

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204326Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA #: 204326

SUPPL #

HFD #: 130

Trade Name: ADZENYS XR-ODT

Generic Name: Amphetamine Extended-Release Orally Disintegrating Tablets

Applicant Name: Neos Therapeutics, Inc.

Approval Date, If Known: 1/27/2016

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) NDA

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.

The sponsor solely used Adderall XR as a RLD and submitted bioequivalence data to comparing their product to the innovator to support approval.

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?

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# 021303 *Adderall XR*

NDA# 011522 *Adderall*

NDA# 208147 *Dynavel XR*

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:

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"):

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 #

YES ☐

!

! NO ☐

! Explain:

Investigation #2

!

IND #

YES ☐

!

! NO ☐

! Explain:

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

Investigation #1

YES ☐

Explain:

!

!

! NO ☐

! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! Explain:

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

YES ☐

NO ☐

If yes, explain:

=====

Name of person completing form: Kofi Ansah, Pharm.D., RAC

Title: Senior Regulatory Project Manager

Date: 1/26/16

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

Title: Director, Division of Psychiatry Products

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/

KOFI B ANSAH
01/27/2016

MITCHELL V Mathis
01/27/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 204326 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Adzenys XR-ODT Established/Proper Name: Amphetamine Extended-Release Orally Disintegrating Tablets Dosage Form: Orally Disintegrating Tablets (i.e., ODT)		Applicant: Neos Therapeutics, Inc. Agent for Applicant (if applicable):
RPM: Kofi B. Ansah, Pharm.D., RAC		Division: Division of Psychiatry Products (DPP)

<u>NDA and NDA Efficacy Supplements:</u> NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)	<u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): ADDERALL XR (NDA 021303) Provide a brief explanation of how this product is different from the listed drug. <i>This application provides for a change in dosage form, (b) (4) to extended-release ODT. The application also proposes (b) (4) (b) (4)</i> ☐ This application does not rely upon a listed drug. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ This application relies on (explain) <u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☒ No changes ☐ Updated Date of check: 1/27/16 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.
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❖ Actions	
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¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

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

- Proposed action - User Fee Goal Date is <u>1/27/16</u>	☒ AP ☐ TA ☐ CR								
Previous actions (<i>specify type and date for each action taken</i>)	☐ None CR (9/24/13)								
❖ 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									
Review priority: ☒ Standard ☐ Priority (*but for the 2 nd Cycle reviewed on a 6-moth/priority review clock) Chemical classification (new NDAs only): <table border="0" style="width: 100%;"> <tr> <td>☐ Fast Track</td> <td>☐ Rx-to-OTC full switch</td> </tr> <tr> <td>☐ Rolling Review</td> <td>☐ Rx-to-OTC partial switch</td> </tr> <tr> <td>☐ Orphan drug designation</td> <td>☐ Direct-to-OTC</td> </tr> </table> <table border="0" style="width: 100%;"> <tr> <td style="vertical-align: top;"> 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 </td> <td style="vertical-align: top;"> 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 </td> </tr> </table> Comments:		☐ Fast Track	☐ Rx-to-OTC full switch	☐ Rolling Review	☐ Rx-to-OTC partial switch	☐ Orphan drug designation	☐ Direct-to-OTC	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
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❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates								
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No								
❖ Public communications (<i>approvals only</i>)									
Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No								
Press Office notified of action (by OEP)	☐ Yes ☒ No								
Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other								

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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i>	☒ No ☐ Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire _____
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i>	☐ N/A (no paragraph IV certification) ☒ Verified

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

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

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

☒ Yes ☐ No

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

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

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

☐ Yes ☐ No

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

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

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

☐ Yes ☐ No

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

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

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

☐ Yes ☒ No

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

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

☒ Yes ☐ No

Note: The 30 month stay expired on 9/1/2015

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

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

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.

CONTENTS OF ACTION PACKAGE

- ❖ Copy of this Action Package Checklist⁴

Yes

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*)

Action(s) and date(s): AP 1/27/16 & CR Letter 9/24/13

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.
- Original applicant-proposed labeling
- Example of class labeling, if applicable

1/25/16 & 12/30/15 Labeling Edits; 7/27/15 resubmitted Label
12/2/12 Original Submission Label
Adderall XR

⁴ Fill in blanks with dates of reviews, letters, etc.

❖ 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. If it is division-proposed labeling, it should be in track-changes format.	1/25/16 & 12/30/15 Labeling Edits;
• Original applicant-proposed labeling	7/27/15 resubmitted Label & 12/2/12 Original Submission Label
• Example of class labeling, if applicable	Adderall XR
❖ 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	
❖ Proprietary Name • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.	Acceptability: 1/22/16 & 11/2/15 Unacceptability: 04/04/13 DMEPA Reviews – 1/26/16; 1/13/16; 1/6/16; 11/6/15; 10/28/15
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☒ RPM - PLR Format Review (03/12/13) ☐ DMEPA ☒ DMPP/PLT (DRISK) Memo 09/11/13 ☒ ODPD (DDMAC) 12/11/15 ☐ SEALD ☒ CSS 1/14/16 ☒ Other reviews DMPP/PLT 12/14/15; PMHS 12/9/15; DPMH 12/9/15
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM Filing/SRPI Reviews 03/12/13
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 12/22/15; 9/16/13
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☐ Not a (b)(2) 1/27/16
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	☒ Included
• Applicant is on the AIP	☐ Yes ☒ No
• 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>12/16/15</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☒ Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	☒ Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	Included
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	☒ No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	☐ N/A or no mtg Meeting Date(s): 10/2/14; 11/21/13
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	☒ No mtg
• EOP2 meeting <i>(indicate date of mtg)</i>	☐ No mtg 09/13/12
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
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 (see CDTL Memo 1/27/16)
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	☐ None 1/27/16; 09/17/13
PMR/PMC Development Templates <i>(indicate total number)</i>	☐ None 1/27/16
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	
• Clinical review(s) <i>(indicate date for each review)</i>	1/26/16; 08/20/13; 02/13/13
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	☐ 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 <i>(indicate date of review/memo)</i>	see MO's review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	☐ Not applicable None
❖ Risk Management	
• REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i>	
• REMS Memo(s) and letter(s) <i>(indicate date(s))</i>	
• Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i>	☒ None

⁶ Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	☐ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☒ None
Clinical Microbiology Review(s) (indicate date for each review)	☒ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ None
Statistical Team Leader Review(s) (indicate date for each review)	☒ None
Statistical Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology review(s) (indicate date for each review)	☐ None 12/29/15; 08/29/13; 02/15/13
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☐ None 1/25/16; 12/14/15; 08/06/13; 01/25/13
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ None
• Supervisory Review(s) (indicate date for each review)	☒ None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None 08/22/13 (primary); 02/26/13 (filing)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	☒ None requested

Product Quality		☐ None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		☒ None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		☐ None CMC – 12/21/15 & 09/12/13 (final); 05/01/13 (primary); 01/08/13 (initial) Biopharmaceutics – 09/11/13 (final); 05/01/13 (primary); 02/13/13 (initial)
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		☐ None Facility- 05/17/13 Process – 05/03/13
❖ Environmental Assessment (check one) (original and supplemental applications)		
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		01/08/13
☐ Review & FONSI <i>(indicate date of review)</i>		
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <u>NOT</u> include EER Detailed Report) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>		Date completed: Facility- 05/17/13 Process – 05/03/13 ☐ Acceptable ☒ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research



DATE: 01/27/2016

TO: Adzenys XR-ODT (amphetamine Extended-Release Orally Disintegrating Tablets) File (NDA 204326)
Dyanavel XR (amphetamine) Extended-Release Oral Suspension File (NDA 208147)

FROM: CDER Exclusivity Board

SUBJECT: Whether 3-Year Exclusivity for Dyanavel XR (amphetamine) Extended-Release Oral Suspension (NDA 208147) blocks the approval of Adzenys XR-ODT (amphetamine (b) (4)) Orally Disintegrating Tablets File (NDA 204326)

This memorandum addresses whether the unexpired 3-year exclusivity FDA recognized for Dyanavel XR (amphetamine) extended-release (ER) oral suspension (Dyanavel XR) (NDA 208147) blocks approval of Adzenys XR-ODT (amphetamine (b) (4)), orally disintegrating tablets (NDA 204326) (Adzenys XR-ODT).

Dyanavel XR was approved on October 19, 2015, for the treatment of Attention Deficit-Hyperactivity Disorder (ADHD) and received 3-year exclusivity, which is denoted in the Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") as "new product" (NP) exclusivity. Upon review of the administrative record related to the approval of NDA 208147, the Exclusivity Board (Board) in the Center for Drug Evaluation and Research (CDER), in consultation with the Division of Psychiatry Products (Division), concludes that the exclusivity-protected condition of approval for which new clinical investigations were essential is the oral ER suspension formulation¹ of Dyanavel XR associated with its drug release profile, and thus recommends that 3-year exclusivity for Dyanavel XR should not block the approval of Adzenys XR-ODT because Adzenys XR-ODT, a solid oral dosage form (orally disintegrating tablets) is , associated with a drug release profile different from that of Dyanavel XR.

¹ The term "formulation" as used in this memo includes aspects of the product's formulation that contribute to its drug release mechanism and resulting PK profile.

A discussion of the Board's reasoning follows.

I. FACTUAL AND PROCEDURAL BACKGROUND

A. Dyanavel XR

On December 19, 2014, Tris Pharma, Inc. (Tris Pharma) submitted NDA 208147 for Dyanavel XR (amphetamine) extended-release oral suspension, 2.5 mg amphetamine base per ml (eq. 2.5 mg base/mL),² for the treatment of ADHD with a once-daily dosing regimen. Tris Pharma's NDA was submitted as a 505(b)(2) application that relied upon FDA's finding of safety and/or effectiveness for Adderall immediate-release (IR) tablets (Teva Women's; NDA 011522).³ Dyanavel XR comprises an ion-exchange resin (polystyrene sulfonate) complexed with amphetamine to provide an extended-release profile for once daily treatment of symptoms of ADHD.⁴ This product was formulated to provide convenience for patients who prefer oral dosage forms but have difficulty swallowing pills or capsules, especially pediatric patients.⁵

To support the safety and efficacy of Dyanavel XR, Tris Pharma conducted a dose-optimized, randomized, double-blind, placebo-controlled study in pediatric subjects 6-12 years of age with ADHD (Study TRI102-ADD-001).⁶ Assessments for ADHD symptoms and behaviors were measured by Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) and Permanent Product Measure of Performance (PERMP) assessments in an abbreviated analog classroom at each clinical site.⁷

In addition to Study TRI102-ADD-001, the sponsor also conducted a pharmacokinetic (PK) study in children (6 – 12 years), and a single-dose relative bioavailability and food effect trial in healthy adult subjects to support this application.⁸ The Division determined that an adequate link was established between the amphetamine ER oral suspension and amphetamine IR tablets through a relative bioavailability study, and that the PK profile of amphetamine following the administration of amphetamine ER oral suspension supported once-daily dosing.⁹ Total exposure ($AUC_{0-\infty}$), $AUC_{(0-t)}$ and C_{max} of both *d*- and *l*-amphetamine were equivalent between the amphetamine ER oral suspension and amphetamine IR tablets; partial(p) $AUC_{(0-4)}$ and $pAUC_{(0-5)}$ of both *d*- and *l*-amphetamine were not, however, equivalent, although $pAUC_{(5-t)}$ of *d*- and *l* amphetamine was equivalent.¹⁰ The Agency found that the similarity of PK profiles in adults, adolescents (13 – 17 years), and children (6 – 12 years) in combination with the prior

² Amphetamine ER Oral Suspension is a formulation of the (b) (4) amphetamine (b) (4) (b) (4) (v) (4) e with a ratio of *d*- to *l*-amphetamine at approximately 3:1.

³ Because Adderall IR tablets (NDA 011522) had been discontinued, the sponsor used a reference drug approved under ANDA 040422 (Teva/Barr Laboratories, Inc.) comprising the mixed amphetamine salts dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate and amphetamine sulfate.

⁴ NDA 208147, Division Director Review (Oct. 19, 2015) (Dyanavel Div. Director Review) at 2

⁵ Id. See also NDA 208147, Clinical Review (Oct. 19, 2015) (Dyanavel Clinical Review) at 2

⁶ Dyanavel Clinical Review at 6-8.

⁷ Id.

⁸ Dyanavel Clinical Review at 5.

⁹ Dyanavel Clinical Review at 4, referencing NDA 208147, Non-Clinical Review (Sep. 21, 2015) (Dyanavel Non-Clinical Review at 7).

¹⁰ Id.

knowledge of the amphetamine IR tablet and clinical practice supported the approval and once-daily dosing recommendations in adolescents and adults.¹¹

The Division determined that study TRI102-ADD-001 supported the efficacy of Dyanavel XR in the treatment of ADHD. Dyanavel XR was approved on October 19, 2015. Dyanavel XR is the first ER oral suspension formulation of amphetamine approved. FDA recognized 3-year exclusivity based on the clinical efficacy trial, which established efficacy of Dyanavel XR's oral suspension formulation. The exclusivity, which expires on October 19, 2018, is currently denoted as "new product" (NP) exclusivity in the Orange Book.

B. Adzenys XR-ODT

On December 27, 2012, Neos Therapeutics, Inc. (Neos) submitted a 505(b)(2) NDA for amphetamine extended-release (ER) orally disintegrating tablets (ODT), tradename Adzenys XR-ODT, for the treatment of ADHD with a once daily dosing regimen (NDA 204326).¹² The strengths for which approval was originally sought by the sponsor are (b) (4), but these were changed to strengths of 3.1, 6.3, 9.4, 12.5, 15.7, and 18.8 mg base amphetamine. This 505(b)(2) NDA relies upon FDA's finding of safety and/or effectiveness for Adderall XR (amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate) 5, 10, 15, 20, 25 and 30 mg strength XR capsules (NDA 021303, Shire) approved on October 11, 2001, for the treatment of ADHD with a once daily dosing regimen.¹³ The Adzenys XR-ODT NDA provides for a new dosage form (b) (4) to ER ODT.¹⁴

Specifically, Adzenys XR-ODT contains amphetamine, in a 3:1 ratio of *d*- to *l*- isomer and is the first amphetamine product formulated in an XR ODT dosage form.¹⁵ It contains amphetamine (b) (4) comprised of a (b) (4) each of which contains a 3:1 ratio of *d*- to *l*- isomer (b) (4) ODT along with other (b) (4) excipients. (b) (4) methacrylic acid copolymer type A and triethyl citrate. (b) (4).

