

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204325Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204325 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Adzenys ER Established/Proper Name: amphetamine Dosage Form: extended-release oral suspension		Applicant: Neos Therapeutics, Inc. Agent for Applicant (if applicable): Dorothy Engelking
RPM: Brendan Muoio, PharmD, RAC		Division: Division of Psychiatry Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 9/6/2017</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>9/15/2017</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

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

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

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

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

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

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

NDAs: Subpart H

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

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- Approval based on animal studies

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

Comments:

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

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s): Approval 9/15/2017
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	Acceptability Letter: 8/11/2017 Non-acceptability Letter: 2/27/2017 Review: 2/23/2017, 8/9/2017
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input type="checkbox"/> None 1/13/2017 DMEPA: <input type="checkbox"/> None 7/21/2017 DMPP/PLT (DRISK): <input type="checkbox"/> None 8/9/2017 OPDP: <input type="checkbox"/> None 8/11/2017 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None DPMH Maternal Health: 6/27/2017, DPMH Pediatric: 8/4/2017
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	1/13/2017
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 505(b)(2) Clearance Committee 9/15/2017, CDER Exclusivity Memo 9/15/2017
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

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

<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> 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>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>8/9/2017</u> If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>) 	Information Request – Patent Certification or Verification: 3/2/2017, Filing Review Issues Identified 1/26/2017
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 6/19/2014
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 5/2/2013
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	Pre-IND Meeting: 1/13/2011
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Division Director Summary Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 9/13/2017
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 8/30/2017
<ul style="list-style-type: none"> PMR/PMC Development Templates (<i>indicate total number</i>) 	<input checked="" type="checkbox"/> None

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review 7/31/2017
• Clinical review(s) (<i>indicate date for each review</i>)	7/31/2017
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Clinical Review: 7/31/2017
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> N/A 8/11/2017
❖ Risk Management <ul style="list-style-type: none"> • 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>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review 8/28/2017
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 8/30/2017
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/28/2017
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested Recommendation to accept data without an on-site inspection: 2/2/2017

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/10/2017
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/28/2017
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/28/2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input type="checkbox"/> None All included in Review: 8/28/2017 Drug Substance/Drug Product Manufacturing Process and Controls/Drug Substance Drug Product Drug Substance/Drug Product Manufacturing Process and Controls Drug Substance Drug Product
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	8/28/2017
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	8/28/2017 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(Notify CDER OND IO)</i>
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

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

/s/

BRENDAN MUOIO
09/19/2017

DATE: September 15, 2017

TO: Adzenys ER (amphetamine) extended-release oral suspension (NDA 204325) File
Dyanavel XR (amphetamine) extended-release oral suspension (NDA 208147)
File
Mydayis (mixed salts of a single-entity amphetamine product) extended-release
capsule (NDA 022063)

FROM: CDER Exclusivity Board

SUBJECT: Whether the 3-year exclusivity for Dyanavel XR (NDA 208147) or Mydayis
(NDA 022063) blocks the approval of Adzenys ER (NDA 204325)

This memorandum addresses whether the unexpired 3-year exclusivity the Food and Drug Administration (FDA) recognized for Dyanavel XR (amphetamine) extended-release (ER) oral suspension (Dyanavel XR) (NDA 208147) or that recognized for Mydayis (mixed salts of a single-entity amphetamine product)¹ ER capsule (NDA 022063) blocks approval of Adzenys ER (amphetamine) ER oral suspension (NDA 208147) (Adzenys ER).

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 FDA's Orange Book as "new product" (NP) exclusivity. Mydayis was approved on June 20, 2017, for the treatment of ADHD in patients 13 years and older and also received 3-year exclusivity, which is denoted the Orange Book as NP exclusivity. Upon review of the administrative record related to the approval of NDAs 208147 and 022063, the Exclusivity Board (Board) in the Center for Drug Evaluation and Research (CDER), in consultation with the Division of Psychiatry Products (Division), recommends that neither the exclusivity recognized for Dyanavel XR nor the exclusivity recognized for Mydayis should block approval of Adzenys ER.

The Board has determined that Dyanavel XR's exclusivity-protected condition of approval for which new clinical investigations were essential to approval is the oral ER suspension formulation² associated with its drug release profile. Similarly, the Board concludes that Mydayis's exclusivity-protected condition of approval is the oral ER capsule formulation³ associated with its drug release profile. Because Adzenys ER comprises a different formulation that results in a drug release profile different from that of Dyanavel XR and Mydayis, the Board

¹ FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) identifies the mixed amphetamine salts as follows: amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate.

² The term "formulation" as used in this memo includes aspects of the product's formulation that contribute to its drug release mechanism and resulting pharmacokinetic (PK) profile.

³ Id.

recommends that the approval of Adzenys ER should not be blocked by the exclusivity for Dyanavel XR or Mydayis.

A discussion of the Board's reasoning follows.

I. FACTUAL BACKGROUND

A. History of Amphetamine Approvals

Amphetamines are a central nervous system stimulant used to treat ADHD and have a long history of use in many FDA-approved drug products. Amphetamine (its base and salts) contains two active moieties: levo-amphetamine and dextroamphetamine (*l*- and *d*-amphetamines). Amphetamines were first approved by FDA in NDA 011522 for Adderall (amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate) tablets on January 19, 1960.⁴ The initial amphetamine formulations, including Adderall, were immediate-release (IR) formulations and often required dosing multiple times a day.

The shift in clinical practice to day-long treatment of ADHD symptoms led to the development of modified-release (MR) amphetamine products with a biphasic release profile and once-daily dosing.⁵ The Agency approved NDA 021303 for Adderall XR, held by Shire Development, LLC (Shire) on October 11, 2001, as the first MR amphetamine product. Adderall XR contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine from Adderall XR compared to the conventional Adderall (IR) tablet formulation.⁶ Adderall XR contains the same mixed amphetamine salts as the IR formulation, Adderall.

(b) (4)

(b) (4)

Approval of Adderall XR was supported by two clinical efficacy studies (Studies 381.201 and 381.301). Study 201 was intended to assess the safety and efficacy of three doses of Adderall XR compared to placebo and IR Adderall, with all study treatments administered once daily. The study was a randomized, double-blind, 5 treatment crossover study.⁹ Assessments of treatment response were obtained in laboratory classroom settings. The Swanson, Kotkin, Agler,

⁴ See 35 FR 12652 (Aug. 8, 1970) for Drug Efficacy Study Implementation (DESI) findings for amphetamines.

⁵ McGough JJ, Biederman J, Greenhill LL, McCracken JT, Spencer TJ, Posner K, Wigal S, Gornbein J, Tulloch S, and Swanson JM, 2003, Pharmacokinetics of SLI381 (Adderall XR) an Extended Release Formulation of Adderall. *J. Am. Acad. Child Adolesc. Psychiatry* 42(6):684-691.

⁶ Woodcock Response Letter, Docket No. FDA-2005-P-0120 (Jun. 22, 2012) at 2.

⁷ Id.

⁸ Id.

⁹ NDA 021303, Clinical Review (Oct. 6, 2001) at 6.

M-Flynn, and Pelham Rating Scale (SKAMP) was the primary efficacy measure.¹⁰ Study 301 was intended to assess the safety and efficacy of Adderall XR in the treatment of children with ADHD. The study was a multicenter, randomized, parallel group, 4-arm, placebo controlled trial. The designated primary efficacy measure was the 10 item Conners Global Index Scale by the teacher (CGIS-T).¹¹

Subsequent to Adderall XR, FDA approved three other MR amphetamine products: Dyanavel XR, Adzenys XR-ODT, and Mydayis.

1. *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),¹² 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 findings of safety and effectiveness for Adderall (mixed amphetamine salts) immediate-release (IR) tablets (Teva Women's; NDA 011522). The active moieties in Dyanavel XR are *d*- and *l*-amphetamine. 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.¹³ This product was formulated to provide convenience for patients who prefer oral dosage forms but have difficulty swallowing pills or capsules, especially pediatric patients.¹⁴

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).¹⁵ Assessments for ADHD symptoms and behaviors were measured by SKAMP and Permanent Product Measure of Performance (PERMP) assessments in an abbreviated analog classroom at each clinical site.¹⁶ The pre-specified efficacy endpoints were based on change from pre-dose baseline SKAMP score to evaluation time (4 hours after dose was the primary endpoint), and multiple evaluation times were tested (1, 2, 4, 6, 8, 10, 12, and 13 hours after dose). Two secondary endpoints of interest were measured: time of onset of clinical effect and duration of clinical effect.¹⁷

In addition to Study TRI102-ADD-001, the sponsor also conducted a pharmacokinetic (PK)

¹⁰ Id.

¹¹ Id. at 10.

¹² [REDACTED] (b) (4)

(b) (4)

¹³ NDA 208147, Division Director Review (Oct. 19, 2015) (Dyanavel Div. Director Review) at 2

¹⁴ Id. See also NDA 208147, Clinical Review (Oct. 19, 2015) (Dyanavel Clinical Review) at 2

¹⁵ Dyanavel Clinical Review at 6-8.

¹⁶ Id.

¹⁷ Dyanavel Div. Director Review at 2.

study in children (6 – 12 years), and a single-dose relative bioavailability and food effect trial in healthy adult subjects to support this application.¹⁸ 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.¹⁹ 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.²⁰ 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 knowledge of the amphetamine IR tablet and clinical practice supported the approval and once-daily dosing recommendations in adolescents and adults.²¹

The Division determined that Study TRI102-ADD-001 supported the efficacy of Dyanavel XR in the treatment of ADHD with once-daily dosing. Dyanavel XR was approved on October 19, 2015. Dyanavel XR is the first ER oral suspension formulation of amphetamine approved. Three-year exclusivity attached to Dyanavel XR as a result of Study TRI102-ADD-001, which established efficacy of Dyanavel XR's oral suspension formulation with the product's specific drug release profile for once-daily dosing. The exclusivity, which expires on October 19, 2018, is denoted as NP exclusivity in the Orange Book.

2. Adzenys XR-ODT

On December 27, 2012, Neos Therapeutics, Inc. (Neos) submitted a 505(b)(2) NDA for amphetamine extended-release (XR) orally disintegrating tablets (ODT), tradename Adzenys XR-ODT, for the treatment of ADHD with a once-daily dosing regimen (NDA 204326).²² The strengths for which approval was originally sought by the sponsor were (b) (4) mg, but these were changed to strengths of 3.1, 6.3, 9.4, 12.5, 15.7, and 18.8 mg base amphetamine. The NDA relied upon FDA's findings of safety and effectiveness for Adderall XR.

The active moieties in Adzenys XR ODT are *d*- and *l*-amphetamine. Adzenys XR-ODT contains amphetamine, in a 3:1 ratio of *d*- to *l*-amphetamine and is the first amphetamine product formulated in an ER ODT dosage form.²³ (b) (4)

¹⁸ Dyanavel Clinical Review at 5.

¹⁹ Dyanavel Clinical Review at 4, referencing NDA 208147, Non-Clinical Review (Sep. 21, 2015) (Dyanavel Clinical Pharmacology Review at 7).

²⁰ Id.

²¹ Dyanavel Clinical Pharmacology Review at 3.

²² Neos resubmitted the NDA on July 27, 2015, almost two years after it received a complete response letter dated September 24, 2013.

²³ Adzenys XR-ODT Clin. Pharm. Review at 8.

The Adzenys XR-ODT development program was based on a single-dose bioequivalence (BE)/food effect clinical study (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.²⁵ No additional clinical safety and efficacy studies were submitted in this application. Study NT0202.1005 demonstrated that Adzenys XR-ODT provided a comparable rate and extent of drug exposure as Adderall XR.²⁶ The Agency determined that Adzenys XR-ODT exhibited a similar PK profile and drug absorption as Adderall XR and thus was expected to have similar efficacy and safety profiles as Adderall XR.²⁷ Adzenys XR-ODT was approved on January 27, 2016.

