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YES ☐

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! NO ☐

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YES ☐

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! NO ☐

!

!

YES ☐NO ☒

=====

Title: Program Coordinator
Date: June 19, 2017

Name of Division Director signing form: Mitchell Mathis, MD
Title: Division Director

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

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

/s/

WILLIAM H BENDER
06/19/2017

MITCHELL V Mathis
06/19/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205489 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Cotempla XR ODT Established/Proper Name: Methylphenidate Extended Release Orally Disintegrating Tablet Dosage Form: 10 mg, 20 mg, and 30 mg Tablets		Applicant: Neos Therapeutics, Inc. Agent for Applicant (if applicable): Dorothy Engelking
RPM: CAPT Bill Bender		Division: Psychiatry Products
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 4/5/2017 <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>June 19, 2017</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☐ None CR-11/6/2015 to 1/09/2015 original submission Resubmission: 12/19/2016
❖ 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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

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

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

³ 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.

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

- | | |
|---|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☐ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☐ Direct-to-OTC |
| ☐ Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: [CST SharePoint](#))

NDAs: Subpart H

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

Subpart I

- ☐ Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- ☐ Approval based on animal studies

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

Comments:

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

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Approval Letter : 6/19/2017 With labeling
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included (final agreed-upon labeling)
Original applicant-proposed labeling	☐ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☒ Medication Guide (final agreed MedGuide) ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included (final agreed labeling)
Original applicant-proposed labeling	☐ Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	Included
Most-recent draft labeling (see DMEPA labeling review)	☐ Included
❖ Proprietary Name	
- Acceptability/non-acceptability letter(s) (indicate date(s)) - Review(s) (indicate date(s))	03/31/2017 03/30/2017
❖ Labeling reviews (indicate dates of reviews)	RPM: ☒ None DMEPA: ☒ 05/17/2017; 05/26/2017 DMPP/PLT (DRISK): ☒ 05/24/2017 OPDP: ☒ 05/23/2017 SEALD: ☐ None CSS: ☐ None Product Quality ☐ None Other: ☒ DPMH (02/06/2017)
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	☐ Not a (b)(2) 06/14/2017
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	Assessment: 06/16/2017
Comments received from (b)(2) committee for when they resubmit...	
❖ NDAs only: Exclusivity Summary (signed by Division Director)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No

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

- This application is on the AIP - If yes, Center Director's Exception for Review memo <i>(indicate date)</i> - If yes, OC clearance for approval <i>(indicate date of clearance communication)</i>	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics <i>(approvals only)</i> Date reviewed by PeRC <u>September 2, 2015</u> If PeRC review not necessary, explain: _____	Meeting Minutes: 09/23/2015
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i>	
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i> <i>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</i>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) <i>(do not include previous action letters, as these are located elsewhere in package)</i>	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	☐ N/A or no mtg
Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	☐ No mtg
EOP2 meeting <i>(indicate date of mtg)</i>	☐ No mtg
Mid-cycle Communication <i>(indicate date of mtg)</i>	☐ N/A
Late-cycle Meeting <i>(indicate date of mtg)</i>	☐ N/A
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) <i>(indicate dates of mtgs)</i>	Complete Response Meeting Minutes: -1/15/2016
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	☒ None
Division Director Summary Review <i>(indicate date for each review)</i>	☒ 06/19/2017
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	☒ 06/19/2017
PMR/PMC Development Templates <i>(indicate total number) -3</i>	☒ 3 of them (06/16/2017)
Clinical	
❖ Clinical Reviews	

Clinical Team Leader Review(s) (indicate date for each review)	☒ No separate review
Clinical review(s) (indicate date for each review)	06/05/2017
Social scientist review(s) (if OTC drug) (indicate date for each review)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)	Included with the original NDA submission on 01/09/201 and the resubmission dated 12/19/2016.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	☒ 05/18/2017
❖ Risk Management - REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) - REMS Memo(s) and letter(s) (indicate date(s)) - Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	☒ 02/17/2017
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ No separate review
Statistical Team Leader Review(s) (indicate date for each review)	☒ No separate review
Statistical Review(s) (indicate date for each review)	☒ Review (05/19/2017)
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology review(s) (indicate date for each review)	☒ Review (06/14/2017)
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☒ Review (05/16/2017)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☐ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	☒ None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	☒ 05/31/2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Original Submission) 01/09/2015
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☒ Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

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

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

/s/

WILLIAM H BENDER
06/19/2017

Bender, William

From: Holovac, Mary Ann
Sent: Wednesday, June 14, 2017 3:31 PM
To: Bender, William
Cc: Locicero, Colleen L; Sharma, Khushboo; Goldstein, Beth A (Duvall); Holovac, Mary Ann
Subject: NDA 205489 Methylphenidate XR-ODT - cleared for full approval action with caveat

Bill,

We discussed the subject application at Monday's 505(b)(2) clearance meeting. The application is cleared for **full approval action** from a 505(b)(2) perspective with the following caveat:

Per our telephone conversation:

FDA will accept the applicant's patent verification statement received on 6/7/2017 and as related to the application resubmission on 12/19/2017. If it is determined the applicant will receive a complete response, please provide a draft of the complete response letter as the 505(b)(2) committee would like an opportunity to add language to the CR letter related to patent certification/re-certification/verification requirements that went into effect on 12/5/2016.

Please make the following changes to the draft assessment before archiving in DARRTS, assuming you are heading towards an approval. If you are not approving this cycle, please make the changes below but defer archiving in DARRTS until you are headed towards approval (in which case you would need to have the application cleared again). If that's the case, please let us know when the resubmission arrives so that we can add it anew to our clearance queue.

