CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204326Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505(b)2
Application Number	204326
Priority or Standard	Standard
Original Submission Date	12/28/2012
Complete Response Sent Date	09/24/2013
Complete Response Received Date	07/27/2015
PDUFA Goal Date	01/26/2016
Reviewer Name	Kavneet Kohli-Chhabra M.D.
Review Completion Date	January 25, 2015
Division/Office	Division of Psychiatry Product (DPP)
Established Name	Amphetamine extended-release orally disintegrating tablets
Trade Name	Adzenys XR-ODT
Applicant	Neos Therapeutics, Inc.
Formulation	Orally disintegrating tablets
Dosing Strengths	3.1, 6.3 , 9.4, 12.5, 15.7, and 18.8 mg tablets
Proposed Indication	Attention Deficit Hyperactivity Disorder (ADHD)
Intended Populations	Patients 6 years and older
Recommended Regulatory Action	Approval

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1 Introduction and Regulatory Background

Neos Therapeutics, Inc. (the applicant) submitted a 505(b)(2) application for amphetamine extended release orally disintegrating tablets (amphetamine XR-ODT) referencing the listed drug (LD) Adderall XR (mixed salt of a single-entity amphetamine product extended release capsule, Shire Laboratories, Inc., NDA 21303). Adderall XR was initially approved on October 11, 2001, for children ages 6 to 12 years. The indicated population was expanded to adults on August 11, 2004, and adolescents on July 21, 2005. Thus, the reference product label includes safety and efficacy information for patients ages 6 years and older. Shire and Neos have entered into a licensing agreement that will allow Neos to market this product immediately on approval even though Shire holds patents for Adderall XR that expire as late as April 21, 2019.

The reference product is a salt; the product under review is not. Table 1 lists the proposed tablet strengths of amphetamine XR-ODT along with the dose strengths of the reference product which contain equivalent amounts of amphetamine base. The development program of amphetamine XR-ODT was initiated under IND 112,991 in September, 2011. The applicant is seeking an indication for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older. Amphetamine is classified as a Schedule II drug under the Controlled Substance Act.

Table 1: Equivalent Doses of Mixed Salts of a Single-Entity Amphetamine Product Extended-Release Capsules and Amphetamine Extended Release Orally Disintegrating Tablets (Adzenys XR-ODT)

Product	**Dose Strengths**					
Amphetamine extended-release orally disintegrating tablets (Adzenys XR-ODT)	3.1 mg	6.3 mg	9.4 mg	12.5 mg	15.7 mg	18.8 mg
Mixed salts of a single-entity amphetamine product extended-release capsules	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg

This NDA application was initially submitted on December 28, 2012. The Agency issued a Complete Response (CR) action on September 24, 2013, primarily due to Chemistry Manufacturing and Controls (CMC) deficiencies. Numerous deficiencies were cited in the CR letter including problems with tablet hardness, (b) (4) and disintegration failures (b) (4) . The current submission is based on data using a reformulated drug product; therefore, it contains an entirely revised CMC section and data from a new single-dose bioequivalence (BE)/food effect clinical study (NT0202.1005) comparing amphetamine XR-ODT to Adderall XR and assessing the effect of food on the pharmacokinetics (PK) of the amphetamine XR-ODT product.

The first cycle clinical review (dated 08/19/2013) was completed by Cara Alfaro, Pharm.D.. In her review, she noted that, among the 112 subjects who participated in a total of four bioequivalence (BE)/PK studies, there were no deaths or serious adverse events (SAEs), and no subjects who discontinued secondary to adverse events (AEs). She concluded that, although there were some AEs in these trials that were not listed in the reference label (e.g., AST increase from 24 to 74 after a single dose of amphetamine XR-ODT in a 22 year-old, resolved), the lack of a placebo group in any of these studies made it difficult to interpret these events. She did not conduct a labeling review due to the planned CR action.

2 Materials Reviewed

Table 2: List of Material Reviewed

Submission Date	Materials
12/28/2012	Data Listings and Clinical Study Reports: Study NT0202.1001 "A single-dose, three-period, three-treatment, three way crossover bioequivalence study of two controlled release tablet formulations of mixed amphetamine polistirex equivalent to 30 mg mixed amphetamine salts and ADDERALL XR 30 mg (mixed amphetamine salts) under fasted conditions" Study NT0202.1002 "The effect of food on the pharmacokinetics of a controlled release oral disintegrating tablet formulation of amphetamine polistirex (equivalent to 30 mg mixed amphetamine salts) in healthy subjects" Study NT0202.1003 "A two-cohort, single-dose, four-period, four-treatment, four-way crossover study of the effect of alcohol on the pharmacokinetics of NT0202, a controlled release orally disintegrating tablet formulation of amphetamine polistirex (equivalent to 30 mg mixed amphetamine salts), in healthy subjects" Study NT0202.1004 "A single-dose, single-period, one-treatment, pharmacokinetic study of a controlled release formulation of mixed amphetamine resins oral disintegrating tablets (equivalent to 30 mg mixed amphetamine salts) under fasted conditions to children (ages 6-12) with attention-deficit hyperactivity disorder" Past clinical review by Cara Alfaro, Pharm.D., and other discipline reviews.