3. *Mydayis*

On July 21, 2006, Shire submitted a 505(b)(1) NDA 022063 for Mydayis, an ER capsule comprising the same mix of amphetamine salts as in Adderall and Adderall XR, and received an approvable letter on May 18, 2007. On December 20, 2016, Shire submitted a complete response to the approvable letter.²⁸ The rationale for the Mydayis formulation was to extend the benefits from the 12-hour duration of effect expected for Adderall XR to 16 hours with use of Mydayis.²⁹ The active moieties in Mydayis XR are *d*- and *l*-amphetamine. The Mydayis ER capsule contains three types of drug-releasing beads, which provide immediate release, (b) (4) delayed release, and delayed, extended release of the mixed amphetamine salts.³⁰ The clinical development program consisted of 16 clinical studies, 13 of which were included in the original NDA and 3 of which were included in the resubmission.

Approval of Mydayis was supported by two clinical efficacy studies (Studies SHP465-306 and SHP465-305). Study 306 was a phase 3, randomized, double-blind, multicenter, placebo-controlled, forced-dose titration, safety and efficacy study in adults aged 18 to 55 years with ADHD. The primary measure of efficacy was the clinician administered ADHD Rating Scale with Adult Prompts (ADHD-RS With Prompts). The study demonstrated that reduction from baseline in ADHD-RS With Prompts total score was significantly greater in the Mydayis

²⁴ Id.

²⁵ Id.

²⁶ The 90% confidence intervals for the log-transformed exposure parameters C_{max} , AUC_t , AUC_{∞} , $AUC_{5-\infty}$ were within the 80-125% range for *d*- and *l*-amphetamine. NDA 204326, Cross-Discipline Team Leader Review (Jan. 27, 2016) at 3.

²⁷ Id.

²⁸ NDA 022063, Cross-Discipline Team Leader Review (Jun. 20, 2017) (Mydayis CDTL Review) at 1.

²⁹ Id.

³⁰ NDA 022063, Clinical Review (Jun. 20, 2017) (Mydayis Clinical Review) at 8.

treatment groups (12.5 mg and 37.5 mg) compared with the placebo treatment group.³¹ Study 305 was a phase 3, randomized, double-blind, multicenter, placebo-controlled, dose-optimization, safety and efficacy study in children and adolescents aged 6 to 17 year with ADHD. The primary measure of efficacy was the clinician administered ADHD Rating Scale, DSM-IV (ADHD-RS-IV). The study demonstrated that reduction from baseline in ADHD-RS-IV total score was significantly greater in the Mydayis treatment groups (12.5 mg or 25 mg) compared with the placebo treatment group.

Mydayis was approved on June 20, 2017, and is indicated for treatment of ADHD in patients 13 years and older.³² Three-year exclusivity attached to Mydayis as a result of studies SHP465-306 and SHP465-305, which established efficacy of the Mydayis formulation, with its specific drug release profile. The exclusivity, which expires on June 20, 2020, is denoted as NP exclusivity in the Orange Book.

B. Adzenys ER

On November 15, 2016, Neos submitted a 505(b)(2) NDA for Adzenys ER, an amphetamine ER oral suspension, 1.25 mg/mL, for the treatment of ADHD with a once-daily dosing regimen, relying on the listed drug Adderall XR (NDA 021303). The active moieties in Adzenys ER are *d*- and *l*-amphetamine. Adzenys ER is a suspension of *d*- and *l*-amphetamine (b) (4) (b) (4) for oral administration. A portion of the amphetamine is IR, and a portion is (b) (4) for delayed release of amphetamine.³³ (b) (4) (b) (4)

Adzenys ER is intended to be an extension of the Adzenys product line. As with Adzenys XR-ODT, Neos did not conduct any clinical efficacy studies to support approval of Adzenys ER.³⁵ Rather, Neos relied for approval on FDA's findings of safety and effectiveness for Adderall XR.³⁶ Neos supported this reliance through the submission of comparative bioavailability studies. The pivotal comparative bioavailability study (Study NT021.1008) demonstrated that Adzenys ER is bioequivalent to Adderall XR.³⁷ As described in the Clinical Pharmacology Review for NDA 204325, Adzenys ER had a similar PK profile to Adderall XR, and therefore,

³¹ Mydayis CDTL Review at 5.

³² The Mydayis labeling includes a limitation of use noting that pediatric patients 12 years and younger experienced higher plasma exposure than patients 13 years and older at the same dose and experienced higher rates of adverse reactions, mainly insomnia and decreased appetite. See Mydayis labeling available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022063s0001bl.pdf.

³³ NDA 204325, Clinical Review (Aug. 28, 2017) (Adzenys ER Clinical Review) at 7.

³⁴ NDA 204325, Clinical Pharmacology Review (Aug. 28, 2017) (Adzenys ER Clin. Pharm. Review) at 2.

³⁵ Adzenys ER Clinical Review at 13.

³⁶ Id.

³⁷ Adzenys ER Clin. Pharm. Review at 11.

the safety and efficacy of Adzenys ER would be expected to be similar to that of Adderall XR.³⁸ A suspension dose of 18.8 mg is equivalent to 30 mg of Adderall XR, and the suspension can be dosed as 5, 10, 20, 25, or 30 Adderall XR-equivalent mg.³⁹

II. SUMMARY OF LEGAL BACKGROUND⁴⁰

Section 505(c)(3)(E)(iii) and (c)(3)(E)(iv) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) describes which applications are eligible for 3-year exclusivity, as well as which 505(b)(2) NDAs will be barred or blocked from approval by another application's 3-year exclusivity. Under the Agency's interpretation of this statutory provision, for a single-entity drug to be potentially barred or blocked by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety(ies) as the drug with 3-year exclusivity. As discussed in greater detail in Appendix A, 3-year exclusivity provides the holder of an approved NDA limited protection from new competition in the marketplace for the exclusivity-protected "conditions of approval," which FDA has interpreted to be the innovation represented by its approved drug product that is supported by new clinical investigations essential to approval. Thus, when a 505(b)(2) application for a single-entity drug seeks approval for the same drug (active moiety(ies)) to which exclusivity has attached, FDA will examine the conditions of approval supported by the new clinical investigations (other than bioavailability studies) that were essential to approval of the application with exclusivity.

If a pending 505(b)(2) application for a single-entity drug is seeking approval for the same drug for an exclusivity-protected condition of approval, the pending application will be blocked from approval for the exclusivity-protected condition of approval until the exclusivity period expires. Three-year exclusivity does not extend beyond the scope of the approval for the NDA and does not cover aspects of the drug product for which new clinical investigations were not essential to approval. Therefore, 3-year exclusivity does not block approval of a pending 505(b)(2) application containing the same drug (active moiety or moieties) that is not seeking approval for an exclusivity-protected condition of approval for the approved NDA with exclusivity.

As explained in greater detail in the appendix, the scope of 3-year exclusivity for a drug product may be affected by a previous approval for a drug product containing the same active moiety or moieties. The exclusivity protected condition of approval, and thus the scope of 3-year exclusivity generally does not cover an innovation already approved for another drug product containing the same active moiety. A drug product may, however, qualify for exclusivity for a condition(s) of approval that differs from the conditions of approval of the earlier-approved drug product. In sum, because 3-year exclusivity generally covers only a different condition(s) of approval from any previously approved product with the same active moiety or moieties, as a practical matter a later-approved product is likely to have a narrower scope of exclusivity than the product approved previously with the same active moiety or moieties.

³⁸ Id.

³⁹ Adzenys ER Clinical Review at 7.

⁴⁰ A more detailed description and analysis of relevant statutory and regulatory provisions is provided in the appendix to this memorandum.

III. DISCUSSION

Dyanavel XR and Mydayis both have unexpired 3-year exclusivity. Dyanavel XR, Mydayis, and Adzenys ER are all “single-entity” amphetamine products with the same active moieties, *d* and *l*-amphetamine. The Board must therefore consider whether Neos is seeking approval of Adenzys ER for any of the exclusivity-protected conditions of approval for Dyanavel XR or Mydayis such that the 3-year exclusivity FDA recognized for either Dyanavel XR or Mydayis blocks approval of Adzenys ER.

As stated above, FDA interprets the scope of 3-year exclusivity for a particular product to be related to the scope of the underlying new clinical investigations that were essential to the approval of the product. Given the close relationship between plasma concentration and clinical effect of amphetamines, without evidence that the proposed product provides a rate and extent of drug exposure comparable to that of a listed drug, a demonstration of clinical efficacy throughout the day is especially important. As Dyanavel XR did not provide a rate and extent of exposure comparable to the listed drug relied upon (Adderall IR), Study TRI102-ADD-001 was essential to demonstrate the safety and efficacy of Dyanavel XR’s formulation and associated drug release profile.^{41,42} Accordingly, Dyanavel’s formulation and associated drug release profile is the innovation protected by exclusivity. Thus, because Dyanavel XR is a different formulation with a different drug release profile than Adzenys ER, Dyanavel XR’s exclusivity should not block approval of Adzenys ER.

In the case of Mydayis, the product was developed and is formulated to extend the 12-hour duration of effect for Adderall XR to 16 hours. Studies SHP465-306 and SHP465-305 were conducted to demonstrate safety and efficacy of the Mydayis formulation with its particular drug release profile (which results in an expected duration of clinical effect of 16 hours). The Mydayis formulation with its particular drug release profile is the innovation represented by Mydayis for which clinical investigations were essential. In contrast, Adzenys ER, as noted above, is formulated with a different drug release profile than Mydayis. Because Adzenys ER is a different formulation with a different drug release profile than Mydayis, the exclusivity recognized for Mydayis should not block approval of Adzenys ER.

IV. CONCLUSION

For the reasons described above, the Board recommends that neither Dyanavel XR’s exclusivity nor Mydayis’s exclusivity should block approval of Adzenys ER.

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⁴¹ See CDER Exclusivity Board Memo to NDAs 204326 and 208147 (Jan. 27, 2016) assessing whether Dyanavel XR’s exclusivity blocks approval of Adzenys XR-ODT.

⁴² In contrast, as described in section I.A.2, even though Adzenys XR-ODT was the first amphetamine orally disintegrating tablet to be approved, no clinical efficacy study was necessary because the product demonstrated a rate an extent of drug absorption comparable to that of Adderall XR.

APPENDIX

Legal and Regulatory Background for Exclusivity Determinations

I. Drug Approval Pathways Under the FD&C Act

Section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act establishes approval pathways for three categories of drug applications: (1) 505(b)(1) new drug applications (NDAs), (2) 505(b)(2) NDAs, and (3) 505(j) abbreviated new drug applications (ANDAs).

A. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(1) of the FD&C Act requires that an application contain, among other things, “full reports of investigations” to show that the drug for which the applicant is seeking approval is safe and effective.⁴³ NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference are referred to as *505(b)(1) NDAs* or *stand-alone NDAs*.

FDA will approve a 505(b)(1) NDA if it finds that the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling, and it meets other applicable requirements.⁴⁴

B. 505(b)(2) NDAs and ANDAs: Abbreviated Pathways

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)⁴⁵ amended the FD&C Act to add section 505(b)(2) and 505(j) as well as other conforming amendments. These provisions describe abbreviated pathways for 505(b)(2) NDAs and ANDAs, respectively.⁴⁶ The Hatch-Waxman Amendments reflect Congress’s efforts to balance the need to “make available more low cost generic drugs by establishing a generic drug approval procedure” with new incentives for drug development in the form of exclusivity and patent term extensions.⁴⁷ These pathways permit sponsors to rely on what is already known about the previously approved drug, which both allows for a speedier market entry than would be

⁴³ See section 505(b)(1)(A) of the FD&C Act. A 505(b)(1) NDA must also include: a full list of the articles used as components of the proposed drug product; a full statement of the composition of such drug; a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; samples of the drug as necessary; proposed labeling for the drug; and pediatric assessments. *Id.*

⁴⁴ See, e.g., section 505(b)(1), 505(c) and 505(d) of the FD&C Act and 21 CFR part 314.