- *Q8a: Please change this answer to YES as Metadata was approved via 505(b)(2).*
- *Q11: Multiple other pharmaceutical alternatives may be listed at the end of this question.*

Please let me know if you have any questions.

Mary Ann

From: Holovac, Mary Ann
Sent: Wednesday, June 14, 2017 11:15 AM
To: Locicero, Colleen L; Bender, William
Subject: RE: NDA 205489 Methylphenidate XR-ODT - bridge information still needed

Yep, I agree.

From: Locicero, Colleen L
Sent: Wednesday, June 14, 2017 11:09 AM
To: Holovac, Mary Ann; Bender, William
Subject: RE: NDA 205489 Methylphenidate XR-ODT - bridge information still needed

Thanks, Mary Ann. I sent an e-mail to the review team on Monday about the need to specifically cite reliance on Ritalin and have not seen anything beyond what was provided yesterday (the e-mail message you've provided) about the bridge from ORP or OCC, so I'm assuming, at this point, that this is their final position.

Colleen



NDA 205489

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Neos Therapeutics, Inc.
2940 N. Hwy 360
Suite 400
Grand Prairie, TX 75050

ATTENTION: Dorothy J. Engelking
Vice President, Regulatory Affairs

Dear Ms. Engelking:

Please refer to your New Drug Application (NDA) Class 2 Resubmission dated and received December 19, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate (b) (4) Extended-Release Orally Disintegrating Tablets, 8.6 mg, 17.3 mg, and 25.9 mg.

We also refer to your correspondence dated and received January 5, 2017, requesting review of the resubmission of your proposed proprietary name, Cotempla XR-ODT.

We have completed our review of the proposed proprietary name, Cotempla XR-ODT and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Alycia Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4270. For any other information regarding this application, contact William Bender, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

Todd Bridges, 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

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

/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
03/31/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205489

MEETING MINUTES

Neos Therapeutics, Inc.
Attention: Dorothy J. Engelking
Vice President, Regulatory Affairs
2940 N. HWY 360, Suite 400
Grand Prairie, TX 75050

Dear Ms. Engelking:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cotelpla XR-ODT (Methylphenidate Extended-Release Orally Disintegrating) 10 mg, 20 mg, and 30 mg tablets.

We also refer to the meeting between representatives of your firm and the FDA on December 17, 2015. The purpose of the meeting was to discuss the deficiencies identified in our November 9, 2015 "Complete Response" (CR) letter.

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

If you have any questions, call CAPT Bill Bender, Senior Regulatory Project Manager at (301) 796-2145 or via email at william.bender@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A (face-to-face meeting)
Meeting Category: NDA
Meeting Date and Time: December 17, 2015 from 3:00 pm to 4:00 pm
Meeting Location: White Oak, Bldg. 22, Room 1315
Application Number: 205489
Product Name: Cotempla XR-ODT
Indication: Attention Deficit Hyperactive Disorder (ADHD)
Sponsor/Applicant Name: Neos Therapeutics, Inc.

FDA ATTENDEES

Mitchell Mathis, M.D.,	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, M.D.,	Deputy Director, DPP
Jing Zhang, M.D.,	Clinical Team Leader, DPP
Ikram Elayan, Ph.D.,	Pharmacology/Toxicology Acting Team Leader, DPP
Hao Zhu, Ph.D.,	Clinical Pharmacology Team Leader, OCP
Praveen Balimane, Ph.D.,	Clinical Pharmacology Reviewer, OCP
David Claffey, Ph.D.,	CMC Lead, OPQ
Andrei Ponta, Ph.D.,	Product Reviewer, OPQ
Ge (Larry) Bai, PhD	Biopharm Reviewer, OPQ
Akm Khairuzzeman, PhD	Process Reviewer, OPQ
John Duan, Ph.D.,	Pharmacology Reviewer, OPQ
Deborah Myers, PharmD.,	DMEPA Team Leader
Danielle Harris, PharmD.,	DMEPA Reviewer
Bill Bender, R.Ph.,	Project Manager

SPONSOR ATTENDEES

Dorothy Engelking	VP Regulatory Affairs, Neos
Mark Tengler	CTO, Neos
Russ McMahan	VP R&D, Neos
Carolyn Sikes, PhD	VP Clinical, Neos
(b) (4)	Consultant to Neos



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

1.0 BACKGROUND

Neos Therapeutics submitted NDA 205489 for Cotempla XR-ODT, 10 mg, 20 mg, and 30 mg tablets on January 9, 2015, seeking an ADHD indication based on the 505(b)(2) pathway with reference to the Listed Drug, Metadate CD. The development program for Cotempla XR-ODT consisted of three Phase 1 pharmacokinetic trials and one Phase 3 trial to assess the efficacy and safety of Cotempla XR-ODT in children 6 to 12 years old with ADHD. FDA took a Complete Response action on this NDA mainly because there was not an adequate bridge between the clinical trial formulation and the to-be-marketed formulation. In our CR letter dated 11/9/2015, we listed the following deficiencies:

DEFICIENCIES WHICH PRECLUDE APPROVAL

Office of Pharmaceutical Quality (OPQ):

1. You must bridge the clinical and to-be-marketed drug product formulations with a bioequivalence study. The to-be-marketed drug product will have (b) (4)% (b) (4) (w/w) delayed-release and (b) (4)% (b) (4) extended-release (b) (4) than the clinical batches. The provided dissolution data cannot be used to support this change. Changes of this extent, especially to the extended-release (b) (4), require bioequivalence studies to establish the bridge between the two formulations. The specifics of these studies are listed under the "Office of Clinical Pharmacology" section below.
2. You must establish, validate and fully justify an unequivocal commercial (b) (4) (b) (4) operation and control—your description of this process in communications during the review cycle contradicts that described in the application. You state in 3.2.P.2.3 that the commercial scale process will use (b) (4) but state in the 20 AUG 2015 amendment (b) (4)