Submitted on and after 07/27/2015	Data Listings and Clinical Study Report: Study NT0202.1005 "A Single-Dose, Three-Period, Three-Treatment, Three-Way Crossover Bioavailability Study of an Investigational Formulation of NT0202 Amphetamine Extended-Release Orally Disintegrating Tablets (XRODT) 30 mg under Fed and Fasted Conditions and Adderall XR Capsule 30 mg under Fasted Conditions." Debarment Certification Financial Disclosure Certification Patent Certification Request for Waiver of Pediatric Studies Draft Labeling (PLR) and Draft carton labelling Proprietary Name Request for Review

3 Other Discipline Reviews

3.1. Product Quality

The Quality Assessment is dated December 21, 2015. The review team for this application included Drug Substance, Drug Product, Process, Microbiology, Facility, and Biopharmaceutics reviewers, as well as a Project/Business Process Manager and Application Technical Lead. The Quality team recommends approval, noting that the issues that resulted in a CR action in the previous review cycle have been resolved by reformulation of the drug product. The team did not recommend any post-marketing studies.

3.2. Nonclinical Pharmacology/Toxicology

No pharmacology/toxicology review was conducted during this review cycle. No new non-clinical information was submitted with this application. Shiny Mathew, Ph.D., completed a review during the first review cycle (dated 8/22/13). At that time, she concluded that the Agency's previous findings of safety and efficacy for Adderall XR are considered adequate to support the clinical doses of amphetamine in this product. No impurities, degradants, or novel excipients in amphetamine extended release tablets that would require additional toxicological characterization were identified.

3.3. Clinical Pharmacology

The PK studies were reviewed by Praveen V. Balimane, Ph.D., in his review dated December 29, 2015. He concluded that the amphetamine XR-ODT product demonstrated similar pharmacokinetic profile and exposure as compared to Adderall XR and is anticipated to have similar efficacy and safety profiles to Adderall XR, and that the

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

3.4. Controlled Substances Staff

In his review dated January 14, 2015, Edward Hawkins, Ph.D., provided labeling recommendations. He also noted that, despite a dissolution study and swine study demonstrating that ethanol increased dissolution of the API at 40% or 20% ethanol, respectively, a clinical study in humans (NT0202.1003) determined that ethanol did not lead to dose dumping.

3.5. Pediatric and Maternal Health

Donna Snyder, M.D., completed the DPMH review on December 9, 2015. She recommended changes to the applicant's proposed labeling in Highlights, Section 5.2, and Section 8.4.

4 Financial Disclosures

On July 27, 2015, Dorothy J. Engelking, Vice President of Regulatory Affairs for the applicant, certified that Neos had not entered into any financial arrangement with the principal or sub-investigators whereby the value of the compensation could have been affected by the outcome of the study. Also, she certified that each investigator required to disclose a proprietary interest in the product or significant equity interest in the applicant did not disclose any such interests. She further certified that none of these investigators was the recipient of significant payments of other sorts.

5 Review of Clinical Studies

Four Phase 1 BE/PK trials were conducted in support of the initial NDA submission:

NT0202.1001 "A single-dose, three-period, three-treatment, three-way crossover bioequivalence study of two controlled release tablet formulations of mixed amphetamine polistirex equivalent to 30 mg mixed amphetamine salts and ADDERALL XR 30 mg (mixed amphetamine salts) under fasted conditions"

NT0202.1002 "The effect of food on the pharmacokinetics of a controlled release oral disintegrating tablet formulation of amphetamine polistirex (equivalent to 30 mg mixed amphetamine salts) in healthy subjects"

NT0202.1003 "A two-cohort, single-dose, four-period, four-treatment, four-way crossover study of the effect of alcohol on the pharmacokinetics of NT0202, a controlled release orally disintegrating tablet formulation of amphetamine polistirex (equivalent to 30 mg mixed amphetamine salts), in healthy subjects"

NT0202.1004 "A single-dose, single-period, one-treatment, pharmacokinetic study of a controlled release formulation of mixed amphetamine resins oral disintegrating tablets (equivalent to 30 mg mixed amphetamine salts) under fasted conditions to children (ages 6-12) with attention-deficit hyperactivity disorder"

Study reports and data sets for the above trials were reviewed by Cara Alfaro, Pharm.D., in the initial review cycle. The applicant has since reformulated this product and submitted additional data from that trial in support of the current application; this review will focus on the new BE/food effect study, NT0202.1005.