The Adzenys XR-ODT development program is based on a single-dose bioequivalence (BE)/food effect clinical study (NT0202.1005) demonstrating similarity in PK profile and exposure between Adzenys XR-ODT and Adderall XR, and assessing the effect of food on the pharmacokinetics of Adzenys XR-ODT.¹⁶ No additional clinical safety and efficacy studies were submitted in this application. The Agency determined that Adzenys XR-ODT demonstrated a similar PK profile and exposure as Adderall XR and thus anticipated to have similar efficacy and safety profiles to Adderall XR.¹⁷ The Agency also determined that Adzenys

¹¹ Dyanavel Non-Clinical Review at 3.

¹² Neos resubmitted the NDA on July 27, 2015, almost two years after it received a Complete Response letter dated September 24, 2013.

¹³ NDA 204326, Clinical Pharmacology Review (Dec. 29, 2015) (Adzenys XR-ODT Clin. Pharm. Review) at 3.

¹⁴ Id.

¹⁵ Adzenys XR-ODT Clin. Pharm. Review at 8.

¹⁶ Id.

XR-ODT has no clinically meaningful food effect and thus can be administered with or without food.

II. STATUTORY AND REGULATORY BACKGROUND

The availability of a 3-year exclusivity period for a new drug application is described in sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The statute states:

If an application ...for a drug which includes an active ingredient (including any salt or ester of the active ingredient) that has been approved in another application approved under subsection (b) is approved ... and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to approval of the application and conducted or sponsored by the applicant, the Secretary may not make approval of the application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of approval under subsection (b) for such drug.¹⁸

Thus, the standard under the FD&C Act for determining whether an application for a drug containing a previously approved active ingredient is eligible for 3-year exclusivity is that the approval of the application be supported by clinical investigations that are: (1) new, (2) not bioavailability studies, (3) essential to approval, and (4) conducted or sponsored by the applicant. If any one of the four requirements is not met, then the application is not eligible for 3 years of exclusivity. FDA's regulation on 3-year exclusivity mirrors the corresponding statutory framework on exclusivity.¹⁹

Under applicable regulations, a "clinical investigation" means "any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects."²⁰ For purposes of exclusivity determinations, the Agency interprets the phrase "new clinical investigations" in the 3-year exclusivity statutory provisions to mean an investigation conducted on humans "the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the Agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product."²¹

An investigation is conducted or sponsored by the person submitting the application if "before or during the investigation, the applicant was named in Form FDA-1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted

¹⁷ Id.

¹⁸ Section 505(j)(5)(F)(iii) of the FD&C Act; see also section 505(c)(3)(E)(iii) of the FD&C Act.

¹⁹ 21 CFR 314.108(b)(4).

²⁰ 21 CFR 314.108(a).

²¹ Id.

or the applicant or the applicant's predecessor in interest provided substantial support for the investigation.”²²

In addition, the Agency interprets the phrase “essential to approval” to mean that “with regard to an investigation . . . there are no other data available that could support approval of the application.”²³ In the preamble to the final rule, FDA explained that to meet this standard, a clinical investigation must be “vital” to the application or supplement and there must not be any published studies (other than the applicant's) or other information available to FDA that would allow the Agency to approve the proposed drug product as safe and effective.²⁴ In other words, the application or supplement could not be approved without the investigation. Finally, with respect to the scope of protection 3-year exclusivity provides, FDA has not read the exclusivity provision to recognize exclusivity for all conditions of approval of the NDA. Rather, exclusivity is limited to those conditions of approval for which new clinical investigations were essential to approval (and conducted or sponsored by the person submitting the application).²⁵

III. DISCUSSION

Dyanavel XR satisfies the legal requirements for 3-year exclusivity under sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act and 21 CFR 314.108. Specifically, Study TRI102-ADD-001 is a new clinical investigation essential to the approval of Dyanavel XR that was conducted or sponsored by Tris Pharma.

The issue before the Board in this instance is whether the 3-year exclusivity FDA recognized for Dyanavel XR blocks approval of Adzenys XR-ODT. As noted above, Dyanavel XR is the first ER oral suspension of amphetamine intended to be dosed once-daily for the treatment of ADHD. Also, as previously noted, this product was formulated to provide convenience for patients who prefer oral dosage forms but have difficulty swallowing pills or capsules, especially pediatric patients.

As stated above, FDA interprets the scope of exclusivity to be related to the scope of the underlying new clinical investigations that were essential to the approval. Study TRI102-ADD-001 was conducted to demonstrate the safety and efficacy of Dyanavel XR's ER oral suspension formulation and associated drug release profile for the treatment of ADHD. In contrast to Dyanavel XR, Adzenys XR-ODT is the first ER-ODT dosage form of amphetamine formulated

²² Id.

²³ Id.

²⁴ 59 FR 50338, 50357 (Oct. 3, 1994). See also FDA's Exclusivity Summary in which the Agency further explains that an investigation is not considered essential to approval if there is other information that would be sufficient to provide approval of the change (such as what is already known about a previously approved product or from published literature or other public information that would have supported the change approved in the application).

²⁵ Although the FD&C Act and implementing regulations (21 CFR 314.108(a) and 314.108 (b)(4)(iv)) do not define “conditions of approval” for purposes of determining the scope of 3-year exclusivity, the preamble to the Agency's 1989 Proposed Rule on ANDA regulations makes clear FDA's view that 3-year exclusivity covers the innovative change to the previously approved drug that is supported by the new clinical investigations (Proposed rule, “ANDA Regulations,” 54 FR 28872 (July 10, 1989) at 28896-97). FDA thus interprets the scope of exclusivity to be related to the scope of the underlying new clinical investigations that were essential to the approval. Exclusivity does not extend beyond the scope of the approval and does not cover aspects of the drug product for which new clinical investigations were not essential.

so as to produce a PK profile similar to Adderall XR tablets. Therefore, Dyanavel XR's exclusivity should not block approval of Adzenys XR-ODT.

IV. CONCLUSION

For the reasons described above, the Board concludes that Dyanavel XR's exclusivity should not block approval of Adzenys XR-ODT.

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/s/

KOFI B ANSAH
01/27/2016

MITCHELL V Mathis
01/27/2016

From: Ansah, Kofi
To: ["Dorothy Engelking"](#)
Subject: RE: FDA final Labeling (USPI/MG, Blister & Carton Labels) for Agreement -- NDA 204326/Adzenys XR-ODT (amphetamine Extended-Release ODT)
Date: Wednesday, January 27, 2016 6:11:00 PM

Hi Dorothy,

Again, thank you for confirming agreement on Labeling – Best Regards.

Kofi.

From: Dorothy Engelking [mailto:DEngelking@NEOStx.com]
Sent: Wednesday, January 27, 2016 9:53 AM
To: Ansah, Kofi
Cc: David, Paul A
Subject: RE: FDA final Labeling (USPI/MG, Blister & Carton Labels) for Agreement -- NDA 204326/Adzenys XR-ODT (amphetamine Extended-Release ODT)

Dear Kofi,

We have reviewed the final labeling and confirm we have agreement with all components of the labeling.

Best Regards,
Dorothy

From: Ansah, Kofi [<mailto:Kofi.Ansah@fda.hhs.gov>]
Sent: Tuesday, January 26, 2016 11:17 PM
To: Dorothy Engelking <DEngelking@NEOStx.com>
Cc: David, Paul A <Paul.David@fda.hhs.gov>; Ansah, Kofi <Kofi.Ansah@fda.hhs.gov>
Subject: FDA final Labeling (USPI/MG, Blister & Carton Labels) for Agreement -- NDA 204326/Adzenys XR-ODT (amphetamine Extended-Release ODT)
Importance: High

Dear Dorothy,

We acknowledge receipt of your 1/25/16 and 1/26/16 emails providing the revisions we requested you made to the USPI and Carton labels, respectively. We note that you have incorporated all the labeling revisions we requested and we have accepted the counter-proposal you made in Section 11 of the USPI and your other minor editorial changes in the USPI. Attached is the final Labeling (i.e., USPI & MG, Blister Labels, and Carton Labels) we are proposing.

Note: The word versions of the PI & MG have a tracked editorial change on the last page of each document. And the pdf USPI_MG is clean with those changes accepted.

Please respond stating your confirmation that we have agreement on this Labeling – Kindly provide your response by 11:00 am EDT tomorrow, 1/27/16.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA

CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

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/s/

KOFI B ANSAH
01/27/2016

From: Ansah, Kofi
To: ["Dorothy Engelking"](#)
Cc: [David, Paul A](#); [Ayalasomayajula, Vasantha](#)
Subject: Comments for Blister & Carton Labeling (submitted 1-15-16) -- NDA 204326/Amphetamine Extended-Release - ODT
Date: Tuesday, January 26, 2016 12:30:00 PM
Importance: High

Dear Dorothy,

We acknowledge receipt of the blister and carton label you emailed to us 1/14/16 (formally submitted on 1/15/16). We have completed our review and we have the following additional comments for you.

We request that the equivalency statements on side and main panel of the carton labeling be revised to read: "Each tablet contains x.x mg of amphetamine (equivalent to that in a Y mg strength mixed salts of a single-entity amphetamine product)".

Please make the recommended changes and resubmit new labeling, as soon as possible, but no later than tomorrow morning; preferably by 11:00 am EDT on 1/27/16. Please for completeness, resubmit both the Blisters & Carton Labeling. Thank you.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA, RAC

CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

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/s/

KOFI B ANSAH
01/26/2016

From: Ansah, Kofi
To: [Dorothy_Engelking \(DEngelking@NEOSTx.com\)](mailto:Dorothy_Engelking@NEOSTx.com)
Cc: [David, Paul A](#)
Subject: FDA Label (USPI & MG) edits/comments for Agreement (revised) -- NDA 204326/Amphetamine Extended-Release - ODT
Date: Friday, January 22, 2016 2:04:00 PM
Attachments: [01-22-16 final FDA PI-Adzenys XR ODT \(v.01-06-16\) \[CLEAN\].docx](#)
[01-22-16 final FDA PI-Adzenys XR ODT \(v.01-06-16\) \[MARKED-UP\].pdf](#)
[01-22-16 final FDA MG-Adzenys XR ODT \(v.01-06-16\).docx](#)
Importance: High

Dear Dorothy,

Find attached your draft Label (provided via email & formally submitted to your NDA on 1/6/16 in response to our 2nd round label edits/comments dated 12/29/15) with our final set of edits/comments. Please review our edits and comments to the attached PI and resubmit labeling that addresses our comments. Please be sure to work off (i.e., use) the word documents we are sending you and track any edits/counter-proposal(s) you may have (include your own comments as necessary).

Please note that we did not make any additional edits to the MG – We find your comments and the minor edits to the MG acceptable – We have included it in this email for completeness. Do not merge the PI and MG at this time.

Note: Confirm the label conforms to the requirements listed on this FDA website. To help you, the Agency provides a 42-item checklist (scroll down to Selected Requirements of Prescribing Information (SRPI) - <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

Additionally, with regard to the question you posed in your email dated 1/20/16, please find your question and our response below.

Question: After careful consideration of the requirement to note the dose of the product in terms of amphetamine base, Neos would like to discuss the possibility of defining the dose with a whole number instead of a number with one decimal place (i.e. 3 mg instead of 3.1 mg, etc.). We feel this would be very important to the prescribing physician and would alleviate safety concerns if a decimal is not written clearly and the dose is misinterpreted by the pharmacist.

FDA Response: *We considered this idea extensively in our earlier review of the labeling and have reconsidered this again upon receipt of your 1/20/16 email. We prefer to keep the single decimals because they describe the product more accurately, alert prescriber/pharmacists that this is a different product, and avoid the overlapping 15 mg strength that may lead to dosing errors. With the 15mg strength, it would be hard to tell if the prescriber really meant 15.7mg of Adzenys XR-ODT or 15mg of Adderall XR (MAS ER), which would be 9.4mg of Adzenys XR-ODT. Please refer to the comment in labeling regarding why “MAS ER” is preferred.*

*We also remind you that the conditional approval of the proprietary name, **Adzenys XR-ODT** is based upon the strengths 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7 mg, and 18.8 mg. Further modification of the strengths will trigger a need to re-review the name, and the ultimate acceptability of the proposed name will be a matter of review.*

Finally, please provide the requested labeling changes/information to me via email as soon as possible but no later than Monday, 1/25/16. In your response, please state whether or not we have agreement on this PI and MG.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA
CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products
FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112
Silver Spring, MD 20993 - 0002
Phone: (301) 796-4158
Fax: (301) 796-9838

Email: Kofi.Ansah@fda.hhs.gov

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

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/s/

KOFI B ANSAH
01/25/2016

From: [Ansah, Kofi](#)
To: [Dorothy Engelking](#)
Subject: RE: PMR/PMC Communication -- NDA 204326/amphetamine Extended-Release ODT
Date: Thursday, January 21, 2016 10:07:27 PM

Hi Dorothy,

Thank you for the prompt response.

By way of a heads-up, since it will require a quick turnaround, we hope to get you our final Label comments for your review and agreement tomorrow along with our response to the question you posed yesterday.

Please stay tuned for our email.

Thanks,
Kofi.

From: Dorothy Engelking <DEngelking@NEOStx.com>
Date: January 21, 2016 at 4:50:51 PM EST
To: Ansah, Kofi <Kofi.Ansah@fda.hhs.gov>
Subject: RE: PMR/PMC Communication -- NDA 204326/amphetamine Extended-Release ODT

Dear Kofi,

Please see our commitments below. I will prepare a formal submission and get it filed through the gateway tomorrow. I made the correction to commitment number one.

Any comment on our label questions that I sent yesterday?

Best,
Dorothy

From: Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]
Sent: Thursday, January 21, 2016 2:02 PM
To: Dorothy Engelking <DEngelking@NEOStx.com>
Cc: David, Paul A <Paul.David@fda.hhs.gov>
Subject: PMR/PMC Communication -- NDA 204326/amphetamine Extended-Release ODT
Importance: High

Dear Dorothy,

We have the following Postmarketing Requirements, below, which you must agree to prior to the Agency taking a final action on your new drug application. Please respond and provide dates for the Postmarketing Requirement studies. Given that the PDUFA date is next week, we are requesting a response no later than tomorrow, 1/22/16.

1. A single-dose, open-label, randomized pharmacokinetic study of ADZENYS XR-ODT (amphetamine extended-release orally disintegrating tablets), in male and female children (4 to less than 6 years of age) with ADHD.