Office of Clinical Pharmacology (OCP):

1. As stated in the product quality section above, an adequate bridge between the clinical trial formulation (Lot: 2E116E) and the to-be-marketed formulation has not been established. Due to this lack of an adequate bridge, the findings from the efficacy and safety trial (NT0102.1004) based on the clinical trial formulation may not inform the safety and effectiveness of the to-be marketed product.
2. An adequate bridge has not been established between the to-be-marketed formulation, and the listed drug (Metadate CD). Thus, the Agency's finding of efficacy and safety for Metadate CD may not be used to support the approval of the to-be marketed product until a bridge is established.
3. Pediatric pharmacokinetic information obtained with the clinical pharmacology formulation (Lot: 1E101A) is insufficient to support extrapolation of efficacy findings (based on clinical trial formulation) from children into adolescents (b) (4) for the to-be-marketed formulation.
4. Food effect findings based on the clinical pharmacology formulation (Lot: 1E101A) may not inform the food effect on the to-be-marketed formulation. The to-be-marketed formulation contains the (b) (4) amount of release-controlling (b) (4) among the three formulations. Because the level of interaction between food and the release controlling (b) (4) is unclear, it may not be appropriate to extrapolate the food effect findings from the clinical pharmacology formulation to the to-be-marketed formulation.

Based on the Office of Clinical Pharmacology's assessment, the following remedy actions are necessary:

- The sponsor should conduct a bioequivalence study to bridge the to-be-marketed formulation with the clinical trial formulation (Lot: 2E116E) under fasted condition.
- Food effect on the to-be-marketed formulation should be assessed. It can be evaluated by adding one more arm (i.e., to-be-marketed formulation in fed state) in the above bioequivalence study.

We also described several Chemistry deficiencies under the title "OTHER DEFICIENCIES/ COMMENTS in the CR letter. You have requested this meeting to discuss the deficiencies identified in said letter. In response to our request, you have proposed a single three-arm bioavailability/bioequivalence study to bridge the clinical trial material and the to-be-marked drug product. The materials to be studied will be the Clinical Trial Formulation (Lot 2E116) used in study NT0102.1004, and the to-be-marketed formulation manufactured at commercial scale. In each arm of the study, a 60 mg equivalent methylphenidate hydrochloride dose will be administered as two (2) 30 mg XR-ODTs. The following arms will be studied: 1) Clinical Trial Formulation 60 mg in the fasted state; 2) Commercial Scale Formulation 60 mg in the fasted state; and 3) Commercial Scale Formulation 60 mg in the fed state.

2.0 DISCUSSION

2.1 Deficiencies Which Preclude Approval

Clinical Pharmacology

Questions 1 and 2: BE Study Design (OPQ Question #1 and OCP Questions #1-4)

Does the proposed single, three-arm BA/BE study design appear adequate to assess the oral bioavailability/bioequivalence of the to-be-marketed formulation of Cotempla XR-ODT to the clinical trial material?

Preliminary Comments:

1. *Yes, on face we agree with your proposed 3-arm BA/BE study design. However, considering the bi-modal PK profile of methylphenidate from the XR formulation product and the similarity of PK and PD profile of current product with CONCERTA, we that request you provide the following:*
 - *To establish BE, the following PK parameters need to be statistically compared for the clinical formulation (lot 2E116) vs. to-be-marketed formulation: C_{max}, AUC_{0-inf}, AUC_{0-t}, and partial AUCs (AUC_{0-3h}, AUC_{3-7h}, AUC_{7-12h})*
 - *For food effect on to-be-marketed formulation, the following PK parameters should be statistically compared: C_{max}, AUC_{0-inf}, AUC_{0-t}, and exploratory (partial AUCs = AUC_{0-3h}, AUC_{3-7h}, AUC_{7-12h})*
 - *Additionally, please include the following intra-subject variability analyses for BOTH the BE and food effect study:*
 - *Table with the ratios (Test/Ref.) of all PK parameters applied for BE testing for each individual.*
 - *Table with the number and percentage of the subjects with calculated ratios that meet the indicated criteria (>200%, >125%, <80%, <50%) for all PK parameters applied for BE testing.*
 - *Scatter plot of the individual ratios and the geometric least square mean ratio for all PK parameters applied for BE testing. Reference lines drawn at 200%, 125%, 85% and 50%.*
2. *We request that you manufacture the BE batches using the commercial scale equipment, especially the commercial scale (b) (4).*
3. *We remind you that the approval of the proposed strengths not tested in in vivo studies should be supported by comparative dissolution data in multiple dissolution media with similarity testing calculation (e.g., f₂ testing). Note that if the lowest strength(s) and the highest strength of your proposed drug product are not proportionally similar in composition, a bracketing BE approach needs to be applied to support their approval.*

Discussion at Meeting:

1. *The sponsor agreed to perform BE testing on partial AUCs in addition to C_{max}, AUC_{0-t}, and AUC_{0-inf}. However, they suggested using AUC 0-3h, AUC 3-5h, and AUC 5-12h*

for bioequivalence testing because the pharmacokinetic profile of their product has inflection points at 3 hours and 5 hours post-dose. The Agency clarified that the recommended partial AUCs (AUC 0-3h, AUC 3-7h, and AUC 7-12h) for BE testing are selected for major methylphenidate products with a 12-hour treatment duration, which is consistent with the sponsor's current product. The rationale for using AUC 0-3h, AUC 3-7h and AUC 7-12h in a fasted BE study for methylphenidate products is based on both PK profile as well as clinical relevance.