⁴⁵ Public Law 98-417 (1984).

⁴⁶ Section 505(j) of the FD&C Act generally requires that an applicant for an ANDA demonstrate that its product is bioequivalent to the listed drug it references (RLD) and is the same as the RLD with respect to active ingredient(s), dosage form, route of administration, strength, previously-approved conditions of use, and, with certain exceptions, labeling. As the pending matter involves only 505(b)(2) NDAs, it is not necessary to discuss the ANDA pathway here.

⁴⁷ See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

possible with a full, stand-alone 505(b)(1) NDA and leads to increased competition.⁴⁸

Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c) of the FD&C Act. A 505(b)(2) NDA must meet both the “full reports” requirement in section 505(b)(1)(A) and the same safety and effectiveness standard as a stand-alone NDA. Unlike a stand-alone NDA though, in a 505(b)(2) NDA, some or all of the safety and/or effectiveness information relied upon for approval comes from investigations not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.⁴⁹ Thus, the difference between a 505(b)(2) NDA and a stand-alone NDA is the source of the information relied on for approval. Whereas a stand-alone NDA is supported entirely by studies that the sponsor owns or to which it has a right of reference, the 505(b)(2) applicant may rely on sources such as: its own studies; published reports of studies to which the applicant has no right of reference; the Agency’s findings of safety and/or effectiveness for one or more previously approved drugs; or a combination of these and other sources to support approval.⁵⁰

A 505(b)(2) application can be submitted for either a change to a previously approved drug or for a new chemical entity (NCE),⁵¹ and, in some instances, may describe a drug product with substantial differences from a listed drug.⁵² When a 505(b)(2) applicant seeks to rely on a finding of safety and effectiveness for a previously approved drug product, the applicant must establish that its basis for relying on a previous approval is scientifically justified. A 505(b)(2) applicant can *bridge*⁵³ its proposed product to the previously approved product by submitting, for

⁴⁸ See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); see also *Bristol-Meyers Squibb Co. and E.R. Squibb & Sons, Inc. v. Royce Labs., Inc.*, 69 F.3d 1130, 1132-34 (Fed. Cir. 1995).

⁴⁹ Section 505(b)(2) of the FD&C Act provides for approval of an application:

for a drug for which the [safety and efficacy investigations] . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted

See 21 CFR 314.3(b) (defining *right of reference or use*).

⁵⁰ See Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Katherine M. Sanzo, Esq., Lawrence S. Ganslaw, Esq., Morgan, Lewis & Bockius LLP; Jeffrey B. Chasnow, Esq., Pfizer Inc.; Stephan E. Lawton, Esq., Gillian R. Woollett, Ph.D., Vice President Regulatory Affairs, Biotechnology Industry Organization; William R. Rakoczy, Esq., Lord, Bissell & Brook LLP (Oct. 14, 2003) (originally assigned Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 and changed to Docket Nos. FDA-2001-P-0369, FDA-2002-P-0390, and FDA-2003-P-0274, respectively, as a result of FDA’s transition to Regulations.gov) (505(b)(2) Citizen Petition Response).

⁵¹ See 21 CFR 314.108(a) (defining *new chemical entity*).

⁵² In October 1999, the Agency issued a draft guidance for industry entitled “Applications Covered by Section 505(b)(2)” (505(b)(2) Draft Guidance) which states that “[a] 505(b)(2) application may be submitted for an NCE when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference.” 505(b)(2) Draft Guidance at 3, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁵³ The “bridge” in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug, or between the proposed product and a product described in published literature, to justify reliance scientifically on certain existing information for approval of the 505(b)(2) NDA.

example, studies that measure the relative bioavailability (BA)⁵⁴ of the two products, or other appropriate scientific information.

FDA has described its interpretation of section 505(b)(2) of the FD&C Act in a series of public statements and proceedings beginning in 1987, including the 1989-1994 Hatch-Waxman rulemaking process, the 505(b)(2) Draft Guidance, and previous citizen petition responses.⁵⁵ FDA's interpretation of section 505(b)(2) is intended to permit a sponsor to rely to the greatest extent possible under the law on what is already known about a drug. FDA's interpretation of section 505(b)(2) avoids requiring drug sponsors to conduct and submit studies that are not scientifically necessary. The conduct and review of duplicative studies would (1) divert industry resources that could be used to undertake innovative research, (2) increase drug costs, (3) strain FDA review resources, and (4) slow the process for drug approval, with no corresponding benefit to the public health. In addition, the conduct of duplicative studies may raise ethical concerns because it could subject human beings and animals to medically or scientifically unnecessary testing. The 505(b)(2) pathway permits sponsors and the Agency to target drug development resources to studies needed to support the proposed difference or innovation from the drug on which the 505(b)(2) application seeks to rely.⁵⁶

II. Three-Year Exclusivity Under the FD&C Act

A. General Framework

An application for a drug containing a previously approved active moiety (including a 505(b)(2) application) is generally eligible for 3 years of exclusivity if the statutory and regulatory standards are satisfied. The statute and regulations for 3-year exclusivity describe which original NDAs and supplements are eligible for 3-year exclusivity and which are barred or blocked from approval by that exclusivity.

For NDAs, section 505(c)(3)(E)(iii) of the FD&C Act states:

If an application submitted under subsection (b) [of this section] for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) [of this section], is approved after [September 24, 1984,] and if

⁵⁴ Bioavailability data provide an estimate of the amount of the drug absorbed, as well as provide information related to the pharmacokinetics (PK) of the drug. See, e.g., FDA's Draft Guidance for Industry: "Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations" (March 2014) (BA/BE NDA/IND Draft Guidance), at 3.

⁵⁵ See, e.g., 505(b)(2) Citizen Petition Response and Letter from Steven K. Galson, M.D., M.P.H., Director, CDER, FDA, to Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP; Stephan E. Lawton, Esq., Biotechnology Industry Organization; Stephen G. Juelsgaard, Esq., Genentech (May 30, 2006) (originally assigned Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355 and changed to Docket Nos. FDA-2004-P-0339, FDA-2003-P-0003, FDA-2004-P-0214, and FDA-2004-N-0059, respectively, as a result of FDA's transition to Regulations.gov) (2006 Citizen Petition Response).

⁵⁶ 21 CFR 314.54(a) states that a 505(b)(2) application "need contain only that information needed to support the modification(s) of the listed drug."

*such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) [of this section] for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) [of this section] if the investigations described in clause (A) of subsection (b)(1) [of this section] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.*⁵⁷

The first clause (italicized) in section 505(c)(3)(E)(iii) of the FD&C Act, often referred to as the eligibility clause, describes the applications eligible for 3-year exclusivity. FDA has interpreted the term “active ingredient” in the phrase “active ingredient (including any ester or salt of the active ingredient)” to mean active moiety. Under the eligibility clause in section 505(c)(3)(E)(iii), applications for single-entity drugs that are not eligible for 5-year NCE exclusivity (because they contain an active moiety “that has been approved in another application”)⁵⁸ are eligible for 3-year exclusivity if they include new clinical investigations (other than bioavailability studies), essential to approval of the application, that were conducted or sponsored by or on behalf of the applicant. FDA’s implementing regulations interpret certain aspects of the statutory language regarding 3-year exclusivity. Among other things, they define the terms *clinical investigation*,⁵⁹ *new clinical investigation*,⁶⁰ *essential to approval*,⁶¹ and *conducted or sponsored by the applicant*.⁶²

⁵⁷ See Section 505(c)(3)(E)(iii) of the FD&C Act (emphasis added); see also 21 CFR 314.108(b)(4)(iv).

⁵⁸ The longest and most protective period of exclusivity provided under the Hatch-Waxman Amendments is 5-year NCE exclusivity. See section 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act. A 5-year exclusivity period is provided for a drug “no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under [section 505(b)].” For single-entity drugs, this exclusivity generally has been interpreted to prevent an applicant from submitting a 505(b)(2) NDA or ANDA for a drug that contains the active moiety approved in the protected drug for a 5-year period from the date of approval of the protected drug. Five-year NCE exclusivity does not block submission or review of stand-alone 505(b)(1) NDAs.

⁵⁹ “Clinical investigation” is defined as “any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects.” 21 CFR 314.108(a).

⁶⁰ “New clinical investigation” is defined, in relevant part, as “an investigation in 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 CFR 314.108(a).

⁶¹ “Essential to approval” means “with regard to an investigation, that there are no other data available that could support approval of the NDA.” 21 CFR 314.108(a).

⁶² “Conducted or sponsored by the applicant” is defined, in relevant part, as “that 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, or the applicant or the applicant’s predecessor in interest, provided substantial support for the investigation.” 21 CFR 314.108(a).

The second clause in section 505(c)(3)(E)(iii) of the FD&C Act (underlined), often referred to as the bar clause, describes which 505(b)(2) NDAs will be barred or blocked from approval by the 3-year exclusivity and thus describes the scope of 3-year exclusivity. The Agency's interpretation of the bar clause and thus a determination of the scope of 3-year exclusivity under section 505(c)(3)(E)(iii) involves two steps. One step of the scope inquiry focuses on the drug at issue. The phrase "such drug in the approved subsection (b) application" in the bar clause refers to the earlier use of the term "drug" in the eligibility clause. The term "drug" in the eligibility clause refers to "a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application," that is, the drug which includes a previously approved active moiety. Thus, for a single-entity drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity.⁶³

The second step of the scope inquiry focuses on the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant. Under this aspect of the inquiry, the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant determines the "conditions of approval" for which certain subsequent applications are barred.

Although neither the statute nor the regulations defines the phrase *conditions of approval* for purposes of determining the scope of 3-year exclusivity,⁶⁴ the preamble to FDA's proposed rule governing exclusivity (1989 Proposed Rule)⁶⁵ provides the Agency's interpretation. It makes clear FDA's view that 3-year exclusivity covers the innovative change that is supported by the new clinical investigations:

Exclusivity provides the holder of an approved new drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product. Thus, if the innovation relates to a new active moiety or ingredient, then exclusivity protects the pioneer drug product from other competition from products containing that moiety or ingredient. If the innovation is a new dosage form or route of administration, then exclusivity protects only that aspect of the drug product, but not the active ingredients. If the innovation is a new use, then exclusivity protects only that labeling claim and not the active ingredients, dosage form, or route of administration.⁶⁶

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

⁶³ See Letter from Janet Woodcock, M.D., Director, CDER, FDA to William H. Carson, M.D., President & CEO, Otsuka Pharmaceutical Development & Commercialization, Inc. and Ralph S. Tyler, Esq., Venable L.L.P. (Oct. 5, 2015) (Docket No. FDA-2015-P-2482), aff'd *Otsuka Pharmaceutical Co. v. Burwell*, Case No. 1:15-cv-01688-KBJ (D.D.C. July 28, 2016) (upholding FDA's conclusion that, for a single-entity drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity), aff'd *Otsuka Pharmaceutical Co. v. Price*, No. 16-5229 (D.C. Cir. Aug. 29, 2017).

⁶⁴ 21 CFR 314.108(a) and 314.108(b)(4)(iv).

⁶⁵ See generally, Abbreviated New Drug Application Regulations, 54 FR 28872 (July 10, 1989) (1989 Proposed Rule).

⁶⁶ 1989 Proposed Rule at 28896-97.

the scope of the approval and does not cover aspects of the drug product for which new clinical investigations were not essential. Courts have upheld FDA's view of the relationship between *new clinical investigations* that were essential to the approval and the scope of 3-year exclusivity.⁶⁷

Thus, in the case of an application submitted for a single-entity drug that contains a single active moiety that has been previously approved (a non-NCE), if the application contains reports of new clinical investigations essential to approval of the application that were conducted or sponsored by or for the applicant, section 505(c)(3)(E)(iii) bars FDA from approving a 505(b)(2) NDA for such drug (i.e., another single-entity drug containing that active moiety) for the exclusivity-protected conditions of approval for a period of 3 years. This exclusivity, however, does not bar FDA from approving a 505(b)(2) NDA for a drug containing a different active moiety. Neither does it block a 505(b)(2) NDA that does not otherwise seek approval for the exclusivity-protected conditions of approval (i.e., the conditions of approval for which new clinical investigations were essential).