Final Protocol Submission: **January 2017**

Study Completion: **May 2018**

Final Report Submission: **November 2018**

2. A randomized, double-blind, placebo-controlled, flexible-dose titration study of ADZENYS XR-ODT (amphetamine extended-release orally disintegrating tablets), in children ages 4 to 5 years diagnosed with ADHD.

Final Protocol Submission: **January 2017**

Study Completion: **December 2019**

Final Report Submission: **June 2020**

3. A one year Pediatric Open-Label Safety Study of patients age 4 to 5 years (at the time of entry into Study 1 or Study 2, or at the time of enrollment if directly enrolled into this study) diagnosed with ADHD treated with ADZENYS XR-ODT (amphetamine extended-release orally disintegrating tablets).

Final Protocol Submission: **January 2017**

Study Completion: **May 2020**

Final Report Submission: **November 2020**

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA, RAC

CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

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/s/

KOFI B ANSAH

01/25/2016

Correspondence sent to sponsor on 1/21/16.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204326

**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) Class 2 Resubmission dated and received July 27, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Amphetamine Extended-Release Orally Disintegrating Tablets, 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7 mg, and 18.8 mg.

We also refer to:

- Your correspondence, dated and received August 5, 2015, requesting review of your proposed proprietary name, Adzenys XR-ODT
- Our email, dated January 3, 2016, requesting resubmission of the proposed proprietary name with updated product strengths for a re-review
- Your correspondence, dated and received January 6, 2016, requesting a re-review of your proposed proprietary name, Adzenys XR-ODT

We have completed our review of the proposed proprietary name, Adzenys 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 Kofi Ansah, Regulatory Project Manager in the Office of New Drugs, at 301-796-4158.

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

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/s/

TODD D BRIDGES
01/22/2016

From: [Dorothy Engelking](#)
To: [Ayalasomayajula Vasantha](#)
Subject: RE: Proposed Proprietary Name for NDA 204326
Date: Monday, January 04, 2016 1:00:47 PM

Dear Vasantha,

Neos is in receipt of your request and will have the proprietary name resubmitted in the next couple of days.

Best Regards,
Dorothy

From: Ayalasomayajula, Vasantha [mailto:Vasantha.Ayalasomayajula@fda.hhs.gov]
Sent: Sunday, January 3, 2016 9:37 PM
To: Dorothy Engelking <DEngelking@NEOSTx.com>
Cc: Jenkins, Darrell <Darrell.Jenkins@fda.hhs.gov>; Ansah, Kofi <Kofi.Ansah@fda.hhs.gov>; Flowers, Louis <Louis.Flowers@fda.hhs.gov>
Subject: Proposed Proprietary Name for NDA 204326

Dear Ms. Engelking,

Please refer to your New Drug Application (NDA) Class 2 Resubmission dated and received July 27, 2015 submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Amphetamine Extended Release Orally Disintegrating Tablets, (b) (4).

We also refer to

- Your correspondence, dated and received August 5, 2015, requesting review of your proposed proprietary name, Adzenys XR-ODT.
- Our letter dated November 4, 2015, notifying that we had completed our review of the proposed proprietary name, Adzenys XR-ODT and had concluded that it is conditionally acceptable.

In the letter we also mentioned that If any of the proposed product characteristics as stated in your August 5, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. We received information that the product strengths will have to be changed and hence the proposed proprietary name needs to be resubmitted with updated product strengths for a re-review

To request re-review the above proprietary name or to submit a new proprietary name for consideration; please submit a new, complete, request with updated product strengths. Include the statement "REQUEST FOR PROPRIETARY NAME REVIEW" in bold capital letters, at the top of your cover letter and on the first page of the main submission document (please refer to the complete submission guidance link below). The review of this name will be initiated when the new submission is received.

If you require additional information on developing proprietary names for drugs or proposing alternative proprietary names for consideration, we refer you to the following:

* Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs,
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)

* 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 any other aspects of the proprietary name review process, feel free to contact me directly.

Thanks,
Vasantha

Sincerely,
Vasantha Ayala
Senior Regulatory Project Manager
Office of Surveillance and Epidemiology | Project Management Staff
Ph: 240-402-5035 (O)
Email: Vasantha.ayalasomayajula@fda.hhs.gov

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VASANTHA S AYALASOMAYAJULA
01/14/2016

From: Ansah, Kofi
To: [Dorothy Engelking \(DEngelking@NEOSbx.com\)](mailto:DEngelking@NEOSbx.com)
Cc: [Ayalasomayajula, Vasantha](#)
Subject: FDA/DMEPA Comments for Blister & Carton Labeling (submitted 12-04-15) -- NDA 204326/Amphetamine Extended-Release - ODT
Date: Friday, January 08, 2016 1:28:00 PM
Importance: High

Dear Dorothy,

We have completed our review of your Blisters and Carton Labeling you resubmitted on December 4, 2015; and we have the following comments and recommendations for you. DMEPA recommends that the following be implemented prior to approval of this NDA:

A. Blister Labels and Carton Labeling

-
1. Update all labels and labeling using the (b) (4) base amphetamine strength, as previously communicated by the review division.

2. (b) (4)
(b) (4)
(b) (4) Accordingly, adjust the font presentation of the proprietary name and established name to improve the readability of the information.

3. (b) (4)
(b) (4)

4. The large statement of strength has the unit of measure below the numerical strength. This impairs the readability of the statement. Place the unit of measure on the same line as the numerical strength (e.g., (b) (4) mg) in order to improve the readability of the statement.

5. The colors used to differentiate the (b) (4) strengths are similar. Consider the use of a different color (and one that is not similar to the other strengths) for the (b) (4) strength in order to improve the differentiation of strengths within the product line.

B. Blister Labels

1. The Neos name and the associated graphic are too prominent and compete for space on the label distracting attention away from product identifying information on the labels such as the proprietary name, established name and strength. Decrease the size of the name and graphic. (b) (4)

2. The drug barcode is often used as an additional verification and is therefore an important safety feature. Therefore, we request you add a linear barcode to each individual blister label as required per 21 CFR 201.25(c)(2).

C. Carton Labeling

1. The Medication Guide statement lacks prominence. Increase the size of the statement and use a bold font.
2. The net quantity statement [REDACTED] (b) (4) is unclear. Please clarify whether the carton contains [REDACTED] (b) (4) blister cards. Also state the number of tablets contained in each blister card [REDACTED] (b) (4). Please revise the net quantity statement accordingly, if needed, e.g., 30 Tablets (5 x 6-count blister card).
3. On the principal display panel (PDP), the statement "Do not crush or chew tablets" lacks sufficient prominence. Relocate this statement to an area below the established name and dosage form, increase its size, and use a bold font.
4. The "Rx Only" statement is too prominent due to its bold font which distracts attention from other information on the PDP. Unbold the font.

(b) (4)

Please make the recommended Blister & Carton labeling changes and resubmit new labeling, as soon as possible, but no later than COB 1/15/16. The resubmitted labeling will be used for further labeling discussions.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA, RAC

CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I

10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

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KOFI B ANSAH
01/08/2016

From: Ansah, Kofi
To: [Dorothy Engelking \(DEngelking@NEOStx.com\)](mailto:DEngelking@NEOStx.com)
Subject: 2nd Round of FDA Label (PI & MG) Edits/Comments -- NDA 204326/Amphetamine Extended-Release - ODT
Date: Wednesday, December 30, 2015 12:38:00 AM
Attachments: [12-29-15 draft PI \(v.11-16-15\).docx](#)
[12-29-15 draft MG \(v.11-16-15\)\[MARKED-UP\].pdf](#)
[12-29-15 draft MG \(v.11-16-15\).docx](#)
Importance: High

Dear Dorothy,

Find attached your draft Label (provided via email on 11/16/15 and formally submitted to your NDA on 11/17/15 in response to our initial label edits dated 11/10/15) with our second round of edits/comments. Please review our edits and comments to the attached PI & MG and resubmit labeling that addresses our comments. Do not merge the PI and MG at this time.

Please be sure to work off (i.e., use) the word documents we are sending you and track any edits/counter-proposal(s) you may have (include your own comments as necessary).

Provide the requested labeling changes/information to me via email as soon as possible but no later than Wednesday, 1/6/16. The resubmitted labeling will be used for further labeling discussions.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA

CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
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KOFI B ANSAH
12/30/2015

From: [Ansah, Kofi](#)
To: ["Dorothy Engelking"](#)
Cc: [Ayalasomayajula, Vasantha](#)
Subject: FDA/DMEPA Comments for Blister & Carton Labeling -- NDA 204326/Amphetamine Extended-Release - ODT
Date: Wednesday, November 18, 2015 2:00:48 PM
Attachments: [image002.png](#)
Importance: High

Dear Dorothy,

We have completed our initial review of your Blisters and Carton Labeling and have the following comments and recommendations for you from DMEPA.

A. Blister Labels

1. The established name and dosage form are not on the labels. Add the established name and dosage form and place them below the proprietary name; consider using two lines if space is limited. Place the statement of strength below the established name and dosage form (see Example 1).

Example 1:

Proprietary Name
Established Name & Dosage Form
Strength

2. The location of the lot number and expiration date is not indicated on the labels. Indicate the location of the lot number and expiration date in accordance with 21 CFR 201.10(i)(l).

B. Carton Labeling

1. The Medication Guide (MG) statement is on a side panel and lacks prominence in that location. Revise and relocate the MG statement to the principal display panel (PDP) in accordance with 21 CFR 208.24(d). For example: "Dispense the enclosed Medication Guide to patient."

2. The equivalency statement is distracting from the critical information on the PDP. Relocate the equivalency statement so that it does not interfere with the proprietary name, established name and strength statement on the PDP (e.g., to the side panel of the carton labeling).

3. The net quantity statement is incomplete. Revise the statement to read (or use similar verbiage): "30 tablets (5 x 6-count blister card)".

4. The proprietary name and strength are on a side panel. However, the established name and dosage form are not. Place the established name and dosage form below the proprietary name.

5. The carton labeling lacks a usual dosage statement. Add a usual dosage statement to the carton labeling in accordance with 21 CFR 201.55.

6. The carton will contain a travel case; however, this is not indicated on the PDP of the carton labeling. Add a statement to the PDP that indicates the carton contains a travel case.
7. Add the following statement to the PDP: "Do not chew or crush tablets."

Please make the recommended Blister & Carton labeling changes and resubmit, as soon as possible. The resubmitted labeling will be used for further labeling discussions.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA

CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
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KOFI B ANSAH
11/18/2015

From: [Ansah, Kofi](#)
To: [Dorothy Engelking \(DEngelking@NEOSTx.com\)](mailto:DEngelking@NEOSTx.com)
Subject: Initial FDA Labeling Edits/Comments -- NDA 204326/Amphetamine Extended-Release - ODT
Date: Tuesday, November 10, 2015 1:46:34 PM
Attachments: [11-10-15 FDA edits Sponsor's draft Label Amphetamine XR-ODT \(v. 07-27-15\)\[MARKED-UP\].docx](#)
[11-10-15 FDA edits Sponsor's draft Label Amphetamine XR-ODT \(v. 07-27-15\)\[MARKED-UP\].pdf](#)
Importance: High

Dear Dorothy,

Find attached your draft Label (as proposed on 7/27/15) with our initial round of edits and comments. Please review our edits and comments and resubmit labeling that addresses our comments.

Please be sure to work off (i.e., use) the word document we are sending you and track any edits/counter-proposal(s) you may have at this point (include your own comments as necessary).

Provide the requested labeling changes/information to me via email as soon as possible but no later than Monday, 11/16/15. The resubmitted labeling will be used for further labeling discussions.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA

CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

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KOFI B ANSAH
11/10/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204326

**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) Class 2 Resubmission dated and received July 27, 2015 submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Amphetamine Extended Release Orally Disintegrating Tablets, (b) (4)
(b) (4)

We also refer to your correspondence, dated and received August 5, 2015, requesting review of your proposed proprietary name, Adzenys XR-ODT.

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

If any of the proposed product characteristics as stated in your August 5, 2015, submission 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 Kofi Ansah, Regulatory Project Manager in the Office of New Drugs, at 301-796-4158.

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

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/s/

TODD D BRIDGES
11/02/2015

From: [Ansah, Kofi](#)
To: [Dorothy Engelking \(DEngelking@NEOSTx.com\)](mailto:Dorothy.Engelking@NEOSTx.com)
Subject: Clinical Pharmacology Information Request-2 -- NDA 204326/Amphetamine Extended-Release - ODT
Date: Tuesday, October 06, 2015 2:42:51 PM

Dear Dorothy,

Regarding your NDA 204326 resubmission, currently under review, we have the following additional Clinical Pharmacology information request; as noted below.

Please provide the following information (in a precise table format) for the validated bioanalytical method used for all analytes:

- Method summary
- Analytes
- Internal Std.
- Method description
- Limits of quantitation (ng/mL)
- Average recovery of drug (% mean)
- Standard curve concentrations (ng/mL)
- LLOQ concentration
- LLOQ intra-batch precision (%CV)
- LLOQ inter-batch precision (%CV)
- LLOQ intra-batch accuracy (%bias)
- LLOQ inter-batch accuracy (%bias)
- QC intra and inter batch accuracy and precision
- Bench top stability
- Stock stability
- Freeze thaw stability
- Long term storage stability
- Assay specificity
- Any/all OTHER parameters that are relevant

Please provide the requested data within a week (i.e., by October 13, 2015).

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA, RAC

CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: Kofi.Ansah@fda.hhs.gov

Commissioned Corps of the United States Public Health Service- "Protecting, promoting, and advancing the health and safety of the Nation"

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APPEARS THIS WAY ON ORIGINAL

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KOFI B ANSAH
10/06/2015

From: [Ansah, Kofi](#)
To: [Dorothy.Engelking \(DEngelking@NEOSTx.com\)](mailto:Dorothy.Engelking@NEOSTx.com)
Subject: Clinical Pharmacology Information Request -- NDA 204326/Amphetamine Polistrex Extended-Release - ODT
Date: Friday, September 04, 2015 8:52:25 PM
Importance: High

Dear Dorothy,

Regarding your NDA 204326 resubmission, currently under review, we have the following Clinical Pharmacology information request; as noted below.