Based on the discussion, the sponsor agreed to perform BE testing including AUC 0-3h, AUC 3-7h and AUC 7-12h as the primary pharmacokinetic variables. The sponsor may perform exploratory analysis with other partial AUCs.

2. Neos confirmed that, as requested they will manufacture the BE batches using the commercial scale equipment, including the commercial scale (b) (4).
3. No further discussion

Does the agency agree that a positive outcome indicating that the to-be-marketed formulation is bioequivalent to the clinical trial formulation (Lot 2E116E) be sufficient to establish the bridge to the efficacy and safety findings of Metadate CD and the bioavailability results of the pediatric trials conducted by Neos?

Preliminary Comments: Yes, please see response to Q1.

Discussion at Meeting: No further discussion.

Chemistry, Manufacturing and Controls

Question 3: Validation and Control of the (b) (4) Process (OPQ Question #2)
Does the Division agree that (b) (4) will provide the assurance needed that the process is controlled?

Preliminary Comments: As per the CR letter dated 11/06/2015, we would like to restate that your proposal to (b) (4) could be acceptable, in principle, upon full validation of the approach and assumptions. The proposed (b) (4) % of target (b) (4) level appears acceptable. Note that a (b) (4) % (b) (4) would, of course, not be acceptable (as per SUPAC MR guidance).

Provide dissolution profiles (b) (4)
(b) (4). These data are needed to support your proposed (b) (4) % (wt/wt) of the target. The dissolution data should be generated using a discriminating dissolution method.

Discussion at Meeting:

Neos confirmed that they intend (b) (4) the delayed release and extended release (b) (4) (b) (4) % of a specified regulatory target weight (b) (4) They intend (b) (4) % of a specified target. The Agency reiterated that, in order to pursue this route, the (b) (4) calculations must be fully validated. (b) (4)

Neos raised the possibility of using an (b) (4) (b) (4)

The Agency stated that they would discuss the proposed (b) (4) operation internally and provide feedback in the meeting minutes.

Post Meeting Feedback: After further internal discussion, we do see the (b) (4) approach as a possible way forward once it includes scientifically-justified limits (b) (4)

(b) (4). We expect that (b) (4) be established and scientifically justified.

Regardless of the approach you implement, we recommend that you determine the source of process variability and control it. The variability may be wholly or in-part a result of (b) (4) variability. Such process understanding will aid in developing a more robust process.

Please be aware that the omission of information on the (b) (4) operation from the Pharmaceutical Development section of this NDA (despite the Agency's previous concern about this process) has made the evaluation of your application unnecessarily difficult. For us to be most helpful to you in making innovative products available to the American public, we request that you provide a complete and upfront accounting of your data. Although, we are unable to carry out a complete review outside of a formal resubmission, we are willing to provide our available resources to provide input, but the information submitted must be complete.

2.2 Other Deficiencies/Comments

Question 4: Basis of Dosage Strength (OPO #1):

Does the Division agree to Neos' proposal to use the (b) (4) for calculation of the methylphenidate content?

Preliminary Comments: *The Agency requests that you employ the more accurate factor of 0.8648 to calculate the nominal dosage strength.*

Discussion at Meeting: Neos agreed to use the recommended 0.8648 factor. (b) (4)

The Agency pointed out that the label will likely include (b) (4) salt – base equivalency. Neos requested guidance on rounding the methylphenidate base strengths. The Agency indicated that it was current Agency thinking to round to one decimal.

Question 5: (b) (4) Dissolution Testing Using a Two-Stage Method to Evaluate In Vitro Performance (OPO #2):

Does the Division agree that the method development and validation documentation adequately addresses the potential degradation levels of methylphenidate in the proposed dissolution media?

Preliminary Comments: *We recommend that you develop a single-stage method; however, on face, the proposed method appears adequate. A final determination of its acceptability will be a review matter.*

Discussion at Meeting: Neos stated that they will follow the Agency recommendation for single-stage dissolution test.

Question 6: Sampling Time Points for (b) (4) Dissolution Assay (OPQ #3)
Does the Division agree that the discriminating ability of this validated test method along with its capability to predict the release of methylphenidate from the ODT drug product provide sufficient justification for not choosing a final time point which exhibits greater than (b) (4) % release of methylphenidate (b) (4) ?

Preliminary Comments: This is a review matter. Include the full method validation and justification for the lack of the (b) (4) % drug release in the resubmitted application; however as stated in the CR letter, we recommend that you add a time point to ensure the release of at least (b) (4) % of the drug.

Discussion at Meeting: Neos stated that extension of the dissolution method to control (b) (4) % drug release would be burdensome and would result in a less discriminatory test. The Agency reiterated that this was a recommendation and that the application should include full method validation and justification for the lack of a timepoint controlling (b) (4) % drug release.

Question 7: (b) (4)
?
?

Preliminary Comments: They appear acceptable.

Discussion at Meeting: No further discussion.

Question 8: (b) (4)
?
?

Preliminary Comments: This approach appears acceptable for assay uniformity. (b) (4).
we recommend that (b) (4) be similarly demonstrated, or provide justification why this is not expected to be an issue.

Discussion at Meeting: No further discussion.

Question 9: Batch Formula Information (OPO #7)

Does the Division agree that the proposed formulation information will be sufficient for the resubmission?