Study NT0202.1005

Study Objectives:

1. To compare the rate of absorption and oral bioavailability of amphetamine XR-ODT 18.8 mg and oral Adderall XR 30 mg following an overnight fast of at least 10 hours.

2. To assess the effect of food on the rate of absorption and oral bioavailability of amphetamine XR-ODT 18.8 mg.

Study Design:

This was a single-dose, open-label, randomized, three-period, three-treatment, crossover study with a 7-day washout period between each treatment period. Forty-two healthy adult subjects aged 18 to 72 years old received a single doses of amphetamine XR-ODT 18.8 mg under fasted conditions, amphetamine XR-ODT 18.8 mg under fed conditions, and Adderall XR 30 mg under fasted conditions.

Subjects remained inpatient for 36 hours after study drug administration and returned for outpatient visits at approximately 48 and 60 hours post-dose in each study period. A detailed listing of study assessments can be found in Table 3.

When subjects received amphetamine XR-ODT, they were instructed to place the tablet in their mouths and allow it to disintegrate without chewing or crushing. Adderall XR 30 mg was administered with 4 oz. water to swallow the capsule. All subjects fasted for 4 hours after dose administration.

Healthy male and non-pregnant, non-breastfeeding female subjects ages 18 and were eligible for inclusion in this study. Female subjects were required to either be postmenopausal (at least 2 years prior to dosing) or to agree to use an acceptable form of birth control from screening until 14 days after completion of the study. A Body mass index (BMI) between 18 and 32 kg/m2 (inclusive), weight $\geq$ 50 kg (110 lbs), and heart rate (40-100 bpm) and blood pressure (90-145/50-95 mmHg) within specified parameters were also required for inclusion.

Subjects were excluded if they had any current or past cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease; suicidal ideation or behavior as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS, Baseline version); positive urine drug screen or history of substance abuse; or any other condition that, in the opinion of the Investigator, may have jeopardized the safety of the subject or the validity of the study results. Additional exclusion criteria relate to health status, laboratory assessments, and concomitant medications.

Table 3: Schedule of Assessments

PROCEDURE	Screening	Periods 1 through 3			End-of-Study/ Early Termination
		Check-in	Day 1	Day 2	
Informed consent	X				
Medical and medication history	X	X			
ECG	X				X
Vital signs[1]	X		X	X	X
Physical examination	X				X
Biochemistry, hematology, urinalysis	X				X
Serology	X				
FSH test (postmenopausal female subjects)	X				
Pregnancy test (all female subjects)[2]	X	X			
C-SSRS (Baseline version)	X				
Urine cotinine screen	X	X			
Urine drug screen	X	X			
Urine alcohol screen		X			
Drug administration			X		
Blood sample collection for pharmacokinetic analysis[3]			X	X	
Outpatient visit[4]				X	X
AEs		X	X	X	X

1. Blood pressure, pulse rate, respiration rate, and temperature were measured at screening, prior to each administration of NT0202 Amphetamine XR-ODT, and at the end-of-study visit (prior to last pharmacokinetic blood collection, when possible). Blood pressure and pulse rate were measured at approximately 2, 4, 6, 8, 12, 24, 36, and 48 hours after each dose of study drug.
2. All female subjects underwent a serum pregnancy test at screening and a urine pregnancy test at each check-in.
3. Blood samples (1 x 4 mL) were collected at 0 hours (predose) and at 1.0, 2.0, 3.0, 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, and 60.0 hours after dosing.
4. Subjects were to remain in the research center until completion of the 36-hour procedures and were to return for outpatient visits at approximately 48 and 60 hours postdose in each study period.

(Source: NT0202.1005 Appendix 16.1.1 Protocol, Table 12.1, page 30)

A total of 42 subjects participated in the study, and 39 subjects completed all three study periods. Among the subjects who did not complete the study, two withdrew consent and one had a positive urine drug screen. There were no significant protocol deviations during the conduct of the study.

The bioequivalence data was reviewed in detail by Praveen Balimane, Ph.D., in his review dated December 29, 2015. He determined that the PK profile and exposures for amphetamine XR-ODT

and Adderall XR were similar and that the amphetamine XR-ODT product has no clinically meaningful food effect.