Study# NT0102.1005 (BE and Food Effect Study): Please provide the following individual subject data :

- Table (for food-effect) with the ratios (fed/fasted) of all PK parameters applied for BE testing (e.g., pAUC0-5, pAUC5-T, Cmax, AUC0-t, AUC0-inf) for each individual.
- Table (for food-effect) with the number and percentage of the subjects with calculated ratios that meet the indicated indications (>200%, >125%, < 80%, <50%) for all PK parameters above.
- Scatter plots (for food-effect) of the individual ratios and the geometric least square mean ratio for all PK parameters above. Reference lines drawn at 200%, 125%, 85% and 50%.

– Please provide the requested data within a week (i.e., by September 12, 2015).

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA, RAC

CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

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Email: Kofi.Ansah@fda.hhs.gov

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/s/

KOFI B ANSAH
09/04/2015

Flowers, Louis

From: Flowers, Louis
Sent: Tuesday, August 18, 2015 1:27 PM
To: Dorothy Engelking
Cc: Jenkins, Darrell; Ayalasomayajula, Vasantha
Subject: RE: Proprietary Name Submission

Good afternoon Dorothy,

Proprietary names that include brand name extensions are evaluated on a case-by-case basis. Each request for review of a proposed proprietary brand name extension will be evaluated to consider whether:

- Products share at least one common active ingredient
- Products are differentiated by labeling (carton and container)
- Modifiers used are appropriate and effectively differentiate the product among members of the same product line

In some cases, brand name extensions have posed problems when the same root proprietary name is used for multiple products without modifiers that adequately differentiate among the products. Depending on your unique product and product characteristics, there may be additional considerations.

We recommend you consider this information when evaluating the appropriateness of your proprietary name and include the rationale for your proposed name along with any supporting data you deem appropriate when you submit your Proprietary Name Request.

Louis R. Flowers III, PharmD, MS, CPH
Captain - USPHS
Team Leader, Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
BLDG 22, Room 4476
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3158
Email: louis.flowers@fda.hhs.gov

From: Flowers, Louis
Sent: Friday, August 14, 2015 11:53 AM
To: 'Dorothy Engelking'
Subject: RE: Proprietary Name Submission

Good morning Dorothy,

DMEPA acknowledges receipt of your email. DMEPA will provide a response to you ASAP.

Thanks,

Louis R. Flowers III, PharmD, MS, CPH
Captain - USPHS
Team Leader, Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
BLDG 22, Room 4476
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3158
Email: louis.flowers@fda.hhs.gov

From: Dorothy Engelking [<mailto:DEngelking@NEOStx.com>]
Sent: Thursday, August 06, 2015 4:47 PM
To: Flowers, Louis
Subject: Proprietary Name Submission

Dear Louis,

I would like to ask for your advice, since you have worked on our previous proprietary name review for our amphetamine XR-ODT product. Neos recently submitted a new proprietary name request for our amphetamine XR-ODT product (Adzenys XR-ODT) and we also have an (b) (4), for which we will be filing an NDA later this year. We would like to (b) (4). What is the view of DMEPA on a family of drug products with the same trade name?

I would appreciate any insight you have on this or if someone else could help answer my question, I would appreciate that information as well.

I look forward to hearing from you.

Best Regards,
Dorothy

Dorothy J. Engelking
VP Regulatory Affairs



2940 N. HWY 360, Suite 400
Grand Prairie, TX 75050
Office: 972-408-1312
Mobile: (b) (6)
Fax: 972-408-1143
dengelking@neostx.com

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/s/

LOUIS R FLOWERS
08/20/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204326

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

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

Dear Ms. Engelking:

We acknowledge receipt on July 27, 2015, of your resubmission to your supplemental new drug application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Amphetamine (b) (4) Extended-Release Orally Disintegrating Tablets (b) (4), (b) (4).

We consider this a complete, class 2 response to our September 24, 2013 action letter. Therefore, the user fee goal date is January 27, 2016.

If you have any questions, please contact CDR Kofi Ansah, at either Kofi.Ansah@fda.hhs.gov or at (301) 796-4158.

Sincerely,

{See appended electronic signature page}

CDR Renmeet Grewal, Pharm.D., RAC
Team Leader/ Senior Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

RENMEET GREWAL
08/10/2015

From: Ansah, Kofi
To: ["Dorothy Engelking"](#)
Subject: FDA/OCF Response -- RE: NDA 204326 - Request for Advice/Clin Pharm Info (SN0013)
Date: Tuesday, March 24, 2015 7:39:00 PM

Dear Dorothy,

We acknowledge receipt of the information you submitted on February 25, 2015. On face, we agree that an in vivo drug-alcohol interaction study is not a requirement.

Thanks,
Kofi.

From: Dorothy Engelking [<mailto:DEngelking@NEOStx.com>]
Sent: Wednesday, February 25, 2015 6:03 PM
To: Ansah, Kofi
Subject: NDA 204326 - Request for Advice

Dear Kofi,

Today, Neos submitted a document that outlines our data with respect to the revised formulation amphetamine XR-ODT and drug-alcohol interactions. This was a topic of discussion at the Type-A meeting held in November of 2013. We are requesting that the Division review this information and respond to our request that a human drug-alcohol interaction study will not be required for the re-submission of the NDA.

If you have any questions, please feel free to contact me. I'll follow up to see what time frame we could expect a response once your team has a chance to see the submission.

Best Regards,
Dorothy

Dorothy J. Engelking
VP Regulatory Affairs



2940 N. HWY 360, Suite 400
Grand Prairie, TX 75050
Office: 972-408-1312
Mobile: (b) (6)
Fax: 972-408-1143
dengelking@neostx.com

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/s/

KOFI B ANSAH
03/24/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 112991
NDA 204326

MEETING MINUTES

Neos Therapeutics, Inc.
Attention: Dorothy Engelking, M.S., RAC
Vice President, Regulatory Affairs
2940 N. Highway 360, Suite 400
Grand Prairie, TX 75050

Dear Ms. Engelking:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) and your New Drug Application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amphetamine (b) (4) Extended-Release Orally Disintegrating Tablet.

We also refer to the meeting between representatives of your firm and the FDA on October 2, 2014. The purpose of the meeting was to discuss the results of the bioequivalence trial comparing the (b) (4) manufactured amphetamine XR-ODT to the Reference Listed Drug (Adderall XR®).

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, contact CDR Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@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

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance Meeting

Meeting Date and Time: October 2, 2014; 11:00 am – 12:00 pm EDT
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: IND 112991 and NDA 204326
Product Name: Amphetamine (b) (4) Extended-Release Orally Disintegrating Tablets
Indication: Attention Deficit Hyperactivity Disorder (ADHD)
Sponsor/Applicant Name: Neos Therapeutics, Inc.

Meeting Chair: Mitchell V. Mathis, M.D.

FDA Attendees/Participants:

Mitchell Mathis, M.D.	Director, Division of Psychiatry Products (DPP)
Tiffany Farchione, M.D.	Deputy Director (acting), DPP
Mark Ritter, M.D.	Medical Team Leader (acting), DPP
Cara Alfaro, Pharm.D.	Clinical Reviewer, DPP
Hao Zhu, Ph.D.	Clinical Pharmacology, Team Leader
Praveen Balimane, Ph.D.	Clinical Pharmacology Reviewer
David Claffey, Ph.D.	CMC Lead, Office of New Drugs QA (ONDQA)
Okpo Eradiri, Ph.D.	Biopharmaceutics Reviewer, ONDQA/OPS
Kofi Ansah, Pharm.D.	Senior Regulatory Project Manager, DPP

Neos Therapeutics, Inc.'s Attendees:

Name	Title and Affiliation
Vipin Garg, Ph.D.	President & Chief Executive Officer, Neos Therapeutics, Inc.
Dorothy Engelking	Vice President, Regulatory Affairs, Neos Therapeutics, Inc.
Carolyn Sikes, Ph.D.	Vice President, Clinical Development, Neos Therapeutics, Inc.
Mark Tengler	Chief Technical Officer, Neos Therapeutics, Inc.
Russ McMahan	Vice President, Research & Development, Neos Therapeutics, Inc.
(b) (4)	(b) (4)

Meeting Minutes

Page 2

1.0 BACKGROUND

Neos Therapeutics submitted a 505(b)(2) NDA application (NDA 204326) on December 28, 2012 for an amphetamine extended release orally disintegrating tablet (amphetamine XR-ODT) for the treatment of Attention Deficit Hyperactivity Disorder. This 505(b)(2) application references ADDERALL XR as the reference listed drug (RLD).

During review of the application, the Division raised questions about physical test data that was submitted with respect to hardness, disintegration and (b) (4) and the fact that the excipient (b) (4) had changed and the product had been reformulated with the new excipient. The Division sent a Discipline Review letter on May 29, 2013 that outlined the deficiencies noted in the application. While many of the deficiencies were adequately addressed by Neos Therapeutics, a number of deficiencies were not and the Division subsequently issued a Complete Response on September 24, 2013. A Type-A meeting was held on November 21, 2013 and Neos Therapeutics agreed to make additional batches (b) (4), gain new registration batch stability on multiple product strengths, and conduct a new bioequivalent (BE) study of the (b) (4) product compared to ADDERALL XR, the RLD.

In response to the CR letter, Neos Therapeutics conducted a BE study with this new formulation of the amphetamine XR-ODT dosage form. The BE study (Protocol NT020.1005) was a single-dose, three-way crossover study of amphetamine XR-ODT (equivalent to 30 mg mixed amphetamine salts) under fed and fasted conditions and Adderall XR 30 mg capsule under fasted conditions conducted in 42 healthy adult subjects. Neos Therapeutics also submitted summary data comparing the pharmacokinetic parameters of the amphetamine XR-ODT produced at the (b) (4) to that produced at the (b) (4).

The purpose of this meeting is to review and discuss the results of the BE study conducted with Neos (b) (4) amphetamine XR-ODT compared to ADDERALL XR.

2. DISCUSSION (Questions from the Sponsor and FDA Responses)

Following are Neos' specific questions and FDA/DPP's responses/ preliminary comments.

2.1. Bioequivalence/Clinical Questions

Question 1: Based on the arguments presented below that 1) the BE trial demonstrated a matched pharmacokinetic profile to the RLD; 2) the (b) (4) product exhibited a nearly identical pharmacokinetic profile to the (b) (4) product; and 3) the pharmacokinetic profile of the amphetamine XR-ODT under fed and fasted conditions lies between that of ADDERALL XR under fed and fasted conditions, Neos believes that the rate and extent of absorption of amphetamine XR-ODT produced with the (b) (4) process exhibits a pharmacokinetic profile that would support a resubmission of the 505(b)(2) NDA that is based on the previous findings of safety and efficacy for ADDERALL XR. **Does the Agency concur?**

Meeting Minutes

Page 3

Preliminary Comments: You may resubmit your NDA. However, whether your amphetamine XR-ODT is considered bioequivalent to ADDERALL XR, the RLD, will be a review issue. We noted that the lower bound of the 90% confidence interval of pAUC0-5 is lower than 80%. You should provide strong rationale to justify why efficacy and safety profiles of your formulation are expected to be similar to ADDERALL XR. In addition to comparing the pharmacokinetic profile difference following the administration of ADDERALL XR under fast or fed conditions, you may consider using PK/PD modeling and simulation, and any other additional supportive analysis.

If you plan to submit your NDA, in your study report, please provide ratios of all PK parameters applied for BE testing (e.g., pAUC0-5, pAUC5-t, Cmax, AUC0-t, AUC0-inf) between the test and reference products for each individual. You should plot the ratios in figures by using scatter plots and provide the calculated data in tabular format. In addition, please provide the percentage of the subjects with calculated ratios greater than 125%, 200%, or less than 80%, 50%, stratified by each PK parameters for BE testing.

Discussion at Meeting: The agency reiterated that the current bioequivalence study does not represent a filing issue. However, the determination of bioequivalence between amphetamine XR-ODT and ADDERALL XR will be a review issue. To support the bioequivalence claim, the sponsor is advised to provide a comprehensive information package rationalizing the efficacy and safety similarity of their product to ADDERALL XR. In addition to including PK/PD modeling strategies, individual subject PK parameter comparison, and efforts to obtain intra-subject variability of ADDERALL XR data, they were requested to consider including any/all other supportive data/information. If the sponsor intends to use PK/PD modeling, it is advised to provide sufficient information on model validation.

2.2. Quality/Chemistry, Manufacturing, and Controls (CMC) Questions

Question 2: Amphetamine XR-ODT produced at the proposed (b) (4) performs nearly identical to the (b) (4) clinical batch that was used to demonstrate bioequivalence to ADDERALL XR. Neos believes that the recently completed bioequivalence trial demonstrates that the formulation change and the aggregate minor changes had little to no impact on the bioavailability or the performance of the drug product and that the Agency's concerns with scaling the process have been adequately addressed. **Does the Agency concur?**

Preliminary Comments: On face, your bridging approach seems adequate. However, the acceptability of the results of the cross-study comparison is a review issue under the NDA.

Discussion at Meeting: No further discussion.

3.0 OTHER IMPORTANT MEETING LANGUAGE SECTIONS:**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>.

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 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.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

MANUFACTURING FACILITIES

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

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

Meeting Minutes

Page 6

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

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

If you intend to submit a 505(b)(2) application that relies for approval, in part, 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.

Meeting Minutes

Page 7

If you intend to rely, in part, 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, in part, 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 (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor’s Table of Ratios (Test/Reference) and Scatter Plot for all PK Parameters.

Table 1: Ratios (Test/Reference) for all PK parameters applied for BE testing.