Preliminary Comments: *Provide batch information, including batch size and formulation, for all batches manufactured as part of the resubmission.*

Additionally, ensure the following information is included in the resubmission:

- *The targeted drug product composition (mg and w/w%)*
- *The minimum acceptable amount of each excipient ((b) (4), sucralose, triethyl (b) (4), ethylcellulose, methacrylic acid (b) (4)) for a drug product composition (mg and w/w%)*
- *The maximum acceptable amount of each excipient (b) (4), sucralose, triethyl (b) (4), ethylcellulose, methacrylic acid (b) (4) for a drug product composition (mg and w/w%)*

Discussion at Meeting: No further discussion.

Question 10: Release Data and Stability Program (OPO #8)

Does the agency agree that the proposed release data and stability commitment are adequate for supporting the resubmission?

Preliminary Comments: *Submitting three months of accelerated and long-term data from three lots of the 30 mg and 10 mg to-be-marketed drug product and one lot of the 20 mg to-be-marketed drug product along with the commitment to continue long-term stability studies through 24 months is acceptable.*

Discussion at Meeting: No further discussion.

Question 11: (b) (4) Particle Size Specification (OPO #9)

Does the Division agree that the (b) (4) particle size specification as recommended by the manufacturer is appropriate for testing and release (b) (4) ?

Preliminary Comments: *As no details of this control were provided, this will be a review matter on resubmission where full details and justification are expected to be provided. We expect that a three-tier (e.g., d10, d50, d90) acceptance criterion will be employed (b) (4)*

Discussion at Meeting: No further discussion.

2.3 Additional Question

Question 12: Packaging Configurations

Do the Division and DMEPA agree that the proposed package configuration proposal is adequate for the resubmission?

Preliminary Comments: *No, we do not agree. You have not provided any new data to alleviate DMEPA's concerns expressed during the July 15, 2015, teleconference* (b) (4)

As previously mentioned during our teleconference, (b) (4) *is not a standard unit-dose packaging design for methylphenidate products and may lead to confusion and contribute to wrong dose errors. In addition, we previously expressed safety concerns regarding Computerized Provider Order Entry (CPOE) systems, automated dispensing cabinets, and automated controlled substance inventory systems that still may not safely support this* (b) (4) *configuration proposal. Furthermore, the variability of the* (b) (4)

) may also contribute to confusion and errors. Given the simplicity of the dosing regimen for Cotelma XR ODT (1 or 2 tablets daily), there is inadequate justification to introduce the proposed (b) (4) *configuration given the risk for medication errors. Thus, we do not agree with your proposal.*

Discussion at Meeting: No further discussion.

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

/s/

MITCHELL V Mathis
01/15/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205489 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Cotempla XR ODT Established/Proper Name: Methylphenidate Extended Release Orally Disintegrating Tablet Dosage Form: 10 mg, 20 mg, and 30 mg Tablets		Applicant: Neos Therapeutics, Inc. Agent for Applicant (if applicable): Dorothy Engelking
RPM: CAPT Bill Bender		Division: Psychiatry Products
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>November 9, 2015</u>		☐ AP ☐ TA ☒ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

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

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

³ 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.

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

- | | |
|---|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☐ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☐ Direct-to-OTC |
| ☐ Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: [CST SharePoint](#))

NDAs: Subpart H

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

Subpart I

- ☐ Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- ☐ Approval based on animal studies

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

Comments:

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

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action and date CR: 11/06/2015
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included
• Original applicant-proposed labeling	☐ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling (<i>see DMEPA labeling review</i>)	☐ Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)	04/20/2015
• Review(s) (<i>indicate date(s)</i>)	04/20/2015
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: ☒ None 03/22/2015 DMEPA: ☒ None 08/18/2015;09/11/2015 DMPP/PLT (DRISK): ☒ None 09/11/2015 OPDP: ☒ None 09/11/2015 SEALD: ☐ None CSS: ☐ None Product Quality ☐ None Other: ☒ None DPMH (09/22/2015)
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	03/22/2015; Filing Letter (03/24/2015)
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee <i>Comments received from (b)(2) committee for when they resubmit...</i>	☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☐ Included CR action
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) Date reviewed by PeRC <u>September 2, 2015</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☐ N/A or no mtg
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg 01/31/2014 under IND 109108
EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg
Mid-cycle Communication (<i>indicate date of mtg</i>)	☐ N/A
Late-cycle Meeting (<i>indicate date of mtg</i>)	☐ N/A
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 11/05/2015
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 10/25/2015
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ None Will be Pediatric PMR when they resubmit.
Clinical	
❖ Clinical Reviews	

• Clinical Team Leader Review(s) (indicate date for each review)	☒ No separate review
• Clinical review(s) (indicate date for each review)	10/11/2015
• Social scientist review(s) (if OTC drug) (indicate date for each review)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)	Included with the original NDA submission on 01/09/2015.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	☐ None requested 06/05/2015; 07/22/2015
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ No separate review
Statistical Team Leader Review(s) (indicate date for each review)	☒ No separate review
Statistical Review(s) (indicate date for each review)	☐ None 10/14/2015; Filing Review(02/26/2015)
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology review(s) (indicate date for each review)	☐ None 10/09/2015; Filing Review(02/26/2015)
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☐ None 10/06/2015; Filing Review(03/13/2015)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☐ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	☒ None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	☐ None 09/09/2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Original Submission) 01/09/2015
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☒ Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

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

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/s/

WILLIAM H BENDER
11/08/2015

**PeRC Meeting Minutes
September 2, 2015**

PeRC Members Attending:

Wiley Chambers (Acting PeRC Chair)