B. Effect of Previously Approved Drug Products on Scope of 3-Year Exclusivity

Generally speaking, the scope of 3-year exclusivity for a drug product may be affected by a previously approved drug product containing the same active moiety. In practice, where two single-entity drug products that have the same active moiety are sequentially approved, the result may be that the scope of exclusivity of the second drug product is limited – often narrower in scope – relative to any exclusivity recognized for the first drug product. This “narrowing” concept, and its statutory and regulatory basis, is described below.

As stated above, 3-year exclusivity provides the holder of an approved NDA limited protection from new competition in the marketplace for the exclusivity-protected “conditions of approval,” which FDA has interpreted to be the *innovation represented by its approved drug product* that is supported by new clinical investigations essential to approval.⁶⁸ Exclusivity is recognized only for new clinical investigations that are “essential to approval,” which “means, with regard to an investigation, that there are no other data available that could support approval of the NDA.”⁶⁹

⁶⁷ *Veloxis Pharms, Inc. v. U.S. Food & Drug Admin.*, 109 F. Supp. 3d 104, at 115-24 (D.D.C. 2015); *Zeneca Inc. v. Shalala*, No. CIV.A. WMN-99-307, 1999 WL 728104, at *12 (D. Md. Aug. 11, 1999) *aff'd*, 213 F.3d 161 (4th Cir. 2000) (“The exclusivity extends only to the ‘change approved in the supplement’”); *AstraZeneca Pharm. LP v. Food & Drug Admin.*, 872 F. Supp. 2d 60, 79 (D.D.C. 2012) *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013) (“[T]he Court concludes that 21 U.S.C. § 355(j)(5)(F)(iv) is ambiguous. The FDA has reasonably interpreted and applied the applicable statute . . .”). Although the latter two cases involved the parallel statutory provision for ANDAs, rather than the provision at issue here (i.e., section 505(c)(3)(E)(iii)), the provision pertaining to ANDAs interpreted by the courts includes the same language regarding the scope of 3-year exclusivity. The courts upheld as reasonable FDA's interpretation of the relationship between the scope of clinical studies that earned exclusivity, the change in the product that resulted, and the scope of the exclusivity earned.

⁶⁸ 1989 Proposed Rule at 28896-97.

⁶⁹ 21 CFR 314.108(a). See 59 Fed. Reg. 50338, 50357 (Oct. 3, 1994) (“The phrase ‘essential to the approval’ suggests that the clinical investigations that warrant exclusivity must be vital to the application or supplement . . . ‘[T]o qualify for exclusivity, there must not be published reports of studies other than those conducted or sponsored by the applicant, or other information available to the agency sufficient for FDA to conclude that a proposed drug product or change to an already approved drug product is safe and effective.’” (internal citations omitted)); 1989 Proposed Rule at 28900 (“In addition, there must not be an already approved drug product for which the applicant

Exclusivity does not cover aspects of the drug product for which new clinical investigations were not essential.

This link between the scope of exclusivity and the new clinical investigations essential to approval means that, in assessing the scope of 3-year exclusivity for a single-entity drug product containing the same active moiety as a previously approved single-entity drug product, the Agency looks at the innovative change(s) represented by the later-approved drug product relative to the previously approved drug product. Exclusivity for the later-approved drug product cannot cover any condition of approval for which “new clinical investigations” were not “essential.” If an earlier-approved drug product was approved for a particular condition of approval, new clinical investigations would not be considered “essential” to support the same condition of approval for a later-approved drug product containing the same active moiety. Rather, the new clinical investigations would be considered essential only to support a condition of approval for the later-approved drug product that is different from the condition of approval of the earlier-approved drug product. Because 3-year exclusivity generally covers only the differences from a previously approved product, as a practical matter a later-approved product is likely to have a narrower scope of exclusivity than the product approved previously.

FDA believes that this interpretation of the statutory language is consistent with Congressional intent. The legislative history indicates that Congress intended 3-year exclusivity to protect only innovations that required the support of new clinical investigations essential to approval.⁷⁰ Under FDA’s interpretation, the scope of 3-year exclusivity generally does not cover an innovation already approved for another drug product containing the same active moiety. A drug product may, however, qualify for exclusivity for an aspect that differs from the earlier-approved drug product, thus providing a continued exclusivity incentive – albeit one that is typically narrower in effect – to conduct new clinical investigations of previously approved drugs.

An example helps illustrate this interpretation in practice:

- The scope of exclusivity based on new clinical investigations that establish *for the first time* that an active moiety previously approved only as a single-entity, IR oral drug product can be formulated as a safe and effective extended-release oral drug product could potentially block approval of subsequent 505(b)(2) NDA for a single-entity, extended-release drug product containing that active moiety.
- Any determination of the scope of exclusivity for a subsequent 505(b)(2) NDA for an extended-release drug product containing the same active moiety would generally follow the framework described above in which the innovative change(s) represented by this product would be assessed relative to the first approved extended-release product. If, for instance, the subsequent product uses different extended-release technology for which

could submit an ANDA or 505(b)(2) application. . . . A study will not be considered essential to approval merely because it was necessary for the applicant to conduct the study to avoid the exclusivity of the pioneer and obtain an immediate effective date of approval.”).

⁷⁰ See 59 Fed. Reg. at 50358.

new clinical investigations were essential, the scope of exclusivity for this subsequent product would only cover this innovative change.⁷¹

⁷¹ See Letter from R. Albrecht, FDA to M. McGuiness, Veloxis Pharmaceuticals, Inc., at 45-49 (Jan. 12, 2015).

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/s/

BRENDAN MUOIO
09/15/2017



NDA 204325

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Dorothy J. Engelking
Vice President, Regulatory Affairs

Dear Ms. Engelking:

Please refer to your New Drug Application (NDA) dated and received November 15, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Amphetamine Extended-Release Oral Suspension, 1.25 mg/mL.

We also refer to your correspondence, dated and received May 19, 2017, requesting review of your proposed proprietary name, Adzenys ER.

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

If any of the proposed product characteristics as stated in your May 19, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Alycia Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4270. For any other information regarding this application, contact Brendan Muoio, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4518.

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
08/11/2017

**PeRC Meeting Minutes
August 9, 2017**

PeRC Members Attending:

John Alexander

Gettie Audain

Meshaun Payne

Donna Snyder

Lily Mulugeta

Wiley Chambers

Greg Reaman

Jinging Ye

Raquel Tapia

Gilbert Burkhart

Dionna Greene

Hari Cheryl Sachs

Thomas Smith

Daiva Shetty

Ikram Elyam

Jackie Yancy

Rosemary Addy

Julia Pinto

Belinda Hayes

Barb Buch

Adrienne Hornatko-Munoz

Agenda

NON-RESPONSIVE

9:00

9:20

9:40

NDA 204325

Adzenys Extended Release
Partial Waiver/Assessment
(with Agreed iPSP)

DPP

Brendan Muoio

Treatment of ADHD in
patients 6 years and older

NON-RESPONSIVE

9:55

10:15

10:35

10:45

Adzenys Extended Release Partial Waiver/Assessment (with Agreed iPSP)

- Proposed Indication – Treatment of ADHD in patients 6 years and older
- The PeRC questioned whether this product triggers PREA, because there is an extended release oral suspension (Dyanavel XR). Therefore, we cannot require studies in the 4-5 year age group.
- *PeRC Recommendations:*
 - The PeRC recommended the division discuss with the sponsor the possibility of them conducting studies in the 4-5 year age group; however, this cannot be required under PREA.

NON-RESPONSIVE

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/s/

MESHAUN L PAYNE
08/23/2017



NDA 204325

**INFORMATION REQUEST
PATENT CERTIFICATION OR VERIFICATION**

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

Dear Ms. Engleking:

Please refer to your New Drug Application (NDA) dated and received November 15, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for amphetamine extended-release 1.25 mg/mL oral suspension.

We also refer to your amendments dated December 29, 2016, January 11, 2017, and February 17, 2017. These amendments do not comply with 21 CFR 314.60(f), which was added by the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (October 6, 2016). The final rule became effective on December 5, 2016.

Section 314.60(f) requires that an amendment to an unapproved 505(b)(2) application contain an appropriate patent certification or statement described in 21 CFR 314.50(i), or a "recertification" for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

- To add a new indication or other condition of use;
- To add a new strength;
- To make other than minor changes in product formulation; or
- To change the physical form or crystalline structure of the active ingredient.

If an amendment to the 505(b)(2) application does not contain a patent certification (or recertification) or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described above.

We recommend that the cover letter for your response to this information request and for future amendments to your unapproved 505(b)(2) application either:

- 1) state that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or

- 2) verify that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

Your response to this information request must clearly reference your amendments dated December 29, 2016, January 11, 2017, and February 17, 2017.

If you have any questions, contact me at (240) 402-4518 or brendan.muio@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Brendan Muoio, PharmD, RAC
Senior Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

BRENDAN MUOIO
03/02/2017



NDA 204325

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Neos Therapeutics, Inc.
2940 N. Hwy 369
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 and received November 15, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Amphetamine Extended-Release Oral Suspension, 1.25 mg/mL.

We also refer to

- Your correspondence dated and received November 30, 2016, requesting review of your proposed proprietary name, Adzenys ER ^{(b) (4)}
- Your amendment to the Request for Proprietary Name Review, dated and received, December 2, 2016.

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

 (b) (4)

 (b) (4)

We recognize that our conclusion differs from the (b) (4) external name study submitted in support of the proposed proprietary name. However, (b) (4) did not provide a safety assessment (b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, 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 the contents of this letter or any other aspects of the proprietary name review process, contact Alycia Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4270. For any other information regarding this application, contact Brendan Muoio, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4518.

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/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
02/27/2017



NDA 204325

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

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

Dear Ms. Engelking:

Please refer to your New Drug Application (NDA) dated and received November 15, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Adzenys ER ^{(b) (4)} (amphetamine extended-release) 1.25 mg/mL oral suspension.

We also refer to your amendments dated November 30, 2016, December 2, 2016, December 29, 2016, and January 11, 2017.

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 September 15, 2017.

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 August 1, 2017.

During our filing review of your application, we identified the following potential review issues:

Product Quality

1. Provide a table with the drug product composition of each drug product batch used to support this application, including developmental, clinical, previous, and newly prepared batches. Include a description of the use of each batch (e.g., microbiological studies, stability studies, clinical studies).
2. Provide in-use stability data demonstrating that the drug product quality remains unaffected through the longest expected period of use at the lowest dose, with daily withdrawals from the container. Assess drug product quality attributes including, but not limited to assay, dose uniformity, and related substances.
3. The storage and handling section of the drug product label indicates that the pharmacist should provide an oral dosing syringe or other suitable measuring device. Provide drug product assay data demonstrating that the labeled doses can be reliably delivered to the patient (in the labeled 3.1 mg increments) when administered using a range of typical delivery devices.
4. The sample preparation procedure for the resuspendibility analytical method indicates that the drug product is to be shaken (b) (4). The label indicates that the drug product must be shaken before use but does not indicate a length of time. Determine the minimum amount of time required to shake the drug product to assure content uniformity.
5. Perform an extractable/leachable study to confirm that the container closure system does not adversely impact the drug product per the guidance for industry, "Container Closure Systems for Packaging Human Drugs and Biologics." Alternatively, provide a justification as to why this study is not necessary.
6. We remind you of the comments from the Agency during the End of Phase 2 meeting from May 22, 2013, and the pre-NDA meeting July 2, 2014. Therein, the Agency recommended that appropriate tests and acceptance criteria for any identified extractables and leachables and deliverable volume be established as part of the release and stability testing. Provide release and stability results for these parameters. Alternately, provide justification, supported by data, for not including these attributes in the proposed drug product specifications.
7. Batch analysis results for assay range from (b) (4)% to (b) (4)%. (b) (4)
(b) (4) Explain the cause for consistently manufacturing batches in the (b) (4)
(b) (4)
8. As part of the stability data discussion you note that all attributes have successfully met the stability acceptance criteria and that the results support a (b) (4) month shelf life; however, the evaluation of the data cannot be found in the application. The ICH Q1E guideline, "Evaluation for Stability Data," provides recommendations on how to use stability data generated to propose a shelf life. ICH Q1E specifically indicates that "a systematic evaluation of the data from formal stability studies should be performed" and that "stability data for each attribute should be assessed sequentially." As described in ICH Q1E, present and evaluate stability information to support the proposed (b) (4) month shelf life.
9. Provide information on how the drug product manufacturing date is set as it is currently unclear.
10. Indicate whether a risk assessment has been performed to identify potential sources for introduction of Burkholderia cepacia complex organisms (BCC) during the manufacturing process and describe any steps that are taken to minimize the risk of BCC organisms in the final drug product. It is recommended that potential sources are examined and sampled (b) (4)

(b) (4) These may include raw materials (e.g., (b) (4)) and the manufacturing environment.