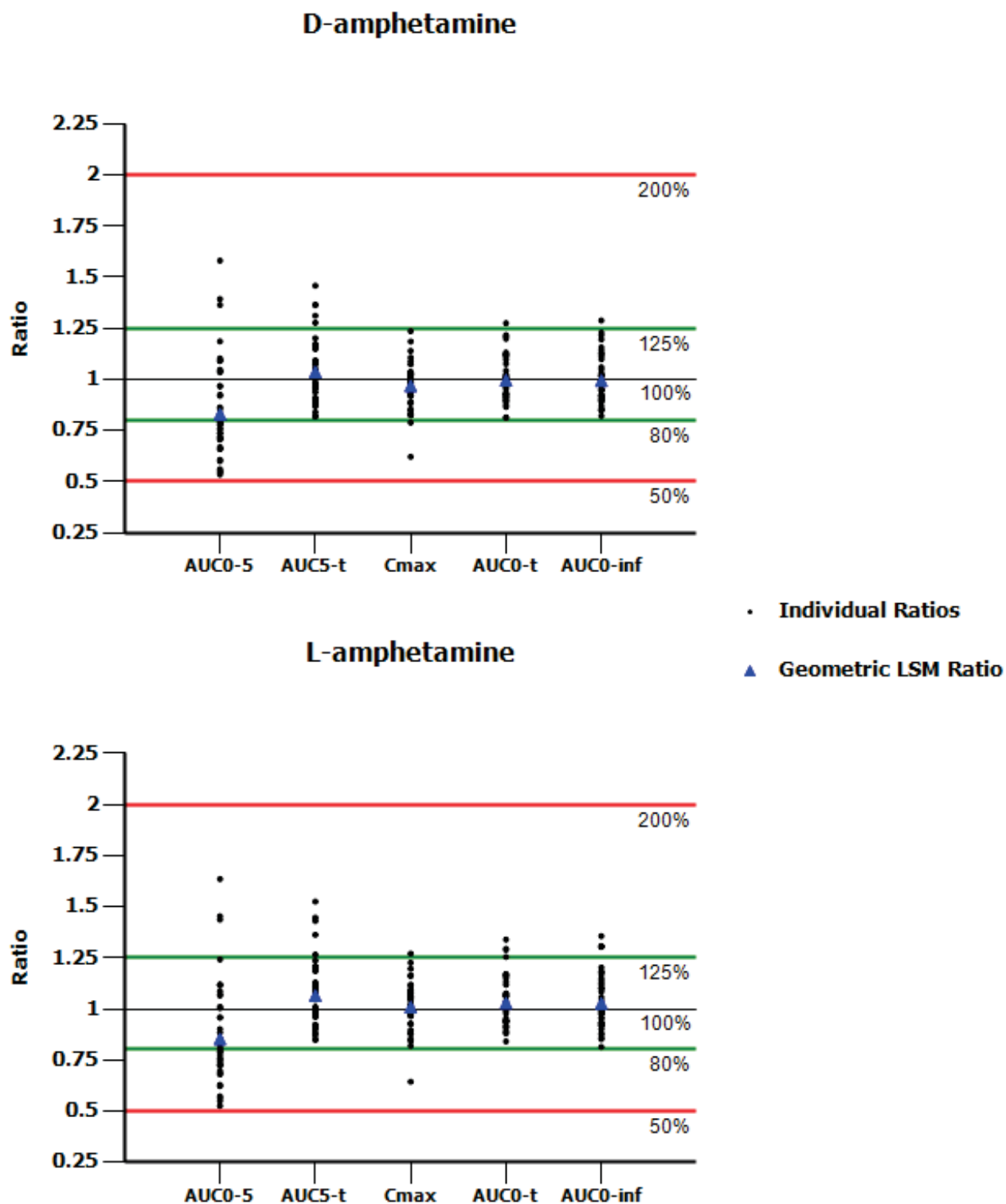
Analyte	Subject	AUC ₀₋₅	AUC _{5-t}	C _{max}	AUC _{0-t}	AUC _{0-inf}
D-amphetamine	101	0.97	1.17	1.07	1.13	1.13
	102	0.74	1.31	1.02	1.20	1.23
	103	1.04	0.96	1.02	0.98	0.97
	104	0.56	1.03	0.98	0.92	0.91
	105	0.66	1.28	1.01	1.10	1.05
	106	1.19	0.98	1.02	1.01	1.02
	108	1.09	0.96	0.83	0.98	0.98
	109	0.72	0.91	0.99	0.87	0.85
	110	1.10	0.91	0.99	0.93	0.93
	111	0.53	1.08	0.83	1.01	0.99
	112	0.76	1.46	0.92	1.28	1.29
	113	0.74	0.94	0.94	0.91	0.92
	114	0.67	1.03	1.03	0.97	0.97
	115	0.83	1.17	0.96	1.12	1.14
	116	1.39	0.82	0.88	0.90	0.90
	117	0.82	0.98	0.85	0.95	0.95
	118	1.05	0.90	1.00	0.93	0.92
	119	0.55	1.09	0.62	0.97	0.97
	120	1.36	0.87	0.99	0.91	0.90
	121	0.76	0.90	0.89	0.88	0.87
	122	0.78	0.82	0.79	0.81	0.82
	123	0.78	1.20	1.02	1.13	1.16
	124	0.85	0.90	1.03	0.89	0.89
	125	1.58	0.84	1.03	0.92	0.91
	126	0.92	1.16	1.19	1.12	1.11
	127	0.86	1.07	0.92	1.02	1.02
	128	0.66	1.15	1.03	1.08	1.10
	130	0.97	1.16	1.03	1.11	1.12
	131	0.92	1.05	0.97	1.02	1.03
	132	1.09	0.88	0.96	0.90	0.85
	133	0.79	0.96	1.01	0.93	0.92
	134	0.71	1.07	0.82	1.01	1.02
	135	0.61	0.88	1.04	0.81	0.85
	137	1.04	0.96	1.11	0.96	0.95
	138	0.60	1.37	1.14	1.21	1.22
	139	0.79	1.09	0.92	1.01	1.02
	140	0.55	1.36	1.09	1.22	1.20
	141	0.71	1.05	0.85	0.97	0.95
	142	0.71	1.09	1.24	1.04	1.06

Analyte	Subject	AUC ₀₋₅	AUC _{5-t}	C _{max}	AUC _{0-t}	AUC _{0-inf}
L-amphetamine	101	1.01	1.21	1.16	1.17	1.17
	102	0.75	1.36	1.05	1.25	1.31
	103	1.07	0.98	1.02	1.00	0.99
	104	0.57	0.99	1.01	0.91	0.88
	105	0.68	1.27	1.11	1.12	1.13
	106	1.24	1.04	1.04	1.06	1.10
	108	1.12	0.98	0.84	0.99	0.99
	109	0.73	0.92	1.01	0.88	0.86
	110	1.12	0.92	1.01	0.94	0.93
	111	0.53	1.07	0.85	1.01	0.98
	112	0.77	1.53	0.97	1.34	1.36
	113	0.76	0.97	0.97	0.94	0.95
	114	0.70	1.05	1.08	1.00	1.00
	115	0.86	1.21	1.02	1.16	1.18
	116	1.45	0.85	0.90	0.93	0.93
	117	0.85	1.01	0.93	0.98	0.98
	118	1.09	0.91	1.06	0.94	0.93
	119	0.56	1.12	0.64	1.01	1.00
	120	1.44	0.90	1.01	0.94	0.92
	121	0.79	0.90	0.93	0.88	0.87
	122	0.80	0.85	0.82	0.84	0.85
	123	0.79	1.24	1.06	1.17	1.20
	124	0.88	0.92	1.09	0.92	0.92
	125	1.64	0.88	1.05	0.95	0.93
	126	0.96	1.19	1.23	1.15	1.14
	127	0.90	1.11	0.99	1.06	1.06
	128	0.68	1.20	1.08	1.13	1.15
	130	1.00	1.20	1.05	1.16	1.18
	131	0.96	1.10	1.01	1.07	1.08
	132	1.12	0.88	0.98	0.89	0.81
	133	0.82	0.96	1.06	0.94	0.92
	134	0.74	1.13	0.88	1.07	1.11
	135	0.63	1.00	1.08	0.91	0.90
	137	1.07	0.99	1.12	1.00	0.96
	138	0.62	1.45	1.20	1.29	1.30
	139	0.80	1.11	0.97	1.04	1.04
	140	0.55	1.43	1.17	1.29	1.30
	141	0.73	1.08	0.88	1.01	0.98
	142	0.72	1.12	1.27	1.08	1.10

Table 2: Number and Percentage of Subjects with calculated ratios that meet the indicated conditions (>200%, >125%, <80%, <50%) for all PK parameters applied for BE testing.

Analyte	Conditions	AUC ₀₋₅	AUC _{5-t}	C _{max}	AUC _{0-t}	AUC _{0-inf}
D-amphetamine (N=39)	>200%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	>125%	3 (8%)	5 (13%)	0 (0%)	1 (3%)	1 (3%)
	<80%	21 (54%)	0 (0%)	2 (5%)	0 (0%)	0 (0%)
	<50%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
L-amphetamine (N=39)	>200%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	>125%	3 (8%)	5 (13%)	1 (3%)	4 (10%)	4 (10%)
	<80%	18 (46%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
	<50%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Figure 1: Scatter plot of individual ratios and geometric least square mean ratio for all PK parameters applied for BE testing. Reference lines drawn at 200%, 125%, 100%, 80%, and 50%.



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/s/

MITCHELL V Mathis
10/03/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204326

MEETING MINUTES

Neos Therapeutics, Inc.

Attention: Dorothy Engelking, M.S., RAC
Vice President, Regulatory Affairs
2940 N. Highway 360, Suite 400
Grand Prairie, TX 75050

Dear Ms. Engelking:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Amphetamine (b) (4) Extended-Release Orally Disintegrating Tablets (b) (4).

We also refer to the meeting between representatives of your firm and the FDA on November 21, 2013. The purpose of the meeting was to discuss your planned responses to the deficiencies listed in the Division's Complete Response letter dated September 24, 2013.

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, contact CDR Kofi Ansah, Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT USPHS
Director (acting)
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
Meeting Category: Guidance

Meeting Date and Time: November 21, 2013
Meeting Location: 2:00 pm – 3:00 pm EDT
Application Number: NDA 204326
Product Name: Amphetamine (b) (4) Extended-Release Orally Disintegrating Tablets (b) (4)
(b) (4)

Indication: Attention Deficit Hyperactivity Disorder (ADHD)
Sponsor/Applicant Name: Neos Therapeutics, Inc.

FDA Attendees/Participants:

Mitchell Mathis, M.D.	Director (acting), Division of Psych Products (DPP)
Ni Khin, M.D.	Medical Team Leader, DPP
Linda Fossom, Ph.D.	Pharmacology/Toxicology Supervisor, DPP
Olen Stephens, Ph.D.	Branch Chief, DNQAI/BRI/Office of New Drugs QA
David Claffey, Ph.D.	CMC Reviewer, Office of New Drugs QA (ONDQA)
Mahesh Ramanadham, Pharm.D	Team Leader (acting), CDER/OC/OMPQ/DGMP/NDMAB
Kavitas Vyas, Ph.D.	Chemist, OPS/ONDQA/DNDQAI/BRIII
Okpo Eradiri, Ph.D.	Biopharmaceutics Reviewer, OPS/ONDQA
Hao Zhu, Ph.D.	Clinical Pharmacology, Team Leader
Praveen Balimane, Ph.D.	Clinical Pharmacology Reviewer
Irene Chan, Pharm.D., BCPS	Team Leader, Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology (DMEPA/OSE)
Loretta Holmes, Pharm.D.	Safety Evaluator, DMEPA/OSE
Kofi Ansah, Pharm.D.	Senior Regulatory Project Manager, DPP

Neos Therapeutics, Inc.'s Attendees:

Meeting Minutes

Name	Title	Affiliation
Vipin Garg, Ph.D.	CEO	Neos Therapeutics
Mark Tengler, B.S.	Co-President and Chief Technical Officer	Neos Therapeutics
Carolyn Sikes, Ph.D.	VP Clinical	Neos Therapeutics
Dorothy Engelking, RAC	VP, Regulatory Affairs	Neos Therapeutics
(b) (4)		

1.0 BACKGROUND

Neos Therapeutics has requested this meeting (November 1, 2013) to gain concurrence with the Division regarding their planned response to the Division's Complete Response letter dated September 24, 2013. The said letter was issued in response to the sponsor's 505(b)(2) application for Amphetamine (b) (4) Extended-Release Orally Disintegrating Tablets for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). This 505(b)(2) application referenced NDA 21-303 Adderall XR® capsules extended-release mixed amphetamine salts.

The sponsor will manufacture proposed commercial process registration batches that encompass the (b) (4)

The sponsor has proposed one bioequivalence (BE) study to be conducted with this new formulation of the amphetamine (b) (4) extended-release ODT dosage form. The proposed BE study will be a single-dose, three-way crossover study of amphetamine extended-release ODT (equivalent to 30 mg mixed amphetamine salts) under fed and fasted conditions and Adderall XR 30 mg capsule under fasted conditions conducted in 42 healthy adult subjects.

2. DISCUSSION (Questions from the Sponsor and FDA Responses)

Following are Neos Therapeutics, Inc.'s specific questions and FDA/DPP's responses/ preliminary comments.

2.1. Office of New Drug Quality Assessment - CMC/Product Quality

Meeting Minutes

Question 1: The performance of the amphetamine XR ODT product produced using the proposed commercial manufacturing process as described above will be assessed in a BA/BE study; therefore, Neos believes that the review of the proposed manufacturing process will be supported by release and stability results and that the suitability of the final product will be supported by the pharmacokinetic data in comparison to the RLD. **Does the Agency concur?**

Preliminary Comments: *The suitability of the product and proposed manufacturing process will be reviewed in light of the overall control strategy, which includes release and stability data in addition to in-process controls that reflect an understanding of the critical quality attributes for the drug product and critical quality process parameters for the manufacturing process. The determination will also include an evaluation of all facilities' ability to manufacture product in conformance with current good manufacturing practices. The data mentioned in your question may support, but will not comprise, the totality of the review. Your understanding of the root causes of the failures observed in the registration batches and the steps taken to ensure that these issues have been resolved will also be part of our evaluation.*

Discussion at Meeting: *No further discussion.*

Question 2: Does the agency have any specific recommendations on setting an appropriate (b) (4) specification for an ODT product based on its prior experience?

Preliminary Comments: *It is not uncommon for an ODT product to adhere to the*

(b) (4)

(b) (4)

Discussion at Meeting: *The sponsor stated that they had identified the root cause of the*

(b) (4)

Meeting Minutes

The sponsor stated that the (b) (4)
(b) (4)

The sponsor asked whether (b) (4)
Agency responded that (b) (4)
(b) (4)

Post-Meeting Comment: *To support the proposed root cause - provide data* (b) (4)
(b) (4)

Question 3: Does the agency agree with the proposed (b) (4) to the stability program?

Preliminary Comments: *The proposed reduced testing approach appears acceptable.*

Discussion at Meeting: *No further discussion.*

Question 4: Would the Agency accept a complete response, within a 12 month time frame from the Complete Response Letter, which includes 6 months of LT and 6 months of ACC stability data on the 12 lots in the (b) (4) program? Additional stability data updates providing one year stability evidence will be provided in a timely manner during the review period.