Gettie Audain

Meshaun Payne

Hari Cheryl Sachs

Lily Mulugeta

Kevin Krudys

Belinda Hayes

Deanna Greene

Peter Starke -

NON-RESPONSIVE

Andrew Mulberg -

NON-RESPONSIVE

Davia Shetty

George Greeley

Shrikant Pagay

Agenda

	NON-RESPONSIVE				
9:00					
10:00					
10:20					
10:40					
11:00					
11:15	NDA 205489	Methylphenidate XR ODT Partial Waiver/ Deferral/ Assessment (with Agreed iPSP)	DPP	William Bender	Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
	NON-RESPONSIVE				

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NON-RESPONSIVE

Methylphenidate XR ODT Partial Waiver/ Deferral/ Assessment (with Agreed iPSP)

- Proposed Indications: Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
- The Division noted that they will be requesting additional studies in a PMR.
- *PeRC Recommendations:*
 - PeRC agreed with the Division's plan to label the product in patients 6 years (b) (4) based on the pediatric trials described in the Agreed iPSP, but to request an additional study for pediatric patients 4 to less than 6 years of age. The request for the additional study would be consistent with the Division's recently revised policy of asking for studies down to 4 years of age in patients with ADHD based on the recent evidence that ADHD medications are being used in a substantial number of 4 and 5 year olds.
 - The PeRC agreed with the Division's granting of a request for a partial waiver for pediatric patients less than 4 years of age because the product would be ineffective and /or unsafe in this pediatric age group.
 - The PeRC agreed to the Division's granting a deferral for studies in patients 4 to less than 6 years of age because of the change in policy necessitating a new study.

NON-RESPONSIVE

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Page 4 of 5

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/s/

GETTIE AUDAIN
09/23/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205489

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Neos Therapeutics, Inc.
2940 N. HWY 360, Suite 400
Grand Prairie, TX 75050

ATTENTION: Dorothy J. Engelking
VP Regulatory Affairs

Dear Ms. Engelking:

Please refer to your New Drug Application (NDA) dated and received January 09, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Extended Release Orally Disintegrating Tablets, 10 mg, 20 mg, and 30 mg.

We also refer to:

- Your correspondence, dated and received January 20, 2015, requesting review of your proposed proprietary name, Cotempla XR-ODT
- Our email, dated January 26, 2015, requesting clarification of the strengths
- Your amendment, dated and received January 28, 2015, clarifying the strengths
- Our email, dated April 02, 2015, requesting rationale for the proposed modifier
- Your amendment, dated and received April 06, 2015, providing the rationale for the proposed modifier

We have completed our review of the proposed proprietary name, Cotempla XR-ODT and have concluded that it is conditionally acceptable.

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

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Vasantha Ayalasomayajula, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-5035. For any other information regarding this application, contact William H Bender, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2154.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy 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/

TODD D BRIDGES
04/20/2015



NDA 205489

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

Neos Therapeutics, Inc.
Attention: Dorothy J. Engelking
Vice President, Regulatory Affairs
2940 N. HWY 360, Suite 400
Grand Prairie, TX 75050

Dear Ms. Engelking:

Please refer to your New Drug Application (NDA) dated and received on January 9, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Methylphenidate (b) (4) Extended Release Orally Disintegrating 10 mg, 20 mg, and 30 mg tablets.

We also refer to your amendments dated January 16, 2015, January 20, 2015, January 28, 2015, February 10, 2015, February 16, 2015, February 27, 2015, March 6, 2015, March 17, 2015 and March 19, 2015.

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 November 9, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 9, 2015.

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

PRESCRIBING INFORMATION

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

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

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

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a partial waiver 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 CAPT Bill Bender, Senior Regulatory Project Manager, at (301) 796-2145 or email at william.bender@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

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/s/

MITCHELL V Mathis
03/24/2015



IND 109108

MEETING PRELIMINARY COMMENTS

Neos Therapeutics, Inc.
Attention: Dorothy J. Frank-Engelking, M.S., RAC
Vice President, Regulatory Affairs
2940 N. Highway 360, Suite 100
Grand Prairie, TX 75050

Dear Ms. Frank-Engelking:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) methylphenidate (b) (4) controlled release orally disintegrating tablet (ODT).

We also refer to your November 15, 2013, correspondence, received November 18, 2013, requesting a meeting to discuss the contents of the planned 505(b)(2) NDA.

Our preliminary responses to your meeting questions are enclosed.

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

If you have any questions, email me at shinye.chang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 6, 2014 11:00 AM - 12:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Application Number: 109,108
Product Name: (b) (4) methylphenidate (b) (4) controlled release orally disintegrating tablet (ODT)
Indication: ADHD
Sponsor/Applicant Name: Neos Therapeutics, Inc.

FDA ATTENDEES (tentative)

Mitchell Mathis, M.D., Division Director, Division of Psychiatry Products (DPP)
Jing Zhang, M.D. Medical Team Leader, DPP
Glenn Mannheim, M.D. Medical Reviewer, DPP
Linda Fossom, Ph.D. Pharmacology/Toxicology Supervisor, DPP
Shiny Mathew, Ph.D. Pharmacology/Toxicology Reviewer, DPP
Shin-Ye Sandy Chang, Pharm.D. Regulatory Project manager, DPP
Olen Stephens, Ph.D., Branch Chief, Office of New Drug Assessment I (ONDQA)
David Claffey, Ph.D. Pharmaceutical Assessment Lead, ONDQA
Sherita McIlmore-Hines, Ph.D., CMC Reviewer, ONDQA
Hao Zhu, Ph.D. Office of Clinical Pharmacology Team Leader
Andre Jackson, Ph.D. Office of Clinical Pharmacology Reviewer
Irene Z. Chan, PharmD, BCPS, Division of Medication Error Prevention and Analysis (DMEPA), Team Leader
Loretta Holmes, BSN, PharmD, Safety Evaluator, DMEPA

SPONSOR ATTENDEES

Dorothy Engelking, VP, Regulatory Affairs, Neos
Vipin Garg, Ph.D., Chief Executive Officer, Neos
Mark Tengler, Co-President and CTO, Neos
Russ McMahan, VP R&D, Neos
Carolyn Sikes, Ph.D., Clinical, Neos

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 6, 2014 11am, between Neos Therapeutics, Inc. and the Division of Psychiatry Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1. BACKGROUND

Neos Therapeutics, Inc. (Neos) intends to submit a 505(b)(2) New Drug Application that will reference safety and efficacy data included in the NDA for METADATE CD (methylphenidate HCl, USP) Extended-Release Capsules (NDA 21-259).