Nonclinical

1. For completeness, a review of nonclinical literature from April, 2012, to the present should be submitted to the application for review.
2. The safety evaluation of the inactive ingredients is a review issue at this time. Provide a summary table of inactive ingredients in the new formulation compared to the Reference Listed Drug (RLD), Adderall XR (NDA 021303), along with the threshold limits for each ingredient based on use in other FDA-approved drugs.
3. A brief review of the list of inactive ingredients indicates that there are three ingredients (b) (4) namely, sorbitol, propylene glycol, and xanthan gum. As indicated in the pre-NDA meeting for IND 110281 (minutes dated July 2, 2014), a detailed summary of nonclinical and/or clinical data that addresses the safety of the levels of sorbitol should be submitted for review. The summary should address safety perspectives based on total amounts of sorbitol rather than percentages of sorbitol in the drug product, and should include safety margins as well. Potential toxicity in conjunction with sodium polystyrene sulfonate (SPS) should also be addressed.

Regulatory

1. Your application appears to reference information in your Adzenys XR ODT application, NDA 204326. Please identify the information in NDA 204326 that you are referencing to support approval of this application for amphetamine extended release oral suspension.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

1. The length of Highlights must be one-half page or less unless a waiver has been granted in a previous submission. The Highlights Boxed Warning does not count against the one-half page requirement.
2. A horizontal line must separate:
 - Highlights from the Table of Contents, **and**
 - Table of Contents from the Full Prescribing Information.
3. White space should be present before each major heading in Highlights. There must be no white space between the Highlights Heading and Highlights Limitation Statement. There must be no white space between the product title and Initial U.S. Approval.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by February 17, 2017. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

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

PROMOTIONAL MATERIAL

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

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

We note that you have submitted pediatric studies with this application for pediatric patients 6 to 12. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

This drug may be appropriately labeled for use in pediatric patients 13 to 17. We will notify you if the current pediatric labeling for that age group is not adequate.

If you have any questions, contact Dr. Brendan Muoio, Senior Regulatory Project Manager, at (240) 402-4518 or brendan.muio@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

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/s/

MITCHELL V Mathis
01/26/2017



IND 110281

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) of the Federal Food, Drug, and Cosmetic Act for Amphetamine (b) (4) Extended-Release Oral (b) (4) Suspension.

We also refer to the meeting between representatives of your firm and the FDA on June 19, 2014. The purpose of the meeting was to provide the Division with the outline and content of your proposed 505(b)(2) NDA and gain concurrence that you have a complete application that is fileable for your product (Amphetamine (b) (4) Extended-Release Oral (b) (4) Suspension) in the treatment of Attention Deficit Hyperactivity Disorder.

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



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA Meeting
Meeting Date and Time: June 19, 2014; 11:00 am – 12:00 pm EDT
Meeting Location: 10903 New Hampshire Avenue
 White Oak Building 22, Conference Room: 1315
 Silver Spring, Maryland 20903
Application Number: IND 110281
Product Name: Amphetamine (b) (4) Extended-Release Oral (b) (4) Suspension
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)
 Mark Ritter, M.D. Medical Team Leader (acting), DPP
 Christina Burkhart, M.D. Medical Reviewer, DPP
 Linda Fossom, Ph.D. Pharmacology/Toxicology Team Leader, DPP
 Shiny Mathew, Ph.D. Pharmacology/Toxicology Reviewer, DPP
 Hao Zhu, Ph.D. Clinical Pharmacology, Team Leader
 David Claffey, Ph.D. CMC Lead, Office of New Drugs QA (ONDQA)
 Wendy Wilson-Lee, Ph.D. CMC/Product Quality Reviewer, ONDQA
 Okpo Eradiri, Ph.D. Biopharmaceutics Reviewer, ONDQA/OPS
 Bryan S. Riley, Ph.D. Team Leader (acting), New Drug Microbiology Staff
 CDER/OPS
 Kofi Ansah, Pharm.D. Senior Regulatory Project Manager, DPP

Neos Therapeutics, Inc.’s Attendees:

Name	Title and Affiliation
Mark Tengler	Chief Technical Officer, Neos Therapeutics, Inc.
Dorothy Engelking	Vice President, Regulatory Affairs, Neos Therapeutics, Inc.
Vipin Garg, Ph.D.	President & Chief Executive Officer, Neos Therapeutics, Inc.
Carolyn Sikes, Ph.D.	Vice President, Clinical Development, Neos Therapeutics, Inc.
Jeff Young	Director, Chemistry Manufacturing & Controls, Neos Therapeutics, Inc.
	(b) (4)

Meeting Minutes

1.0 BACKGROUND

Neos Therapeutic Inc. has requested for a Type B, Pre-NDA meeting to discuss the contents of the planned 505(b)(2) NDA for Amphetamine Extended Release (XR) Oral Suspension. The specific objective of the meeting is to provide the Division with the outline and content of the proposed 505(b)(2) NDA and gain concurrence that Neos has a complete application that can be accepted for filing.

Neos has developed a new Amphetamine Extended Release (XR) Oral Suspension formulation that is bioequivalent to ADDERALL XR 30 mg (extended-release mixed amphetamine salts), the reference listed drug (RLD). According to the sponsor, the new formulation provides a bioequivalent in vivo drug release profile through the use of immediate-release and delayed-release forms of amphetamine resinate loaded with a 3:1 ratio of d- and l-isomers. (b) (4)

The dose and dosing schedule for the Amphetamine XR Oral Suspension is the same as that of ADDERALL XR. The product can be dosed in the same equivalent Mixed Amphetamine Salt dosage strengths as ADDERALL XR: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg & 30 mg by administration of different amounts of the suspension ((2.5 mL = 5 mg MAS).

A pre-IND meeting was held on January 13, 2011 in which preliminary development plans were discussed with the Division. The Division agreed that a 505(b)(2) could be supported through proof of bioequivalence to the RLD, ADDERALL XR. The Division indicated that demonstration of bioequivalence of the oral suspension formulation to the RLD would require that the fasted PK time-course match that of the RLD (based on relevant partial AUCs).

The first formulation of the oral suspension formulation that Neos developed was bioequivalent to the RLD in all requested bioequivalence parameters (b) (4) however, during stability testing, an unexpected impurity was identified. Neos conducted studies to determine the nature of the impurity (b) (4)

(b) (4) Neos reformulated the product, replacing the (b) (4) with sorbitol, and conducted new bioavailability/ bioequivalence and food effect studies (NT020 1.1005 and NT0201.1006) against the RLD (ADDERALL XR). In addition, Neos is conducting a pediatric bioavailability study (NT0201.1004) which is currently ongoing. The pediatric bioavailability study (NT0201.1004) should be completed prior to NDA submission.

The complete clinical development program proposed to support a 505(b)(2) NDA submission for Amphetamine Extended Release Oral Suspension is provided in the sponsor's Table 3 :

Table 3: Clinical Development Program for Amphetamine Extended Release Oral Suspension

Protocol Number/ Study Description	Design/Dose	Objectives	Status
NT0201.1005 Bioequivalence/ Bioavailability Study	Open Label Randomized Crossover Single Dose 30 mg Amphetamine XR Oral Suspension vs. 30 mg ADDERALL XR	To demonstrate the BE of Amphetamine XR Oral Suspension to ADDERALL XR in the fasted state	Complete BE parameters met
NT0201.1006 Fasting/Fed with Fed Bioequivalence	Open Label Randomized Crossover Single Dose 30 mg Amphetamine XR Oral Suspension (fed and fasted) vs. 30 mg ADDERALL XR (fed only)	To demonstrate the relative BA of Amphetamine XR Oral Suspension under fasting and fed conditions and to demonstrate BE of Amphetamine XR Oral Suspension to ADDERALL XR in the fed state	Complete No food effect demonstrated for test formulation; BE parameter not met for AUC ₀₋₅ vs. RLD in the fed state

Protocol Number/ Study Description	Design/Dose	Objectives	Status
NT0201.1004 Pediatric Bioavailability	Single Dose 30 mg Amphetamine XR Oral Suspension, Open- Label, Single-Period, One-Treatment	To determine the PK of Amphetamine XR Oral Suspension in children ages 6-12 (stratified into 3 groups: one group 6-7 years old, one group 8-9 years old, one group 10- 12 years old) in the fasted state	Ongoing

NT020 1.1005 BE Study

The sorbitol formulation was demonstrated to be bioequivalent to the RLD (ADDERALL XR), under fasted conditions, based on standard bioequivalence metrics (C_{max}, AUC_{0-last}, AUC_{0-inf}) and all partial AUCs (AUC₀₋₅, AUC₅₋₁₂, and AUC_{5-last}) and was selected for further clinical development.

NT020 1.1006 Fed/Fast BE Study

There was no significant food effect for Amphetamine XR Oral Suspension.

Comparison of the test product in the fed state vs. ADDERALL XR in the fed state was also conducted in this study. The ingestion of a standardized meal prior to administration of

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ADDERALL XR decreased C_{max} and delayed T_{max} of the RLD. When comparing the test formulation to ADDERALL XR under fed conditions, the 90% confidence intervals for comparing early systemic exposure, based on $\ln(AUC_{0-5})$ showed less of a food effect and therefore were not within the accepted 80% to 125% limits for either *d*- or *l*-amphetamine.

Neos concludes that because ADDERALL XR is assumed to be safe and effective when administered in the fasted state and since the test formulation is bioequivalent to the RLD in the fasted state, the observation that the test formulation PK demonstrates no significant change in C_{max} and T_{max} when administered with a standardized meal infers that the test formulation is also safe and effective when administered with food.

Initial Pediatric Study Plan (iPSP)

The Agency agreed with the sponsor's iPSP. The sponsor has requested a waiver for the study of this product in children less than 6 years of age. The sponsor intends to reference existing data from the RLD to support the inclusion of adolescents in the prescribing information and the sponsor plans to provide data for children 6 to 12 years of age (PK bioavailability study NTO201.1004).

2.0 DISCUSSION (Questions from the Sponsor and FDA Responses)

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

2.1. General (administration) Questions

Question 1: Neos has assessed all issues in the Regulatory History section, Table 4, as being fully resolved. **Does the Division concur?**

Preliminary Comments: *There are no outstanding issues from a clinical perspective.*

From a CMC perspective, we agree that all CMC comments have been addressed. However, the adequacy of these responses is a review issue. Include the responses along with all of the supporting data and justifications in the NDA. We reserve the right to ask additional questions regarding these issues based on the review of the NDA in its entirety.

Discussion at Meeting: *No further discussion.*

Question 2: Neos has conducted all of the agreed upon clinical studies as noted in Section 4, Background. No additional clinical studies with the amphetamine XR oral suspension are planned. **Are there any other outstanding issues related to the product or clinical program that require resolution prior to the submission of the NDA?**

Preliminary Comments: *There are no outstanding issues from a clinical perspective.*

From a CMC perspective, this does not apply.