Preliminary Comments: *Considering the failures observed in the original set of drug product stability data and the limited six month review time, it is expected that long-term testing should cover a minimum of 12 month's duration at time of submission (as per ICH Q1A(R2)). Note that 21 CFR 314.110 (c) allows the Agency to grant any reasonable request for an extension of the review period beyond the 12 months stated in the CR letter.*

Discussion at Meeting: *No further discussion.*

2.2. **Clinical Pharmacology**

Meeting Minutes

Question 5: Does the proposed single, three-arm BA/BE study design appear adequate to assess the oral bioavailability/bioequivalence of the proposed commercial process amphetamine XR ODT?

Preliminary Comments: *The proposed study design is acceptable.*

Provide justification for biowaiver of the lower strengths if no additional bioavailability/bioequivalence studies are planned. Note that the submission of BA/BE information for lower strength (s) of your proposed product may be waived if the following CFR requirements are met:

- a) Inclusion of the biowaiver request as part of the NDA submission;*
- b) There is BA/BE data for the highest strength;*
- c) The lower strength (s) and higher strength product have the same dosage form;*
- d) The lower strength (s) product is (b) (4) in its active and inactive ingredients to the highest strength product;*
- e) The lower and highest strength products have the same drug release mechanism; and*
- f) Dissolution profile comparisons between the highest and lower strengths in three different media meet the f2 similarity requirements.*

Because this is an extended release formulation, in vitro assessment for alcohol dose dumping is required. Please see "Additional Biopharmaceutics Comments" below.

Discussion at Meeting: *No further discussion.*

Additional Biopharmaceutics Comments

Due to the changes to the extended release formulation that requires a new bioequivalence trial, repeat the in-vitro alcohol dose-dumping experiments conducted on the original proposed product. If a similar alcohol interaction is observed, you may need to conduct an in-vivo study with the new proposed product, as you did with the original formulation, for labeling purposes.

Discussion at Meeting: *The Sponsor asked for clarification on the labeling issues associated with alcohol-induced dose dumping.* (b) (4)
(b) (4)

Meeting Minutes

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

None

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/s/

MITCHELL V Mathis
12/06/2013

MEMORANDUM of TELECONFERENCE

MEETING DATE: 10 September 2013

TIME: 10:30 AM

LOCATION: FDA White Oak Campus, Bldg 22, Rm 4476

APPLICATION: NDA 204326

DRUG NAME: (b) (4) XR-ODT (Amphetamine (b) (4) Extended Release Orally Disintegrating Tablets)

TYPE OF MEETING: Proprietary Name Review Teleconference (b) (4) XR-ODT)

MEETING CHAIRS: Irene Z. Chan, Team Leader, DMEPA
Louis Flowers, OSE SRPM

FDA ATTENDEES: Loretta Holmes, Safety Evaluator, DMEPA

SPONSOR ATTENDEES:
Dorothy Engelking, VP Regulatory Affairs
Damon Daulerio, Director Regulatory Affairs
Ellen Hoffing, Co-President and COO
Mark Tengler, Co-President and CTO

BACKGROUND:

NEOS Therapeutics submitted the proposed proprietary name “(b) (4) XR-ODT” on June 28, 2013.

MEETING OBJECTIVES:

The purpose of the call was to let Sponsor know that DMEPA has conducted a preliminary review of the proposed proprietary name and has identified a concern.

DMEPA CONCERNS WITH THE PROPOSED NAME

- We called this meeting because we want to work with you to identify an appropriate name prior to your application PDUFA goal date of October 28, 2013.
- A Discipline Review (DR) letter was issued to you on May 29, 2013. In that letter, the Agency expressed concerns regarding the product not meeting the criteria for an “orally disintegrating tablet” dosage form.
- It would be misleading to include the ODT modifier within the proprietary name. Therefore, at this time, we find the proposed name, (b) (4) XR-ODT unacceptable on the basis of the proposed modifier, XR-ODT.

REGULATORY OPTIONS

1. Withdraw the proposed proprietary name, (b) (4) XR-ODT, at this time

2. Wait for DMEPA to issue a denial letter by the OSE PDUFA goal date, September 26, 2013

DISCUSSION:

The Applicant indicated that they plan to submit new data to support the proposed orally disintegrating tablet dosage form designation. The Applicant asked if DMEPA had any concern with the root name, (b) (4), without the proposed modifier, XR-ODT. DMEPA indicated that preliminary review of the root name did not identify any concerns, but a full evaluation would have to be conducted when they resubmit the name and the results are subject to change. The Applicant asked whether they can submit the proposed proprietary name, (b) (4), for the time being until they submit the new data supporting the ODT dosage form. DMEPA indicated that they can submit a new proprietary name to the application after they withdraw (b) (4) XR-ODT; however, DMEPA indicated that they do not hold proprietary names, and DMEPA was unclear what benefit the Applicant believed this would impart given that their intention is to ultimately seek approval of a name containing a modifier that reflects both the extended-release and orally disintegrating properties of the product. The Applicant asked if they could resubmit (b) (4) XR-ODT in the future with new supporting data if they chose to withdraw the proprietary name now. DMEPA responded yes.

ACTION ITEMS

1. NEOS Therapeutics will consider withdrawing the proposed proprietary name (b) (4) XR-ODT at this time. NEOS Therapeutics will let the OSE SRPM know their decision regarding withdrawal of the proposed proprietary name, (b) (4) XR-ODT, by Friday, September 13, 2013.
2. In the future, the Applicant may resubmit a Request for Proprietary Name Review when they have sufficient data to meet the criteria for an “orally disintegrating tablet” dosage form.

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/s/

LOUIS R FLOWERS
09/11/2013

Bouie, Teshara

From: Bouie, Teshara
Sent: Tuesday, July 09, 2013 4:30 PM
To: 'Dorothy Engelking'
Cc: Ansah, Kofi
Subject: RE: NDA 204326 ONDQA Discipline Review Letter - Request for Telephone Conference

Hi Dorothy,

Please see the FDA responses to your questions below. We request a response to this Discipline Review letter by August 1, 2013.

If further clarification is needed, we are open to having a tcon to discuss.

Regards,

Teshara G. Bouie

From: Dorothy Engelking [mailto:DEngelking@NEOStx.com]
Sent: Thursday, June 27, 2013 5:04 PM
To: Bouie, Teshara
Subject: NDA 204326 ONDQA Discipline Review Letter - Request for Telephone Conference

Dear Teshara,

Thank you for accepting these topics for clarification with the ONDQA Reviewers. We have the following topics to discuss with respect to the May 29, 2013 Discipline Review Letter. Neos would like to understand the reviewer's concerns and gain clarity around the perceived issues with our products with a discussion of the four topics below.

(b) (4) (Questions 1 & 6(e))

(b) (4)

FDA Response:

(b) (4)

(b) (4)

(b) (4) (Questions 2 & 5)

Neos reported data in the stability section for

(b) (4)

(b) (4)

(b) (4)

FDA Response: We consider it critical that

(b) (4)

(b) (4)

Disintegration Time (Questions 2 & 3)

(b) (4)

FDA Response:

(b) (4)

(b) (4)

(b) (4)

(Questions 21 & 23a)

(b) (4)

FDA response:

(b) (4)

(b) (4)

Please let me know any available times that we could have a telephone discussion with the reviewers. Your time is much appreciated.

Best Regards,
Dorothy

Dorothy Frank-Engelking
VP Regulatory Affairs



2940 N. HWY 360, Suite 400
Grand Prairie, TX 75050
Office: 972-408-1312
Mobile: (b) (6)
Fax: 972-408-1143
dengelking@neostx.com

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/s/

TESHARA G BOUIE
07/09/2013



NDA 204326

DISCIPLINE REVIEW LETTER

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 December 27, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amphetamine (b) (4) Extended Release Orally Disintegrating Tablets.

We also refer to your amendment dated April 19, 2013.

Our review of the Quality section of your submission is complete, and we have identified the following deficiencies:

PRODUCT AND PROCESS

1)

(b) (4)

In addition address the following:

2) The data provided for the registration batches demonstrate that proposed process does not produce product that will meet the drug product specification for disintegration, hardness and (b) (4). Explain how you consider your process/product to be acceptable.

3) The stability data provided for the registration batches do not meet the proposed

(b) (4)

(b) (4)

Justify why you consider this product to be an ODT.

4)

(b) (4)

5) Regarding the proposed post approval stability protocol:

a) We recommend that all strengths be represented in the Postapproval stability protocol (b) (4)

(b) (4)

b) Clarify the proposed storage temperature of the accelerated stability samples in the post approval stability protocol (stated to be (b) (4)).

c) Considering the significant changes observed in the registration stability lots, we recommend that tablet hardness and (b) (4) be part of the post approval stability protocol.

6) We have identified the following issues regarding the provided batch analysis and stability data. However, some of these questions may not be relevant should you decide to generate stability data on batches manufactured after resolving other issues mentioned in this letter.

a)

(b) (4)

b)

c) Provide the accelerated stability data for registration stability lot 1E089E together with data from the room temperature 3 and 6 month time points.

- d) Provide individual (b) (4) hardness and disintegration results for the registration stability lots. Provide the range and standard deviation for each lot.
- e) (b) (4)
- f) Provide Certificates of Analysis (CoAs) for each of the registration lots.
- g) Provide CoAs for batches of the (b) (4). Describe and justify the manufacturing scale of these batches.
- h) Clarify which drug product lots were used in clinical studies and provide CoAs for these lots. Provide details of any differences in manufacture or storage between the clinical and the to-be-marketed product.
- i) Identify which batch analysis results are from (b) (4)
(b) (4)
- j) Identify any results that are derived from product (b) (4)
(b) (4)
- k) Include tablet hardness results (b) (4).
- l) Include (b) (4) for all the registration lots or justify the absence of these data.
- m) Provide content uniformity data for the registration lots as the data provided in P.5.4 are for (b) (4) lots.
- 7) Clarify whether the (b) (4) is also used for amphetamine concentration determinations ((b) (4)
- 8) Different sample preparation procedures are employed for the assay and content uniformity methods for the (b) (4). Provide the procedures and validation data for the intermediate strengths.
- 9) (b) (4)

10) The dissolution method involves (b) (4)
(b) (4) What controls are in place to ensure that the final pH is as stated? We recommend that a numerical acceptance range for pH be employed.

11) Regarding the drug product specification:

- a) Revise the drug product appearance specification to include criteria for the absence of physical damage (b) (4)
- b) Provide justification for the proposed tablet hardness acceptance criteria (b) (4)
(b) (4)
- c) Provide evidence that tablets manufactured with a (b) (4) at the proposed limit is of adequate quality (e.g. adequate hardness, disintegration, (b) (4) etc.).

12) Provide CoAs for sodium polystyrene sulfonate (b) (4) used during development. Justify the acceptance criterion for particle size. Justify the absence of a lower limit for particle size.

13) (b) (4)
14) (b) (4)
15) (b) (4)

16) Provide details of the container closure system (blister size, etc.) for the (b) (4)
(b) (4).

17) The use of (b) (4) in the established name is not acceptable as the labeled strength refers to amphetamine (b) (4)

18) DMF (b) (4) is currently inadequate to support this application. Deficiencies have been communicated to the DMF holder.

19) Amend both drug substance specifications with a test and limit (b) (4).

20) (b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

29)

(b) (4)

30) Identify the specific testing responsibilities of the facilities listed in this application. Your current submission does not clearly specify the responsibilities of each facility.

31)

(b) (4)

32)

33)

BIOPHARMACEUTICS

1) The proposed dissolution method for your proposed product is not acceptable for the following reasons:

a.

b.

c.

(b) (4)

(b) (4)

d.

e.

f.

g.

- 2) You should therefore continue with the development and optimization of the dissolution method for use in the release testing of your proposed product, taking note of the following guidelines:
- Justification should be provided for selection of the equipment/apparatus, dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.). The dissolution profile should be complete and cover at least (b) (4) % of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least 12 samples per testing. Provide the complete dissolution profile data (*individual vessel, mean, SD, %CV, profiles*) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved *versus* time (*the percentage is based on the product's label claim*).
 - Include the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).
- 3) Due to the deficiencies identified in 1 above, no recommendation on the acceptability of your proposed dissolution acceptance criteria can be made at this time. However, consider the following general guidelines in setting of acceptance criteria once the dissolution method has been optimized:
- Identify the lots/batches selected for setting your proposed dissolution acceptance criteria including the lot numbers, the BA/BE studies in which they were used, and if they were registration batches on stability. Provide tabulations of individual vessel dissolution data for all the selected batches (n = 12) for assessment of variability at the individual time points.
 - Based on the characteristics of your formulation and the mechanism of drug release presented in your NDA, the acceptance criteria in both the Acid and Buffer stages should be set as follows:
 - ◆ **Acid Stage:** *The initial sampling time point for the acid stage should be selected when not less than (NLT) (b) (4) % dissolution is reached*

- ◆ **End of Acid Stage:** At the 2 hour time point, the mean dissolution should not be more than (NMT) (b)(4)% of label claim.
 - ◆ **Buffer Stage:** The sampling time point for the buffer stage should be selected when $Q = (b)(4)\%$ dissolution is reached.
- c. The dissolution acceptance criteria should be set to ensure consistent performance from lot to lot and should not allow release of any lots with dissolution profiles outside those that were tested clinically

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Branch I, Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
05/29/2013

From: Ansah, Kofi
To: ["Dorothy Engelking"](#)
Subject: Follow-up to OCP Info Request in Filing Letter -- NDA204326 - Amphetamine (b) (4) ER - ODT
Date: Wednesday, May 29, 2013 3:15:00 AM

Hi Dorothy,

We had a couple of Clinical Pharmacology comments for you in our 74-day Letter. You seem to have provided some response to the 1st bullet (re. literature searches question) but we can't seem to locate your response to the 2nd bullet. We had requested some re-analysis of data and calculation of pAUC5-24 hr (see below).

- We recommend that the sponsor conduct a thorough literature search on clinical pharmacokinetic data on amphetamine in special populations (e.g., patients with renal or hepatic impaired functions) as well as drug-drug interactions. Based on the collected information, the sponsor should explore the need to update Section 2 (Dosage and Administration), Section 7 (Drug Interactions), Section 8 (Use in Specific Populations), and Section 12 (Clinical Pharmacology) of the label.
- For the pivotal bioequivalence study (NT0202.1001), we request that sponsor submit pAUC_(5-24h) (i.e., partial AUCs between 5 to 24 hours) for each individual subject following different treatment at different period. The data should be submitted using SAS transport file (i.e., *.xpt). In addition, a define file (e.g., define.pdf) that explains each variable used in the dataset should also be provided. The data and define file should be submitted in 2 weeks.