The Neos formulation is intended to provide an extended release in vivo drug release profile through the use of immediate-release and delayed/extended-release forms of methylphenidate

(b) (4) The formulation is comprised of (b) (4).
(b) (4). The doses and dosing schedule for the Methylphenidate XR-ODT are intended to be the same as that of METADATE CD.

Neos intends to submit this 505(b)(2) NDA in eCTD format, requesting approval for three strengths of the ODT in dosages equivalent to 10 mg, 20 mg, and 30 mg of methylphenidate hydrochloride. The electronic submission will be prepared in accordance with FDA's *Guideline for Industry: Providing Regulatory Submissions in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (June 2008), and in accordance with the current ICH/FDA eCTD specifications.

The purpose of this pre-NDA meeting is to provide the Division with the outline and content of the proposed 505(b)(2) NDA and gain concurrence that Neos has a complete application that can be accepted for filing.

The following studies have been completed except for Study 1004, the phase 3 classroom efficacy study, which is still on-going:

- Study 1001: a single dose (two x 30 mg equaling 60 mg dose), open-label, randomized, 3-period, 3-treatment crossover bioequivalence study in healthy adults (N=42), using METADATE CD as the RLD vs. two test formulations of methylphenidate polistirex XR-ODTs
- Study 1002: a single-dose (two 30-mg ODTs equaling 60-mg dose), open-label, randomized, two-period, two-treatment crossover (one fasted treatment period, one fed treatment period) bioavailability study in healthy adults (N=24).
- Study 1003: a single-dose (two 30-mg ODTs equaling 60-mg dose), open-label, single period, one-treatment, pharmacokinetic study under fasted conditions in children (ages 6-12) and adolescents (ages 13-17) with ADHD (N=32).
- Study 1004: a phase 3 efficacy and safety laboratory classroom study in 84 children (6-12 years of age) with ADHD; 4 week dose optimization using 20, 30, 40 or 60 ODT's equivalent, then a 1 week dose stabilization, then a 1 week double blind, parallel treatment period culminating in a laboratory classroom setting. The primary efficacy endpoint is the average of the SKAMP Combined (Attention and Deportment) scores over the test day (not including the baseline score), with assessments taken at baseline, 1, 3, 5, 7, 10, 12, and 13 hours post-dose.

2. DISCUSSION

2.1. General Questions

Question 1: In reference to the Division response dated May 22, 2012 to the Neos Request for Advice dated May 1, 2012, Neos conducted an efficacy and safety study (NT0102.1004) in pediatric patients (ages 6-12 years) with ADHD to demonstrate the efficacy of the Methylphenidate XR-ODT formulation. As per 21 CFR 108(b)(4), Neos plans to request 3 years of Waxman-Hatch exclusivity. Does the Division concur?

FDA Response to Question 1: On face, it appears that you meet the criteria of Waxman-Hatch exclusivity identified under 21 CFR 314.108 (b) (4). However, a final determination can and will be made only at the time of NDA submission and review.

Question 2: Neos has assessed all issues in the Regulatory History section as being fully resolved. Does the Division concur?

FDA Response to Question 2: On face, all issues seem to have been satisfied. However, a final determination can and will be made only at the time of NDA submission and review.

Question 3: Are there any other outstanding issues related to the interactions between Neos Therapeutics and the FDA for Methylphenidate XR-ODT that require resolution prior to the submission of the NDA?

FDA Response to Question 3: On face, all outstanding issues seem to have been satisfied. However, a final determination can and will be made only at the time of NDA submission and review.

Question 4: Does the Division agree that the content and format of the NDA as described below are adequate to support an acceptable filing of a 505(b)(2) NDA?

FDA Response to Question 4: Overall, on face, it appears to be adequate. A determination of filability will be made within 60 days after submission of the NDA.

2.2. NDA Content and Format

Module 2: Common Technical Document Summaries

Question 5: The Summary of Clinical Efficacy (SCE) will include the results of one efficacy study (NT0102.1004) conducted by Neos and will incorporate a literature search of the clinical efficacy of methylphenidate for the treatment of ADHD. Since Neos has conducted only one efficacy study, we are proposing to summarize all efficacy data in Module 2. 7.3 in lieu of a separate ISE in Module 5.3.5.3 (Reports of Analysis from More than One Study) as referenced in the *Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document*. Does the Division concur?

FDA Response to Question 5: Yes.

Question 6: The Summary of Clinical Safety (SCS) will be an assessment of all clinical studies (NT0102.1001, NT0102.1002, NT0102.1003, and NT0102.1004) conducted by Neos and will incorporate the results of a literature search of the safety of methylphenidate for the treatment of ADHD. Neos believes that an in-depth analysis of all safety data can be presented in Module 2.7.4 in lieu of a separate ISS in Module 5.3.5.3. Does the Division concur?

FDA Response to Question 6: Yes.