Discussion at Meeting: *No further discussion.*

Question 3: Does the Division agree that the proposed content and format of the NDA as described below are adequate to support an acceptable filing of a 505(b)(2) NDA?

Preliminary Comments: *We agree that the proposed content and format are adequate to support filing.*

Discussion at Meeting: *No further discussion.*

2.2. Quality/CMC Questions

Question 4: Neos is proposing a scaled-up commercial process in the NDA. Table 7 contrasts the clinical/registration batch process to the proposed commercial process and provides an assessment of the impact of any changes. Neos believes the current registration batch stability program fully supports the proposed commercial process as the resultant intermediate product and finished product meets all quality attributes defined for the product. **Does the Division concur?**

Preliminary Comments: *Based on our review of the information submitted, we determined that the aggregate of process and formulation changes has the potential to have a significant impact on drug product performance. These changes may potentially impact in-vitro and in-vivo release characteristics of your proposed modified-release product. You should, therefore, conduct a bioequivalence study to bridge the commercial to the clinical product. In addition, submit comparative multipoint dissolution data within the NDA in support of the proposed changes in the commercial product relative to the clinical product; the dissolution testing of the commercial and clinical products should be compared as described in Sections IV and VIII of the SUPAC-MR Guidance (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070640.pdf>). The in-vitro alcohol dose dumping studies should be repeated with the proposed commercial product. Based on the results of the BE study, we may accept a reduced stability package (e.g., six months for three batches of highest and lowest strengths) provided that the results demonstrate comparable clinical performance.*

Several of the proposed changes have the potential to impact (b) (4) Recent development studies appear to indicate that some of these changes have not had an immediate impact on the delayed release characteristics. However, changes on storage are also of concern, as changes in drug release are evident in the initial stability time points on the clinical batches. Our major concern is that changes to the commercial process and formulation could possibly result in dose dumping of the commercial product on storage.

Further, ICH Q1A states that the “manufacturing process used for primary batches should simulate that to be applied to production batches.” We accept that many of the changes

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proposed are due to scale-up and recent process development. We agree that many of the individual changes appear to be low risk,

[Redacted]

Discussion at Meeting: *Neos made the following clarifications:*

- [Redacted]
- [Redacted]
- *Neos considered the list of process changes to be improvements but acknowledged that the process was also different to that used for the clinical batches.*

The Agency's response:

- *The Division reiterated that data would be required to demonstrate that the process differences did not result in a product that is significantly different from that used in the clinic.*
- [Redacted]

Neos and the Agency agreed:

- [Redacted]
- *The sponsor stated that they would submit release and stability data to the IND prior to submission of the NDA on three lots of the highest and lowest strength products which were manufactured using the proposed commercial process. The Agency agreed to evaluate these data and provide feedback on whether a BE study would still be required.*

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- *If the alcohol dose-dumping dissolution experimental results for the commercial formulation are similar to the ODT or the pre-change suspension, the same approach should be used to address any observed dose-dumping.*

Post-Meeting Note: *We encourage you to provide as much stability data as possible (e.g., at least six months) in the IND for our evaluation. It would be helpful to have additional stability time points (e.g., 1 & 3 months) in the ambient and accelerated studies to determine if any trends are present.*

Question 5: The proposed finished product specifications for release and stability have been chosen based upon FDA Guidance ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (December 2000). Specification attributes have been selected that are appropriate for a modified release suspension drug product. **Does the Division agree with the selected release and stability tests for the drug product?**

Preliminary Comments: *This is a review issue. Table 7 of the meeting package indicates that an (b) (4) method will be implemented for drug substance identification in the drug product. However, the method listed in Table 8 is HPLC. Confirm which analytical method will be used for the commercial drug product.*

(b) (4)

If a product specific dosing device will be provided, include in the submission evidence that the dosing device delivers the labeled amount of drug product. Also, provide evidence that the dosing device is compatible with the drug product.

Discussion at Meeting: *The sponsor clarified that the (b) (4) method would not be used. The (b) (4) HPLC methods would be used for identity testing. The Agency agreed that this appeared appropriate as (b) (4) methods would be employed.*

Other Comments: (b) (4)

(b) (4)

Excipient Qualification – We cautioned the sponsor about relying solely on the percent data available in the Inactive Ingredients Guide. The sponsor is encouraged to demonstrate the

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amount of sorbitol present in the proposed product is qualified based on daily dose in terms of milligrams.

Additional Comments from CMC Micro & Sterility Assurance Team

The finished product release specification should also include a test for Burkholderia cepacia complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see PDA J Pharm Sci Tech 2011; 65(5): 535-43.

In order to control for the presence of BCC in your product you should consider the following:

- 1. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined (b) (4) These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.*
- 2. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.*

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to ensure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.

For more information, we refer you to Envir Microbiol 2011; 13(1):1-12 and J. Appl Microbiol 1997; 83(3):322-6.

Discussion at Meeting: *No further discussion.*

Question 6: Does the Division concur that the registration stability program based on bracketing and proposed commercial stability commitment is appropriate and, with affirmative data, will

Discussion at Meeting: *No further discussion.*

2.3. Non-Clinical Study Reports Questions

Question 7: In NDA 204326, for a related Neos formulation (amphetamine extended release orally disintegrating tablets (XR-ODT), Neos conducted a thorough literature search from October 11, 2001 (the date of Adderall XR approval) to April 12, 2012 pertaining to the nonclinical toxicology, pharmacology, and pharmacokinetics of amphetamines, as well as the clinical efficacy and safety of amphetamines in relation to the treatment of ADHD. This review of the literature is presented in the NDA for that formulation (NDA 204326). In the proposed NDA for Amphetamine XR Oral Suspension (NDA 204325), Neos proposes to electronically cross reference the literature search performed for NDA 204326. In addition, we propose to (1) perform a literature search from the April 12, 2012 cutoff date to May 16, 2014, the results of which would reside in Sections 4.3 and 5.4, respectively speaking, of the Amphetamine XR Oral Suspension NDA, and (2) summarize the results from both searches in the relevant Module 2 summary documents by briefly touching on the salient points from the first search while placing most of the emphasis on the results of the second search. **Does the Division concur with this approach?**

Preliminary Comments: *Yes, we agree.*

Discussion at Meeting: *No further discussion.*

Question 8: Neos proposes only the written summaries will be included to support the nonclinical pharmacokinetics, pharmacology, and toxicology of Amphetamine XR Oral Suspension; tabulated summaries will not be included. **Does the Division concur?**

Preliminary Comments: *Yes, we agree.*

Additional Nonclinical Comments

Regarding the excipients in your drug product, you should provide a justification, including available safety data, to support the levels of sorbitol in your drug product.

Discussion at Meeting: *The sponsor asked for some clarification and we replied that we do not consider sorbitol to be a “novel excipient,” but that our Chemists had alerted us that sorbitol might be present at levels high enough to require some evidence of clinical safety. From a*

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nonclinical perspective, we recommended that the sponsor provide with their NDA submission a summary of any nonclinical (or clinical) data from the public domain that would address the safety of sorbitol at the amounts that patients would ingest from this drug product. [Also, see CMC comments on Excipient qualification under Question 5, above.]

Question 9: The Summary of Clinical Efficacy (SCE), Module 2.7.3, will consist of the results of the literature search and a summary of the efficacy studies conducted in support of ADDERALL XR. Neos is seeking the Agency's agreement that our proposal is sufficient in lieu of a separate ISE in Module 5.3.5.3 (Reports of Analysis from More than One Study) as referenced in the Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document. **Does the Division Concur?**

Preliminary Comments: *A summary of the efficacy studies conducted in support of ADDERALL XR would not be necessary. You have indicated that you intend to rely on the Agency's finding of safety/effectiveness for Adderall XR. A 505(b)(2) applicant that seeks to rely on the Agency's finding of safety and/or effectiveness for a listed drug may rely on FDA's finding of safety and/or effectiveness as reflected in the FDA-approved labeling for the listed drug.*

Discussion at Meeting: *No further discussion.*

Question 10: Neos is seeking the Agency's agreement to utilize the Summary of Clinical Safety (SCS) in Module 2.7.4 in lieu of a separate Integrated Summary of Safety (ISS) in Module 5.3.5.3. **Does the Division concur?**

Preliminary Comments: *Yes, we agree.*

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,

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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>.

We note that you have an agreed upon PSP as communicated in our letter dated November 21, 2013.

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>.

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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.

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

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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.

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

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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

None.

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

/s/

MITCHELL V Mathis
07/02/2014



IND 110281

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) of the Federal Food, Drug, and Cosmetic Act for (b) (4) Amphetamine (b) (4) (b) (4) Oral (b) (4) Suspension.

We also refer to the meeting between representatives of your firm and the FDA on May 2, 2013. The purpose of the meeting was to discuss the results of your bioequivalence trial and food effect studies in the context of your clinical development program for an acceptable 505(b)(2) filing for the use of your Amphetamine (b) (4) Extended-Release Oral (b) (4) Suspension for the treatment of ADHD. 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 (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 B
Meeting Category: End of Phase 2 (EOP2)
Meeting Date and Time: May 2, 2013
Meeting Location: 2:00 pm – 3:00 pm EDT
Application Number: IND 110281
Product Name: (b) (4) Amphetamine (b) (4) Oral
 (b) (4) Suspension
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 (acting), Division of Psychiatry Products (DPP)
 Robert Levin, M.D. Medical Team Leader, DPP
 Christina Burkhardt, M.D. Medical Reviewer, DPP
 Linda Fossom, Ph.D. Pharmacology/Toxicology Supervisor, DPP
 Hao Zhu, Ph.D. Clinical Pharmacology, Team Leader
 Chhagan Tele, Ph.D. CMC Lead, Office of New Drugs QA (ONDQA)
 Okpo Eradiri, 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

Neos Therapeutics, Inc.’s Attendees:

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

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1.0 BACKGROUND

Neos Therapeutics requested an EOP2 Meeting (5/2/2013) to gain concurrence with the Division regarding the clinical development plan to support a 505(b)(2) application for Amphetamine (b)(4) Extended Release Oral (b)(4) Suspension for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). This 505(b)(2) application will reference NDA 21-303 Adderall XR® capsules extended-release mixed amphetamine salts.

Amphetamine (b)(4) Extended Release Oral (b)(4) Suspension (AMP XR (b)(4)) is an extended-release, oral (b)(4) suspension (b)(4) formulation of amphetamine (b)(4) (AMP) equivalent to 30mg/15 mL mixed amphetamine salts. The dose and dosing schedule for AMP XR (b)(4) is intended to be the same as that of Adderall XR® Mixed Amphetamine Salts (MAS), the reference listed drug (RLD). Neos states that AMP XR (b)(4) can be dosed in the same equivalent Mixed Amphetamine Salt dosage strengths as Adderall XR: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg & 30 mg by administration of different amounts of the liquid suspension.

The sponsor has completed bioequivalence and food effect studies in support of the submission of this new drug application. The bioequivalence study (Protocol NT0201.1005) was conducted on three different formulations of AMP XR OLS. Test Formulation #2 of NT0201 (equivalent to 30 mg mixed amphetamine salts/15 mL) was demonstrated to be bioequivalent to the RLD (Adderall XR), under fasted conditions, based on standard bioequivalence metrics (C_{max} , AUC_{0-last} , AUC_{0-inf}) and all partial AUCs (AUC_{0-5} , AUC_{5-12} , and AUC_{5-last}) and was selected for further clinical development by the Sponsor.

The sponsor has also conducted a food effect study (NT0201.1006) comparing AMP XR OLS and Adderall XR. The 90% confidence interval for comparing the peak concentration of NT0201 administered after a standard meal to that of NT0201 administered after a ten hour fast, based on $\ln(C_{max})$, was within the accepted 80% to 125% limits for *d*- and *l*-amphetamine. The 90% confidence intervals for comparing total systemic exposure of NT0201 administered after a standard meal to that of NT0201 administered after a ten hour fast, based on $\ln(AUC_{0-last})$ and $\ln(AUC_{0-inf})$, were within the accepted 80% to 125% limits for *d*- and *l*-amphetamine. Neos has concluded that there is no significant food effect for AMP XR OLS.