If you haven't yet responded to these comments, please do so as soon as possible. On the other hand, if you have already provided a response, please kindly let us know the date and serial number of that submission. Thank you.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D., MBA

CDR, US Public Health Service

Senior Regulatory Health Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I

10903 New Hampshire Avenue, White Oak Bldg 22, Room 4112

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: Kofi.Ansah@fda.hhs.gov

Commissioned Corps of the United States Public Health Service- "Protecting, promoting, and advancing the health and safety of the Nation"

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/s/

KOFI B ANSAH
05/29/2013



DEPARTMENT OF HEALTH AND HUMAN
SERVICES

Food and Drug
Administration Silver
Spring MD 20993

NDA 204326

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Neos Therapeutics Inc.
2940 North Highway 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) dated December 27, 2012, received December 28, 2012 submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Amphetamine (b)(4) Extended-release Orally Disintegrating Tablets, 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7 mg and 18.8 mg.

We also refer to your correspondence, dated and received January 4, 2013, requesting review of your proposed proprietary name, (b)(4). We have completed our review of the proposed proprietary name, (b)(4), and have concluded that it is unacceptable for the following reasons:

1.

(b)(4)

(b) (4)

We note that you have proposed an alternate proprietary name for review, (b) (4) XR-ODT. We note that this name also contains the “XR-ODT” modifier. We identified some concerns with the XR-ODT modifier in the course of our evaluation of your primary name that you may wish to consider:

- The (b) (4) evaluation of the modifier did not clearly demonstrate that participants understood the meaning of “XR-ODT” since participants stated the product was either extended-release or orally disintegrating but there were no instances noted where responders stated the product was *both* extended-release and orally disintegrating.
- (b) (4) did not investigate the impact of dropping one of the two modifiers (either the (b) (4) or “ODT” portion). In our FDA Name Simulation studies for (b) (4), as well as the (b) (4) studies for (b) (4), there were instances where the XR portion, or ODT portion, or XR-ODT was omitted. Our concern with dropping a portion of the modifiers is that it would undermine your goals of conveying that this product is both extended-release and orally disintegrating.

¹ Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

Although we acknowledge that a modifier may help to distinguish from the currently marketed immediate-release and extended-release amphetamine and mixed-amphetamine products in the marketplace, we recommend you consider the concerns relating to the “XR-ODT” modifier outlined above. If you submit an alternate name containing the “XR-ODT” modifier for evaluation, we recommend you respond to our concerns accordingly. Finally, please be advised that the acceptability of a modifier that links to the dosage form of this product, such as “XR-ODT”, will be influenced by the final determination regarding the official designation of the dosage form by CDER/ONDQA.

If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Rimmel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Kofi Ansah at (301) 796-4158.

Sincerely,

{ See appended electronic signature page }

Kellie Taylor, Pharm D, MPH
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/

KELLIE A TAYLOR
04/04/2013



NDA 204326

FILING COMMUNICATION

Neos Therapeutics, Inc.

Attention: Dorothy Engelking, M.S., RAC

Vice President, Regulatory Affairs

2940 N. Highway 360, Suite 400

Grand Prairie, TX 75050

Dear Ms. Engelking:

Please refer to your New Drug Application (NDA) dated December 27, 2012, received December 28, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (Amphetamine (b) (4) Extended-Release Orally Disintegrating Tablets) (b) (4)

We also refer to your amendments dated January 4, 2013, and January 11, 2013.

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 October 28, 2013.

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 **September 27, 2013**.

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

We request that you submit the following information:

1. We request that you conduct a thorough literature search on clinical pharmacokinetic data on amphetamine in special populations (e.g., patients with renal or hepatic impaired functions) as well as drug-drug interactions. Based on the collected information, you should explore the need to update Section 2 (Dosage and Administration), Section 7 (Drug Interactions), Section 8 (Use in Specific Populations), and Section 12 (Clinical Pharmacology) of the label.
2. For the pivotal bioequivalence study (NT0202.1001), we request that you submit $pAUC_{(5-24h)}$ (i.e., partial AUCs between 5 to 24 hours) for each individual subject following different treatment at different period. The data should be submitted using SAS transport file (i.e., *.xpt).

In addition, a define file (e.g., define.pdf) that explains each variable used in the dataset should also be provided. The data and define file should be submitted in 2 weeks.

LABELING

During our preliminary review of your submitted labeling, we have identified the labeling format issues listed below. We recommend that you review the labeling of a recently approved CNS stimulant, NDA 21777

(http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021977s024s025s026lbl.pdf), when you submit revised labeling.

Highlights (HL)

1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.
2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement). Reformat as 2 columns and request *a waiver if unable to meet the ½-page requirement*.
3. White space must be present before each major heading in HL.
4. Boxed Warning - All text must be bolded.
5. Patient Counseling Information Statement - Must include one of the following three bolded verbatim statements, as applicable (without quotation marks):
If a product does not have FDA-approved patient labeling:
 - “See 17 for PATIENT COUNSELING INFORMATION”If a product has FDA-approved patient labeling:
 - “See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.”
 - “See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.”
6. Revision Date - Bolded revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Contents: Table of Contents (TOC)

1. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
2. All section headings must be **bolded** and in UPPER CASE.
3. All subsection headings must be indented, not bolded, and in title case.

Full Prescribing Information (FPI)

1. **Boxed Warning:** All text is **bolded**.
2. **Patient Counseling Information**

Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements, as applicable, at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

We request that you resubmit labeling that addresses these issues by March 26, 2013. The resubmitted labeling will be used for further labeling discussions.

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

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). 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), Medication Guide, and patient PI (as applicable), 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 full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

Please provide the above requested information within 30 days from the date of this letter.

If you have any questions, contact CDR Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

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/s/

MITCHELL V Mathis
03/12/2013

From: Ansah, Kofi
To: ["Dorothy Engelking"](#)
Cc: [Grewal, Renmeet](#); [David, Paul A](#); [Rimmel, Sandra J](#)
Subject: RE: DMEPA Information Request -- NDA 204326 - (b) (4) (Amphetamine (b) (4) Extended-Release ODT)/ADHD
Date: Monday, March 11, 2013 4:39:00 PM

Hi Dorothy,

DMEPA is modifying their request to ask that you submit "actual size photographs" of the tablets instead. Please note that they would still like a response by COB Thursday, March 14, 2013.

Best Regards,
Kofi.

From: Dorothy Engelking [mailto:DEngelking@NEOSTx.com]
Sent: Friday, March 08, 2013 3:00 PM
To: Ansah, Kofi
Cc: Grewal, Renmeet; David, Paul A; Rimmel, Sandra J
Subject: RE: DMEPA Information Request -- NDA 204326 - (b) (4) (Amphetamine (b) (4) Extended-Release ODT)/ADHD

Dear Kofi,

We will be happy to send you the requested samples of the tablets. We do not have final printed labeling on the blister packs, but can provide examples of what we have for the (b) (4) mg tablets. Would one or two blister cards (6 tablets each) be enough? In addition, since this is a controlled substance (Schedule II) can the FDA provide us with appropriate paperwork so that we can keep our inventory reconciled with the DEA?

Please feel free to call me to discuss how we can get you the samples that you require.

Best Regards,
Dorothy

Dorothy Frank-Engelking
VP Regulatory Affairs



2940 N. HWY 360, Suite 400
Grand Prairie, TX 75050
Office: 972-408-1312
Mobile: (b) (6)
Fax: 972-408-1143
dengelking@neostx.com

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From: Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]
Sent: Friday, March 08, 2013 11:34 AM
To: Dorothy Engelking
Cc: Rimmel, Sandra J; David, Paul A; Grewal, Renmeet
Subject: DMEPA Information Request -- NDA 204326 - (b) (4) (Amphetamine (b) (4) Extended-Release ODT)/ADHD

Hi Dorothy,

Regarding your NDA 204326, currently under review, the DMEPA review team would like to see what the actual (b) (4) tablets look like. They are, therefore, requesting that you provide us with samples of the tablets. We would like a response by COB Thursday, March 14, 2013.

Best Regards,
Kofi.

Kofi Boadu Ansah, R.Ph., Pharm.D.

CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: Kofi.Ansah@fda.hhs.gov

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KOFI B ANSAH
03/11/2013



NDA 204326

NDA ACKNOWLEDGMENT

Neos Therapeutics, Inc.

Attention: Dorothy Engelking, M.S., RAC
Vice President, Regulatory Affairs
2940 N. Highway 360, Suite 400
Grand Prairie, TX 75050

Dear Ms. Engelking:

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

Name of Drug Product: Amphetamine ^{(b) (4)} Extended-Release Orally Disintegrating
Tablets ^{(b) (4)}

Date of Application: December 27, 2012

Date of Receipt: December 28, 2012

Our Reference Number: NDA 204326

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 26, 2013, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

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

If you have any questions please call me at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Kofi Ansah, Pharm.D., CDR USPHS
Senior Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

KOFI B ANSAH
01/19/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 112991

MEETING MINUTES

Neos Therapeutics, Inc.

Attention: Dorothy Frank-Engelking, M.S., RAC

Vice President, Regulatory Affairs

2940 N. Highway 360, Suite 400

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) Amphetamine (b) (4) Release Orally Disintegrating Tablets.

We also refer to the meeting between representatives of your firm and the FDA on September 13, 2012. The purpose of the meeting was to discuss the contents and timing of your planned 505(b)(2) NDA for this (b) (4) Amphetamine (b) (4) -Release ODT product.

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, contact CDR Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.

Director

Division of Psychiatry Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

ENCLOSURE:

Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA Meeting

Meeting Date and Time: September 13, 2012; 11:00 am – 12:00 pm EDT
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: IND 112991
Product Name: (b) (4) Amphetamine (b) (4) Release ODT
Indication: Attention Deficit Hyperactivity Disorder (ADHD)
Sponsor/Applicant Name: Neos Therapeutics, Inc.

Meeting Chair: Thomas Laughren, M.D.

FDA ATTENDEES

Thomas Laughren, M.D.	Director, Division of Psychiatry Products (DPP)
Mitchell Mathis, M.D.	Deputy Director, DPP
Robert Levin, M.D.	Medical Team Leader, DPP
Christina Burkhart, M.D.	Medical Reviewer, DPP
Linda Fossom, Ph.D.	Pharmacology/Toxicology Supervisor, DPP
Shiny Mathew, Ph.D.	Pharmacology/Toxicology Reviewer, DPP
Hao Zhu, Ph.D.	Clinical Pharmacology, Team Leader
Andre Jackson, Ph.D.	Clinical Pharmacology Reviewer
Chhagan Tele, Ph.D.	CMC Lead, Office of New Drugs QA (ONDQA)
Wendy I. Wilson-Lee, Ph.D.	CMC/Product Quality Reviewer, ONDQA
Kareen Riviere, Ph.D.	Biopharmaceutics Reviewer, ONDQA
Kofi Ansah, Pharm.D.	Senior Regulatory Project Manager, DPP
Sandra Griffith, B.Sc., R.N	Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Irene Z. Chan, Pharm.D., BCPS	Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)/OSE
Loretta Holmes, Pharm.D.	Safety Evaluator, DMEPA/OSE
Stephen Sun, M.D.	Medical Reviewer, Controlled Substance Staff

Neos Therapeutics, Inc.'s Attendees:

Name	Title	Affiliation
Dorothy Frank-Engelking, M.S.	VP Regulatory Affairs	Neos Therapeutics
Mark Tengler, B.S.	Co-President and Chief Technical Officer	Neos Therapeutics
Russ McMahan, B.S.	VP Research & Development	Neos Therapeutics
Carolyn Sikes, Ph.D.	VP Clinical	Neos Therapeutics
Jennifer Kelley	Regulatory Affairs Manager	Neos Therapeutics
(b) (4)		

1.0 BACKGROUND

Neos Therapeutics, Inc (Neos) requested this Type B pre-NDA meeting with the Division to discuss the development plans for their (b) (4) Amphetamine (b) (4)-Release Orally Disintegrating Tablets (i.e., (b) (4) ODT) product in the treatment of Attention Deficit Hyperactivity Disorder. The objectives of the meeting are 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. Specifically, Neos wanted to discuss the contents and timing of their planned 505(b)(2) NDA for this (b) (4) ODT product.

Neos intends to provide evidence of bioequivalence to the Reference Listed Drug (RLD) product, Adderall XR[®] and plans to submit a 505(b)(2) application that references NDA 21-303 Adderall XR Capsules extended-release mixed amphetamine salts. This new formulation is intended to provide a comparable *in vivo* drug release profile through the use of immediate-release and delayed-release forms of amphetamine (b) (4). The formulation is comprised of an (b) (4) (b) (4) (b) (4)

The Division held a pre-IND meeting with Neos on January 13, 2011. We reached general agreement on the clinical development plan for a (b) (4) amphetamine product (b) (4) ODT). The Division informed the sponsor that the new product must match the PK time course for the RLD, in addition to meeting standard BE criteria. The Division granted an End-of-Phase I meeting scheduled for 19 October 2011; however, based on the Division's preliminary responses, the sponsor cancelled the face-to-face meeting.

The proposed NDA submission will include data from 4 completed clinical studies:

1. Study 1001 was a single-dose (30 mg of amphetamine polistirex XR ODT), open-label, randomized, 3-period, 3-treatment crossover bioequivalence study in healthy adults (N=16), using Adderall XR as the RLD. Test formulation #1 and test formulation #2 were each bioequivalent to Adderall XR (for *d*-amphetamine and *l*-amphetamine). The parameters assessed included: C_{max} , T_{max} , $T_{1/2}$, AUC_{last} , and AUC_{inf} . The following partial AUCs also met criteria for bioequivalence: AUC_{0-5} , AUC_{5-12} , and AUC_{0-24} . Neos selected formulation #1 for clinical development.
2. Study 1002 was a single-dose (30 mg), open-label, randomized, 2-period, 2-treatment, crossover fed/fasted, bioequivalence study in healthy adults (N=32). A high-fat, high-calorie meal did not have a significant effect on the rate of absorption or oral bioavailability of amphetamine polistirex XR ODT. The C_{max} , AUC_{last} , AUC_{inf} were within the accepted limits for establishing no significant differences.
3. Study 1003 was a single-dose (30 mg), 4-period, 4-treatment, 4-sequence crossover, alcohol interaction study in healthy adults (N=32) administered 4 concentrations of alcohol (0%, 4%,

20%, and 40%) after dosing with the product. Alcohol (4-40%) did not significantly alter the rate and extent of absorption of amphetamine. The 90% CI for comparing C_{max} , AUC_{last} , and AUC_{inf} were within the accepted 80% to 125% limits across all comparisons.