Question 7: The nonclinical safety of NT0102 will be supported solely by published literature on the nonclinical pharmacology, pharmacokinetics and toxicology of methylphenidate. Neos proposes to conduct a literature beginning with the approval date (i.e. April 2001) of the approved reference listed drug, METADATE CD (methylphenidate hydrochloride USP) Extended-release Capsules, UCB, Inc., NDA 21-259. Furthermore, only the written summaries will be included to support the nonclinical pharmacokinetics, pharmacology, and toxicology of methylphenidate; tabulated summaries will not be included. Does the Division concur?

FDA Response to Question 7: Yes (also see our response to Question 11, below).

Module 3: Quality

Question 8: The stability program for the methylphenidate XR-ODT includes all three strengths of the proposed product. A stability bracketing strategy has been adopted that includes three lots at the highest strength (30 mg), three lots at the lowest strength (10 mg), and one lot at the intermediate strength (20 mg) for the clinical and registration pilot-scale lots. To date the available stability data indicate that all three strengths have the same physical performance characteristics which indicate the product is appropriate for the limited bracketing approach. The proposed post-approval commercial stability program will also include all three strengths. Does the Division concur?

FDA Response to Question 8: The proposed stability appears acceptable assuming that there are no strength-specific stability issues.

Question 9:

(b) (4)
For consistency, Neos proposes to remove the word (b) (4) from the proposed established drug name (e.g. Methylphenidate Extended Release Orally Disintegrating Tablet, abbreviated Methylphenidate XR-ODT). Does the Division concur?

FDA Response to Question 9: The proposal to remove the word (b) (4) from the established name is acceptable from a CMC perspective.

Additionally, we note your proposed use of the abbreviation XR-ODT. The acceptability of any abbreviation used as a modifier in either the established name or proprietary name will be a review issue. If you are considering a modifier for your proprietary name, the root name and any proposed modifier(s) will need to be formally evaluated. 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”). Furthermore, submit any information to support a request for a modifier as part of your formal request for proprietary name review. This information will be considered in the Agency’s evaluation of the acceptability of the proposed proprietary name.

Question 10: Neos understands that it is both USP and CDER policy that agreement exist between the established name and the strength of the drug product expressed on the drug product labels and labeling. (b) (4)

(b) (4)

. Does the Division concur with the proposed product dose labeling approach?

FDA Response to Question 10: The acceptability of the proposed established name and labeled strength will be a NDA review issue.

Module 4: Nonclinical Study Reports

Question 11: The nonclinical safety of NTO 1 02 will be supported by published literature related to the nonclinical pharmacology, pharmacokinetics and toxicology of methylphenidate. For this 505(b)(2) application, Neos will also reference the approved reference listed drug, METADATE CD (methylphenidate hydrochloride USP) Extended-Release Capsules, UCB, Inc., NDA 21-259. As such, only the written summaries will be included for pharmacokinetics, pharmacology, and toxicology; tabulated summaries will not be included. Does the Division concur?

FDA Response to Question 11: As you have proposed, you may rely on our previous finding of safety (and efficacy) for METADATE CD. To support such reliance for the nonclinical data, you will need to provide an appropriate scientific bridge; the human pharmacokinetic data you are proposing might provide that bridge.

Written summaries for nonclinical pharmacokinetics, pharmacology and toxicology of methylphenidate from published literature are acceptable.

Module 5: Clinical Study Reports

Question 12: Final Clinical Study Reports for three pharmacokinetic trials and one efficacy trial will be provided in Module 5. Data for these studies will be provided in accordance with the CDISC Study Data Tabulation Model (SDTM) version 1.2 and Implementation Guide (SDTMIG) version 3.1.2 including Amendment 1. Does the Division concur?

FDA Response to Question 12: We concur that the inclusion of the final clinical study reports for the three pharmacokinetic trials and one efficacy trial in Module 5 is acceptable.

Question 13: There were no deaths, serious adverse events, or discontinuations related to adverse events during the clinical trials NTO102.1001, NTO102.1002 and NTO102.1003. Regarding the ongoing study NTO102.1004, we currently have only one discontinuation due to an adverse event. Given the nature of this study, we do not anticipate many more, if any, of the aforementioned events. As a result, we would anticipate that case report tabulations would be of little value to the Agency. Our

proposal would be to provide the SAS datasets in lieu of case report tabulations. Does the Division concur?

FDA Response to Question 13: In addition to the SAS datasets, please provide a descriptive narratives for all subjects who discontinued from a trial because of an adverse event.

Question 14: In a teleconference with the FDA on May 13, 2013, the FDA requested the collection of blood samples during our pivotal efficacy trial in order to explore exposure response relationships and to help establish the most informative partial area-under-the-curve (pAUC) for the product. Neos cited several reasons as to why this would not be acceptable and proposed an alternative approach whereby an exposure-response analysis would be conducted utilizing data obtained from the pediatric PK study (NT0102.1003) to con-elate with the PD parameters from the efficacy study (NT0102.1004). The PK exposure-response analysis datasets and programs files used to generate these datasets will be available to the reviewers upon request. Does the Division concur?

FDA Response to Question 14: This approach appears to be reasonable but the final assessment of its suitability will be a review issue. All analysis data sets and program files should be submitted with the NDA.

3. PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

4. PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements of Prescribing Information](#) website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents, and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

5. 505(b)(2) REGULATORY PATHWAY

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

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

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

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an

NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
(e.g., published literature, name of listed drug)	Nonclinical toxicology
(e.g., specific sections of the 505(b)(2) application or labeling)	Previous finding of effectiveness for indication X
1. Example: Published literature	Previous finding of safety for Carcinogenicity, labeling section XXX
2. Example: NDA XXXXXX	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then

it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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

/s/

SHIN-YE CHANG
01/31/2014