Bioequivalence Results in the Fed State (AMP XR OLS (Fed state) vs. Adderall XR (Fed state): The 90% confidence interval for comparing the peak concentration of NT0201 administered after the feeding of a standard meal to that of Adderall XR administered after a standard meal, based on $\ln(C_{max})$, was within the accepted 80% to 125% limits for *d*- and *l*-amphetamine. The 90% confidence intervals for comparing late and total systemic exposure NT0201 administered after the feeding of a standard meal to that of Adderall XR administered after a standard meal, based on $\ln(AUC_{0-last})$ and $\ln(AUC_{0-inf})$, were within the accepted 80% to 125% limits for *d*- and *l*-amphetamine. The 90% confidence intervals for comparing early systemic exposure, based on $\ln(AUC_{0-5})$ were *not* within the accepted 80% to 125% limits for either *d*- or *l*-amphetamine. In summary, Neos has concluded that AMP XR OLS (Formulation 2) is bioequivalent to the RLD (Adderall XR) under fasted conditions. This formulation was also bioequivalent to Adderall XR under fed conditions for C_{max} , as well as late and total systemic exposure. However,

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the 90% CI for early exposure (AUC_{0-5}) of the test formulation does not fall within the accepted 80% to 125% limits for either isomer. This lack of bioequivalence in the fed condition at early exposure is due to an early food effect for Adderall XR. The ingestion of a standardized meal prior to administration of Adderall XR decreased C_{max} and delayed T_{max} for the RLD. Neos states that this type of food effect on the RLD and on other modified-release formulations using (b) (4) has been demonstrated in the literature and is consistent with the fed/fasted data presented in the US prescribing information for Adderall XR.

The sponsor states that because Adderall XR is assumed to be safe and effective when administered in the fasted state, and since the test formulation is bioequivalent to the RLD in the fasted state, the observation that the test formulation PK demonstrates no significant change in C_{max} and T_{max} when administered with a standardized meal infers that the test formulation is also safe and effective when administered with food.

The proposed clinical development program to support a 505(b)(2) NDA submission for AMP XR (b) (4) is provided in the sponsor's Table 3:

Table 3: Clinical Development Program for AMP XR (b) (4)

Protocol Number/ Study Description	Design/Dose	Objectives	Status
NT0201.1005 Bioequivalence/ Bioavailability Study	Open Label Randomized Crossover Single Dose 30 mg AMP XR OLS vs. 30 mg Adderall XR	To demonstrate the BE of AMP XR OLS to Adderall XR in the fasted state	Complete BE parameters met
NT0201.1006 Fasting/Fed with Fed Bioequivalence	Open Label Randomized Crossover Single Dose 30 mg AMP XR OLS vs. 30 mg Adderall XR (fed only)	To demonstrate the relative BA of AMP XR OLS under fasting and fed conditions and to demonstrate BE of AMP XR OLS to Adderall XR in the fed state	Complete No food effect demonstrated for test formulation; BE parameter not met for AUC_{0-5} vs. RLD in the fed state
NT0201.1007 Pediatric BA	Single Dose open label	To determine the PK of AMP XR OLS in children ages 6-12	Planned

The sponsor notes that the Division has agreed to waive the requirement for conducting an additional alcohol interaction study on the AMP XR (b) (4) product, because the AMP XR Oral Disintegrating Tablet (ODT) product has already undergone such testing, and the mechanism for dose dumping would be similar (b) (4) to both products.

- (i) Neos Therapeutics requests FDA concurrence that the pharmacokinetic and bioequivalence studies of the test formulation in adult subjects be considered completed and be considered sufficient to support approval of a 505(b)(2) NDA. The sponsor believes that any differences in fed pharmacokinetics can be directly addressed in product labeling.

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

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

2.1. Clinical Pharmacology

Question 1 (Fasted Bioequivalence): The sponsor believes that the data presented from the bioequivalence trial of AMP XR OLS vs. Adderall XR demonstrates the test product is bioequivalent to the RLD. Does the Division concur?

Preliminary Comments: *On face, the data looks to be acceptable. But the final determination of Bioequivalence will be a review issue.*

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

Question 2 (Fed/Fasted and Fed Bioequivalence): The sponsor believes that the data presented from the fed/fasted and fed bioequivalence trial indicate that AMP XR OLS can be assumed to be safe and effective when given after eating with no additional clinical studies required for the submission of a 505(b)(2) NDA. Does the Division concur?

Preliminary Comments: *On face, the data looks to be acceptable. We concur that no additional clinical studies be required for the submission of a 505(b)(2) NDA.*

However, for your food effect study, we would like to request two additional analyses on partial AUC 0-5 hours (i.e., pAUC₀₋₅) for both d- and l-amphetamine. In one analysis, you should explore whether (pAUC₀₋₅) following the administration of NT0201 MAR CR under fed condition is significantly higher than that following the administration of Adderall XR under fed condition. In the second analysis, you should explore whether the pAUC₀₋₅ following the administration of NT0201 MAR CR under fasted condition is significantly higher than that under fed condition.

Discussion at Meeting: *The sponsor confirmed that additional analyses we requested will be included in the final clinical study report.*

2.2. Procedural

Question 3 (Proposed Complete Development Program): Based on the clinical data provided by the sponsor, and the proposed complete clinical development program, are there any additional requirements that the Division may have for the submission of a 505(b)(2) application?

Preliminary Comments:

CMC/Product Quality Comments - We offer the following ten (10) points for consideration to support drug product development and eventual submission of a marketing application.

1.  (b) (4)
2. 
3. 
4. *Characterize the leachables and extractables profile of the suspension in the intended commercial container closure system. This information is critical to demonstrating that the proposed container closure is compatible and suitable for use with the drug product.*
5. *Include a description of any proposed dosing device. Demonstrate that proposed dosing devices are compatible and suitable for use with the drug product. This includes demonstrating that the dosing device consistently delivers the required dose and demonstrating that the materials of construction are compatible with the drug product.*
6. *Evaluate that impact of bottle orientation during storage on drug product quality. In addition to samples stored upright, include in the stability program samples stored in alternative orientations such as horizontal or inverted. The stability program should support the drug product storage and handling instructions.*
7. *Include stability testing of the drug product at reduced humidity if the proposed commercial packaging is semi-permeable in accordance with ICH Q1A. The stability program should support the drug product storage and handling instructions.*
8. *Monitor the amount of free drug substance observed in the suspension over time as part of the stability program, establishing criteria as appropriate.*

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9. [REDACTED] (b) (4)
10. *The proposed established name [REDACTED] (b) (4) is not acceptable. Based on our current naming practices, the labeled strength should match the established name. Your proposal to use [REDACTED] (b) (4) would require that the labeled strength [REDACTED] (b) (4).*
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- [REDACTED] (b) (4) *Therefore, it is not an acceptable established name. We recommend the established name Amphetamine Extended Release Oral Suspension. The expressed strength of the drug product should be based on the amphetamine base with a salt equivalency statement included on the labels and in the labeling, if needed.*

Discussion at Meeting: *The sponsor followed-up on CMC points 1, 2, and 10.*

With regards to CMC point #1, the sponsor stated that they understood our concern and accept our comments for consideration. Regarding CMC point #2, the sponsor indicated that they used a performance base approach. We stated that these CMC points were provided for Neos' consideration to ensure that they provided the right set of data with their application.

With regards to CMC point #10, the sponsor stated that they accept our recommendation to use the established name, Amphetamine Extended Release Oral Suspension. But they asked that we re-evaluate our recommendation that the expressed strength of the drug product should be based on the amphetamine base with a salt equivalency statement included on the labels and in the labeling, if needed. We reiterated that these CMC points were provided for Neos' consideration to ensure that they provided the right set of data with their application and that substantive evaluation of such would be a matter for review, upon receipt of their NDA.

Biopharmaceutics Comments - *We notice from your briefing package that your proposed product comprises immediate-release and delayed-release portions of the drug. We have the following comments regarding the dissolution information that should be provided in your NDA.*

- 1) **Dissolution Test:** *Include the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:*
- a. *Solubility data for the drug substance in Acid and Buffer dissolution media;*
 - b. *Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as*

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the optimal test for your product. In particular, justification should be provided for the choice of rotation speed as well as the sampling time points for release testing. We suggest initial sampling time points of 0.25, 0.5, (b) (4) and 2 h in both Acid and Buffer stages, prior to selection of final time points.

- c. 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 with time (the percentage is based on the product's label claim)*
- d. Data to support the discriminating ability of the selected method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., \pm (b) (4)% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent; and*
- e. Include the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).*

2) Dissolution Acceptance Criteria: *For the selection of the dissolution acceptance criteria of your product, the following points should be considered:*

- a) 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).*
- b) Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).*
- c) Specifications in both the Acid and Buffer stages should be as follows, per USP:*
 - ◆ **End of Acid Stage:** *Individual tablets should be within (b) (4)% of label claim.*
 - ◆ **End of Buffer Stage:** *NLT (b) (4)%*

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA review stage. However, the acceptability of the proposed dissolution criteria for your product will be made during the NDA review process based on the totality of the provided dissolution data.

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- 3) *We are concerned that your extended release (ER) product may release its entire contents (“dose dumping”) when used with alcohol, thereby leading to safety concerns. Therefore, we recommend that you conduct a drug-alcohol interaction study with your ER product. You should conduct in vitro drug release testing initially using the highest strength and you may have to follow-up with an in vivo study, depending on the result of the in vitro testing. You should discuss the result of your in vitro study with the Agency prior to NDA submission.*
- a. *The following alcohol concentrations for the in vitro dissolution studies (using 12 units each) are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.*
 - b. *Generally a range of alcohol concentrations in 0.1 N HCl and the QC dissolution medium is recommended. If the optimal dissolution medium has not been identified, then dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.*
 - c. *Report f2 values to assess the similarity (or lack thereof) in the dissolution profiles.*
 - *Examine the shape of the dissolution profiles to see if the extended release characteristics are maintained, especially in the first 2 hours.*

The report should include the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study.

Discussion at Meeting: *The sponsor indicated that they had already conducted in vivo and in vitro testing for their product under their ODT program with the data previously submitted to that IND (i.e., IND 112991) and wanted to know if they needed to redo these studies. We stated that there was no need to redo these studies provided there are no changes to the formulation of the resinates and they reference the data submitted to their other NDA for the ODT.*

Division of Medication Error Prevention and Analysis (DMEPA) Comments - *We recommend the inclusion of an oral dosing device with your product to ensure the accurate delivery of your product. Including an oral dosing device with your product will help patients, parents, and other caregivers use the right amount of medication and ensure that the device has been reviewed for unclear markings or markings that are inconsistent with the labeled dosing of your product. The FDA has published a guidance titled Guidance for Industry: Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products. Although this guidance is specific to devices used with over-the-counter products, there may be information that is helpful to you as you develop your dosing device. Additionally, depending on the proposed dosing device, please be aware that a summative usability study may be required to determine whether intended users are able to correctly and safely use the dosing device.*

Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at:

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<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>.

Additionally, the Agency published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, Applying Human Factors and Usability Engineering to Optimize Medical Device Design and can be found online at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

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

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

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

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. 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.

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We encourage you to identify each section of their 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 (see table below). In your 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 the (b)(2) marketing application relies for approval. If you are proposing to rely on published literature, you should include copies of the article(s) in your submission.

Finally, 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.

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

3.0 OTHER IMPORTANT MEETING LANGUAGE SECTIONS:

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

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. For additional guidance on submission of the PSP, including a PSP

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Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

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>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

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/

MITCHELL V Mathis
05/22/2013



IND 110,281

Neos Therapeutics, Inc.
ATTENTION: Dorothy Frank
2940 N. Highway 360
Grand Prairie, TX 75050

Dear Ms. Frank:

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) (b) (4) Suspension.