4. Study 1004 was a single-dose (30 mg), open-label, single-period, one-treatment PK study in children with ADHD (ages 6-12, N=30). Analysis of the data is ongoing.

In the October 2011 preliminary comments, the Division stated that the sponsor had demonstrated bioequivalence between the new product and the RLD (Adderall XR). For test formulation #1, the $\ln(C_{max})$, $\ln(AUC_{inf})$, and $\ln(pAUC_{(0-5h)})$ parameters were all within the acceptable range of 80-125% compared to the RLD. The Division also agreed that data from the studies in children and adults supported the request for a waiver of the requirement to conduct bioavailability studies in adolescents. The Division also requested *in vitro* dissolution testing in alcohol media to assess the potential of dose dumping when the new product is administered concomitantly with ethanol.

2. DISCUSSION

Following are Neos' specific questions and FDA/DPP's responses/ preliminary comments and discussions at the meeting.

2.1. **General** (administration info and PI) **Questions** [see Module 1; Section 6.2 of Briefing Package]

Question 1: The basis for the Neos ODT product labeling will be the most current version of Adderall XR labeling. Annotated draft labeling will be provided and compared against the RLD Adderall XR labeling. Neos intends to provide unique information in the pharmacokinetics section describing its own pharmacokinetic results. **Does the Division concur with this plan?**

Preliminary Comments: *Generally, the plan is acceptable. Office of Clinical Pharmacology (OCP) will require further explanation of your statement regarding unique information related to the drug's pharmacokinetics.*

Discussion at Meeting: *Neos clarified that by "unique information" they meant unique clinical data with reference to their product. We indicated that this explanation provided the clarification we needed but added that the acceptance of this information in labeling was a matter for review.*

Question 2: Neos will be submitting proposed trade names for review and acceptance by OPDRA at the time of submission of the NDA. We propose a trade name for our product in the following format TRADENAME™ XR ODT. **Does the Division concur?**

Preliminary Comments: *Acceptability of the proposed proprietary name is subject to review. You would need to submit a formal request for proprietary name review for evaluation of the name. The naming format and proposed modifier(s) will need to be formally evaluated, and the Division of Medication Error Prevention and Analysis (DMEPA) cannot comment on acceptability of the proposed format "TRADENAME XR ODT" at this time.*

Discussion at Meeting: *There was discussion surrounding proposing a tradename with dual modifiers, which is uncommon in the market. DMEPA indicated that Neos should submit any information they have to support their request for dual modifiers as part of their formal request for proprietary name review. This information would be considered in the Agency's evaluation of the acceptability of the proposed proprietary name.*

Neos responded that it is their belief that they need to have appropriate descriptors in their product name for clinical relevance and to convey the uniqueness of their product in terms of how it differs from the RLD (Adderall XR) dosage form.

The Division acknowledged the importance for the clinician to know that it is both an extended release product and also a different/new dosage form.

Question 3: Appendix C of the Approved Drug Products List (Orange Book) lists uniform terms for dosage forms. Currently there are no terms that adequately describe the new Neos ODT dosage form. Neos would like to propose a new term of "Tablet, Extended Release, Orally Disintegrating." The established name for the product would be "amphetamine (b) (4) extended release orally disintegrating tablet." **Does the Division concur?**

Preliminary Comments: *The final determination of the established name is a review issue. However, we would like to note that based on the proposed drug product specification limit for disintegration time (i.e., (b) (4)) and the final tablet weight ((b) (4)), your drug product does not comply with the requirements for an orally disintegrating tablet as outlined in Guidance for Industry Orally Disintegrating Tablets. Your submission should include justification for the proposed ODT dosage form designation.*

It is both a USP and CDER policy that agreement exists between the established name and the strength of the drug product expressed on the drug product labels and labeling. Your current proposed established name is based on the amphetamine base (b) (4). The established name and strength should match based on the amphetamine (b) (4) base. For the reasons described above, we recommend removing (b) (4) from the established name. Again, we reiterate, the final determination of the established name is a review issue.

Discussion at Meeting: *Neos proposed an (b) (4). We indicated that the approach seemed reasonable but that the determination of the final specification was a review issue. Neos also indicated that (b) (4).*

(b) (4)

Question 4: As agreed in the comments to our EOP1 briefing package, the Division did not request any additional clinical trials for the submission of this 505(b)(2) NDA. We will therefore request a waiver of a bioavailability study in adolescents based on demonstrated BE to Adderall XR and the similarity between adolescent and adult PK in published literature. **Does the Division concur?**

Preliminary Comments: *OCP would concur with this approach if the data submitted from the BE study in adults demonstrate that the product is bioequivalent to Adderall XR® based upon the established metrics of C_{max} , AUC_{inf} , and pAUC values.*

Discussion at Meeting: *There was no further discussion.*

Question 5: The reference Listed Drug, Adderall XR, provides a Medication Guide to consumers for proper dosing and treatment with amphetamines. There is no specific REMS program in place. Neos proposes to develop a Medication Guide for distribution with the product. **Does the Division concur with these plans?**

Preliminary Comments: *Yes, we agree.*

Discussion at Meeting: *There was no further discussion.*

2.2. Common Technical Data Summaries Questions [Module 2]

Question 6: Since there were no clinical efficacy studies required, Neos does not plan to submit a Summary of Clinical Efficacy with its 505(b)(2) NDA for this product. In addition, Neos seeks the agency's agreement to utilize M2.7.4 (Summary of Clinical Safety) in lieu of a separate ISS in M5.3.5.3 (Reports of Analyses of Data from More than One Study (Including Any Formal Integrated Analyses, Meta Analyses, and Bridging Analyses)) as referenced in the *Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document*. **Does the Division concur?** [Module 2; Section 6.3 of Briefing Package]

Preliminary Comments: *Yes, we agree.*

Discussion at Meeting: *There was no further discussion.*

2.3. Quality/CMC Questions [Module 3]

Question 7: Does the Division concur with the proposed plan to request approval for 6 different tablet strengths based on bioequivalence results/pharmacokinetic data for the (b) (4) mg product and stability for the (b) (4) product? [Section 6.4.1 Summary of Product]

Preliminary Comments: Note that the submission of bioequivalence (BE) and/or bioavailability (BA) information for lower strength (s) of your proposed product may be waived if the following CFR requirements are met:

- Inclusion of the biowaiver request as part of the NDA submission;
- The lower strength (s) and higher strength product have the same dosage form;
- There is BA/BE data for the highest strength;
- The lower strength (s) product is (b) (4) in its active and inactive ingredients to the highest strength product;
- The lower and highest strength products have the same drug release mechanism; and
- Dissolution profile comparisons between the highest and lower strengths in three different media meet the f2 similarity requirements.

Additionally, please refer to our response to Question 12 (below) regarding your proposal to provide stability data for (b) (4) drug product.

Discussion at Meeting: Neos requested confirmation that f2 comparison data between the highest strength product (reference) and the lowest strength product is adequate. We clarified that they should provide the dissolution profile comparison data plus f2 testing for each of the proposed strengths in three different dissolution media (i.e., (b) (4)).

Question 8: Does the Division concur with Neos' plan to reference the API supplier's DMF for sections in 2.3.S and 3.2.S of the NDA? [Section 6.4.2.1 Drug Substance Manufacturers]

Preliminary Comments: This is acceptable. Include Letters of Authorization in the appropriate section of the submission for all referenced Drug Master Files. Include information on the drug substance manufacturers, testers, and packagers along with certificates of analysis or batch analysis results for all drug substance batches used to manufacture the clinical and registration stability drug product batches in Sections 2.3.S and 3.2.S. The proposed test attributes included in the proposed drug substance specifications are reasonable. Include in your submission justification for the proposed acceptance criteria in the drug substance specifications. The final determination of adequacy is a review issue.

Discussion at Meeting: There was no further discussion.

Question 9: Does the Division concur with the proposed final drug product specifications for the ODT (b) (4)? [Section 6.4.3.2 Product Specifications]

Preliminary Comments: *The test attributes listed in the proposed drug product specification appear reasonable. However, the final determination of the adequacy of the associated acceptance criteria is a review issue. Your submission should include acceptance criteria for each tablet strength for which you seek approval. Identify any tests listed on the specification that are performed in-process* (b) (4)

Although some testing occurs at the (b) (4)

(b) (4). *Include appropriate tests and acceptance criteria for microbial contamination in the specification. Include justification, supported by data,* (b) (4)

(b) (4) *Refer to our response to Question 3 regarding the proposed disintegration time limit.*

We reiterate our advice provided in the 30-day safety letter regarding submission of your proposed commercial dissolution method for review prior to NDA submission.

Biopharmaceutics Comments

There is insufficient information to reach a conclusion on the acceptability of your proposed dissolution acceptance criteria. For the selection of the dissolution acceptance criteria of your product, the following points should be considered:

- a) Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).*
- b) A minimum of three time points is recommended to set the specifications. These time points should cover the early, middle, and late stages of the release profile. The last time point should be the time point where at least (b) (4) % of drug has release. If the maximum amount release is less than (b) (4) %, the last time point should be the time when the plateau of the release profile has been reached.*
- c) The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value). This information (raw data and plots) should be included in /during NDA submission.*

Discussion at Meeting: *Neos commented that the Agency recommended as part of the IND 30-Day Safe to Proceed Letter* (b) (4)

(b) (4)

(b) (4)

There was no further discussion on the Biopharmaceutics comments.

Question 10: Does the Division concur with our proposed commercial packaging in blister packs as described in Section 6.4.3.3: Container Closure System?

Preliminary Comments: *The proposed blister packs appear reasonable. However, the final determination of adequacy is a review issue. Include all relevant data to support that the container closure is suitable for its intended use, such as evidence of protection, safety, and compatibility. For each packaging component, list any relevant CFR regulations that support its use.*

Discussion at Meeting: *There was no further discussion.*

Question 11: The proposed blister card layout (Figure 5)

(b) (4)

(b) (4) Does the Division have any additional advice on the requirements for blister packaging of the amphetamine (b) (4) extended release orally disintegrating tablet?

Preliminary Comments: *The blister packaging should comply with the performance standards and test methods outlined in the regulations regarding (b) (4) adult-use effectiveness (16 CFR 1700.20).*

Discussion at Meeting: *There was no further discussion.*

Question 12: Does the Division concur with the

(b) (4)

(b) (4)

Preliminary Comments:

(b) (4)

(b) (4)

(b) (4)

Discussion at Meeting:

(b) (4)

(b) (4)

Question 13: Would the Division accept an NDA for filing with 6 month Accelerated and 9 month Room Temperature stability along with a commitment to provide 12 month Room Temperature stability prior to the 120-day safety update? [Section 6.4.3.4 Stability]

Preliminary Comments: *It is our expectation that the NDA will include at least 12 months of long-term stability data and 6 months of accelerated stability data at the time of submission. Although submission of less stability data will not result in a Refuse to File action, the expiry assigned will be commensurate with the extent and quality of the available stability data. Refer to ICH Guidance "Q1E Evaluation of Stability Data." Additional stability data received by mid-cycle, based on the review clock, will be reviewed as part of the original application, if resources are available. Data received after mid-cycle may not be reviewed during the same review cycle.*

Discussion at Meeting: *There was no further discussion.*

2.4. Non-Clinical Study Reports Questions [Module 4; Section 6.5]

Question 14: The final study report and appendices for the one animal study will be provided in Module 4. Electronic data sets for this study are not proposed to be provided. **Does the Division concur?**

Preliminary Comments: Yes, we agree.

Discussion at Meeting: *There was no further discussion.*

2.5. Clinical Questions [Module 5; Section 6.6]

Question 15: Final Clinical Study Reports for the four completed pharmacokinetic trials will be provided in Module 5. Data for these studies will be provided in SDTM format. These datasets

will include both the pc (pharmacokinetic concentration) and pp (pharmacokinetic parameters) domains. There was no additional analysis performed and therefore there will be no separate analysis datasets provided. **Does the Division concur?**

Preliminary Comments: *Your plan on the study reports and datasets appears reasonable. Submission in SDTM format is acceptable. We request that you also submit the safety datasets.*

Discussion at Meeting: *There was no further discussion.*

Question 16: Does the Division concur with the interpretation that no Case Report Forms will need to be submitted?

Preliminary Comments: *Yes, we agree. You are not required to submit case report forms if there were no deaths, serious adverse events, or discontinuations related to adverse events.*

Discussion at Meeting: *There was no further discussion.*

Additional Comments from Controlled Substance Staff (CSS)

1. *You should compile all abuse-related clinical study information for the NDA submission according to the FDA draft guidance on the Assessment of Abuse Potential of Drugs (January 2010).*
2. *If the product is approved, the abuse and dependence sections in the product label should be updated to reflect the current stimulant class label. You should highlight precautions against misuse, abuse, and diversion for any materials seen by patients and healthcare professionals.*
3. *A discussion in the quarterly periodic safety reports should provide numbers and trends based upon MSSO's Standardized MedDRA Query (SMQ): "Drug Abuse, Dependence and Withdrawal" while the drug is marketed. You should be actively engaged in the surveillance of the potential known and unknown methods for misuse of this new, orally disintegrating formulation.*

Discussion at Meeting: *Neos indicated that they plan to provide a discussion based on literature review with respect to the abuse and diversion of amphetamines and contrast those methods against their product.*

CSS clarified that our request is related to the product in question being a controlled substance, thus, in order to understand the abuse potential for the CII ODT (given that no other CII is currently marketed in this dosage form), Neos needs to compile all available information and provide for review. CSS also indicated that a draft guidance is available on how to arrange this information in the submission. Link to FDA draft guidance on the Assessment of Abuse Potential

of Drugs:

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

3.0 OTHER IMPORTANT MEETING LANGUAGE SECTIONS:

PREA PEDIATRIC STUDY PLAN

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

PRESCRIBING INFORMATION

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

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

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

GENERAL RECOMMENDATIONS REGARDING 505(b)(2) APPLICATIONS

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 is scientifically appropriate. We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

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.

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There are no actionable items at this time.

6.0 ATTACHMENTS AND HANDOUTS

None.

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

/s/

THOMAS P LAUGHREN
09/26/2012