We also refer to the meeting between representatives of your firm and the FDA on January 13, 2011. The purpose of the meeting was to discuss the current status and future plans for the development of your (b) (4) Amphetamine (b) (4) Suspension for Attention Deficit Hyperactivity Disorder (ADHD) in Adults.

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

If you have any questions, contact CDR Kofi Ansah, Senior Regulatory Project Manager, at (301)796-4158.

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

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 13, 2011
TIME: 1:00pm
LOCATION: White Oak CDER Bldg 22, Room 1419
APPLICATION: IND 110281
DRUG NAME: (b) (4) Amphetamine (b) (4) Suspension
TYPE OF MEETING: Type B PRE-IND Face-to-Face Meeting

MEETING CHAIR: Thomas Laughren, M.D.

FDA ATTENDEES:

Thomas Laughren, M.D.	Director, Division of Psychiatry Products (DPP)
Mitchell Mathis, M.D.	Deputy Division Director, DPP
Robert Levin, M.D.	Medical Team Leader
Christina Burkhart, M.D.	Medical Reviewer
Jogaro Gobburu, Ph.D.	Clinical Pharmacology, Team Leader
Andre Jackson, Ph.D.	Clinical Pharmacology Reviewer
Barry Rosloff, Ph.D.	Pharmacology/ Toxicology Supervisor
Linda Fossom, Ph.D.	Pharmacology/ Toxicology Team Leader
Shiny Mathew, Ph.D.	Pharmacology/Toxicology Reviewer
Chhagan Tele, Ph.D.	CMC Lead, Office of New Drugs QA (ONDQA)
ShinYe (Sandy) Chang, Pharm.D.	Regulatory Project Manager, DPP

Neos Therapeutics, Inc.'s Attendees:

Mark Tengler, B.S.	Co-President and Chief Technical Officer
Dorothy Frank, M.S.	Vice President, Regulatory Affairs
Russ McMahan, B.S.	Vice President, Research and Development
Carolyn Sikes, Ph.D.	Vice President, Clinical Development
(b) (4)	(b) (4)

Background:

Neos Therapeutics is developing a new (b) (4) oral formulation of (b) (4) amphetamine (b) (4). The product is intended to be bioequivalent to Adderall XR. The sponsor proposes to submit a 505(b)(2) application that references NDA 21-303 Adderall XR[®] (extended-release mixed amphetamine salts). The 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 and dextroamphetamine resinate. The formulation is comprised of an

(b) (4)

The sponsor proposes that the product have advantages over the existing solid dose product with respect to: 1) the ease of swallowing the product, 2) ease of dose scaling, and 3) improved patient adherence.

The clinical program for the (b) (4) amphetamine (b) (4) suspension will consist of: 1) a single-dose (30 mg) bioequivalence study (in fed and fasted states) comparing the product with Adderall XR[®] 30 mg in 24-36 healthy male and female adults >18 years of age, and 2) a PK study in pediatric patients (6-12 years-old). Neos plans to seek a waiver from the requirement to conduct a bioequivalence study in adolescents, reasoning that there are significant data demonstrating similar pharmacokinetic profiles of amphetamine between adolescents and adults. The sponsor states that pharmacokinetic studies of Adderall XR[®] demonstrated that the plasma kinetics of d- and l-amphetamine are linear over the proposed dose range after single oral doses in adults, adolescents, and children. Body weight appeared to be the primary determinant of differences in the pharmacokinetics of d- and l-amphetamine across the age range; the AUC and C_{max} decrease with increasing body weight. All of the significant differences in pharmacokinetics occurred between the pediatric population and the adult/adolescent populations. Children had higher clearances than adults on a mg/kg body weight basis. Thus, the sponsor proposes to conduct bioequivalence studies in adults and children.

The sponsor seeks confirmation from the Division that the proposed bioequivalence studies will support approval of a 505(b)(2) NDA application if the 90% confidence intervals for the C_{max}, T_{max}, and AUC for d- and l-amphetamines of the new formulation fall within 80% - 125% for the ratio of the product averages for C_{max}, T_{max}, and AUC for the RLD d- and l-amphetamine values.

Questions from the sponsor:

A. Biopharmaceutics

Question 1:

Neos is planning to conduct a single dose bioequivalence study comparing its new oral (b) (4) suspension formulation to the reference listed drug Adderall XR[®] 30 mg under fasting and fed conditions in adults age 18 or greater and a pharmacokinetic study in a pediatric population aged 6-12 years and 11 months. **Is this approach acceptable to the Division?**

Preliminary Comments:

This approach is reasonable. However, please refer to our response to Question 4 regarding the expectation to match the Adderall XR[®]'s PK time-course in a manner that also ensures matching of pharmacodynamic time-courses.

We would suggest that you consider conducting the adults study prior to the pediatric study. We would also suggest that a sufficient number of patients be studied for the planned pediatric study to adequately characterize the PK of the study drug. The full spectrum of age strata in the 6-12 year old continuum should be represented (e.g., 6-7, 8-9, 10-12) and should have at least 4 completers per stratum. We suggest that the study be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution ^{(b) (4)} in each age group. Depending on the outcome of the adult BE study the proposed PK study in pediatrics may also have to address tolerability.

Discussion at Meeting:

The sponsor agreed to conduct the adult study prior to the pediatric study.

Question 2:

The Reference drug labeling indicates a maximum dose of 30 mg once daily for children ages 6-12; the recommended adult dose is 20 mg once daily. The 30 mg dose of **Adderall XR[®]** is the reference listed drug in the Orange Book. Neos proposes to conduct the adult bioequivalence trial in healthy volunteers with the RLD of 30 mg. **Does the Division concur?**

Preliminary Comments:

This approach is acceptable.

Discussion at Meeting:

There was no further discussion.

Question 3:

The Sponsor, Neos, will be requesting approval for labeling identical to that of the RLD that describes dosing recommendations for treatment of ADHD in children (6-12 and 11 months), adolescents (13-17 and 11 months) and adults. Neos is proposing to do a full bioequivalence study in adult healthy volunteers and a pharmacokinetic study in pediatric patients. The proposed BE study, as currently planned, will study male and female individuals ≥ 18 years of age — late adolescence to adulthood. A separate PK study will determine the profile of the test formulation in pediatrics, given that on a mg/kg basis, children eliminate amphetamines faster than adults. The Sponsor will seek a waiver of the obligation to perform a similar study in the adolescent population aged 13-17 and 11 months on the grounds that, in light of information already available in the literature on pharmacokinetics of the API in adolescents, such a study will add no significant information to the other two proposed studies. **May we obtain the requested labeling without a specific study in an adolescent population (12-17 years and 11**

months) since the pharmacokinetic profile of d- and l-amphetamine is similar in adults and adolescents and apparent differences across the age range are largely determined by body weight?

Preliminary Comments:

This approach is acceptable depending upon the outcome of the BE study in adults.

Discussion at Meeting:

There was no further discussion.

B. Clinical (Medical)/ Non-Clinical (Pharmacology/ Toxicology)

Question 4:

The proposed (b) (4) formulation differs from the RLD, Adderall XR[®] formulation, in two ways:

(b) (4)

Each of those differences is contemplated in FDA guidance for the 505(b)(2) approval pathway. **Will the Division accept reference to the Adderall XR[®] NDA for evidence of efficacy and safety with the support of the proposed adult bioequivalence and pediatric pharmacokinetic trials?**

Preliminary Comments:

In addition to the AUC and C_{max} metrics, you must provide data demonstrating that the PK time-course of the (b) (4) product matches the PK time-course of Adderall XR[®]. You should compare appropriate partial AUCs (e.g. AUC_(0-0.5 hours), AUC_(0-2 hours)) and any other metric(s) that you deem relevant to support equivalence (b) (4) to Adderall XR[®]. If both of these criteria are met, the Division would accept reference to the Adderall XR[®] NDA for evidence of efficacy and safety. However, if the data reveal that the time-courses of PK are different, in spite of demonstrating BE based on AUC and C_{max}, then you would be required to conduct a controlled efficacy study.

Discussion at Meeting:

The sponsor acknowledged our requirement that the PK time-course of the (b) (4) product would need to match the PK time-course of Adderall XR[®].

The sponsor also inquired whether there was an alcohol dose dumping guidance. DPP stated that we are not aware of any. We discussed the impact of dumping on the effectiveness and safety of the (b) (4) product. Ideally, the product would have no dose dumping. The amount of dose dumping that would be acceptable would be product specific and a review issue.

Question 5:

Are there any other studies of the Neos (b) (4) formulation to be requested by the Agency for approval of the proposed 505(b)(2) submission?

Preliminary Comments: Refer to our response to Question 4.

Pharmacology/Toxicology:

We remind you that the amounts and specifications for impurities and degradants in drug substance and drug product may require qualification in non-clinical studies (see FDA Guidances Q3A and Q3B.)

(b) (4)

Discussion at Meeting:

There was no further discussion.

Question 6:

Current FDA guidance requires study of new drugs in subjects with impaired renal function. The renal elimination of mixed amphetamine salts has been extensively studied and is well characterized in the package insert for the RLD, Adderall XR[®]. It is known and stated in the RLD package insert that renal or hepatic impairment has the potential to reduce the elimination rate of amphetamines leading to prolonged exposures. As the Neos (b) (4) suspension formulation is not a new chemical entity, and we will demonstrate similarity with the RLD in the proposed studies, we are requesting a waiver from the requirement for separate studies in renally-impaired patients. **Does the Division concur?**

Preliminary Comments:

If bioequivalence has been established, you would not be required to perform separate studies in patients with impaired renal function.

Discussion at Meeting:

There was no further discussion.

C. Chemistry, Manufacturing and Controls

Question 7:

Does the Division have any concerns regarding the quantitative composition statements for the (b) (4) suspension formulation?

Preliminary Comments:

You will need to provide the components/composition of the drug product to be used in your clinical trials.

Discussion at Meeting:

The sponsor agreed to provide the requested information.

Question 8:

Does the Division agree with the proposed specifications for the finished dosage form?

Preliminary Comments:

You utilize peak retention time by HPLC as the drug product identification method. As this is not a specific method (per ICH Q6A), you will need to add an additional identification test or utilize a specific identification method. You need to provide tentative drug product impurities acceptance limits. All impurities must be integrated and reported by relative retention time (RRT) or some other identifier. The acceptability of drug product impurity limits will be a matter of review.

Discussion at Meeting:

(b) (4)

The sponsor agreed to provide data on drug product impurities.

Question 9:

Does the Division have additional requests for the development program for the [REDACTED] suspension?

Preliminary Comments:

CMC Recommendations:

- *Provide Certificate of Analysis of drug product batches to be used in the clinical studies.*
- *We recommend that you provide appropriate stability data to cover the clinical studies.*

Discussion at Meeting:

The sponsor agreed to provide the requested information.

D. Regulatory (Procedural)

Question 10:

In that the development plan is based on a standard 505(b)(2) approach, are there additional requirements that the Division may have for this development program?

Preliminary Comments:

From a regulatory perspective, you will need to provide data to support any differences between your product and the product(s) you reference. You will need to provide an acceptable scientific bridge (e.g. BA/BE study) to the product(s) on which you rely to support your application [Refer to our response to Question 4].

Additionally you will need to submit an appropriate patent certification/statement for each of the applications on which you rely. For additional information about 505(b)(2) application, please refer to our guidance document entitled "Guidance for Industry Applications Covered by Section 505(b)(2)

[<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>].

Discussion at Meeting:

No further discussion.

E. Additional Comments and Discussion

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[REDACTED]

- *DPP stated that standard bioequivalence must be established*

Conclusion

These minutes are the official minutes of the meeting. Neos Therapeutics, Inc is responsible for notifying us of any significant differences in understanding the group has regarding the meeting outcomes.

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
01/20/2011