6 Review of Safety

Given the extensive safety experience to date with amphetamine, the relatively brief duration of the bioequivalence study, and the subject population (healthy adult volunteers), the conducted study is not capable of producing meaningful new safety data that could be extrapolated to the clinical use of Adzenys. There were no deaths, non-fatal serious adverse events, and no adverse events that led to premature discontinuation from the study in any of the studies submitted to support either the original application or this resubmission with the reformulated product. There were no new, unlabeled safety signals identified in the AE reports, physical exam, vital signs, ECGs, or other safety measures. During both the open-label and double-blind Treatment Periods, no subjects reported any occurrences or types of suicidal ideations or behaviors on the C-SSRS.

There were 46 AEs reported by 17 subjects; 16 following amphetamine XR-ODT treatment group under fasted state, 9 following amphetamine XR-ODT treatment under fed state, and 21 following Adderall XR treatment. The most commonly reported AEs following treatment with amphetamine XR-ODT were nausea (n=3; n=2 following Adderall XR) and dry mouth (n=2; n=3 following Adderall XR).

7 Pediatric Plan

The applicant (b) (4) with the original NDA submission; however, because a CR action was taken at the end of the first review cycle, no agreement was reached.

Since that time, the Division has begun requiring studies in children ages 4 to ≤ 6 years old for all newly approved products indicated for the treatment of ADHD. As such, we intend to require three studies in children ages 4 to ≤ 6 years of age with ADHD as Post Marketing Requirements:

- A pharmacokinetic study of amphetamine XR-ODT
- A randomized, double-blind, placebo-controlled efficacy and safety study
- A one year open-label safety study

8 Inspections

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) in the Office of Study Integrity and Surveillance (OSIS) was consulted to inspect the analytical site. Himanshu Gupta, Ph.D., and Sam H. Haidar, R.Ph., Ph.D. conducted the inspection at (b) (4) The lead investigator identified at that analytical site is (b) (4). In their review dated December 14, 2015, they note that no deficiencies were observed and no Form FDA-483 was issued.

The Division of New Drug Bioequivalence Evaluation (DNDBE) in OSIS declined to inspect the clinical site at WCTDDS, Clinical Research Services in San Antonio, TX. The lead investigator identified for the clinical trial was Cynthia A. Zamora, M.D. In her review dated January 25, 2016, Shila Nkah, Consumer Safety Officer, noted that this facility was recently inspected and that inspection outcome at that time was classified as No Action Indicated (NAI).

9 Labeling Review

The applicant references the currently approved labeling language from Adderall XR capsules, using other recently approved amphetamine products as references for format only. The Division provided a number of minor editorial comments; more substantive changes are summarized below.

Overarching Issues

The applicant's initial proposed labeling (b) (4) the relevant issues are discussed in detail in the OPQ Integrated Quality Assessment dated December 21, 2015. Dosage strengths for amphetamine XR-ODT will be expressed in terms of amphetamine base throughout the label.

The proposed label included specific references Adderall XR using the proprietary name. The non-proprietary name for Adderall XR is dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate extended-release capsules; however, it is commonly referred to as "mixed salts of a single-entity amphetamine product extended-release capsules." The final negotiated label contains a reference to Adderall XR in section 2.5 Switching from Other Amphetamine Products. The section includes a table describing how to switch directly from Adderall XR to this product. It then lists (b) (4) (b) (4) the commonly used name, after which the abbreviation "MAS ER" is introduced. Thereafter, in any section where it is necessary to refer to Adderall XR, the phrase

"mixed salts of a single-entity amphetamine product extended-release capsules" will be used for the first reference, then "MAS ER" will be used for any additional references in the section.

Specific Sections

1 INDICATIONS AND USAGE

- Simplified of the I&U statement. (b) (4), the indication statement will refer to patients 6 years and older.

2 DOSAGE AND ADMINISTRATION

- Eliminated (b) (4) for dosing instructions under section 2.2.
- Added advice for switching from other amphetamine products, specifically stating that this product should not be substituted for other amphetamine products on a milligram-per-milligram basis due to the differences in amphetamine base composition. A Table for equivalent doses of mixed salts of a single-entity amphetamine product extended release capsules and Adzenys XR-ODT is created.

5 WARNINGS AND PRECAUTIONS

- A new Warning and Precaution is added under section 5.2 Potential Overdose Due to Medication Errors. This was created to avoid substitution errors and overdosage that could be caused by substituting Adzenys with other amphetamine products on a milligram-per-milligram basis. This section refers to section 2.5, where a table lists the correct equivalent doses of mixed salts of a single-entity amphetamine product extended release capsules to Adzenys XR-ODT.
- For section 5.3 Serious Cardiovascular Reactions under Warning and Precautions (b) (4). This information applies to all ages and is part of the class language.
- The warning for (b) (4) listed under section 5.4 under Warning and Precautions is eliminated as it is no longer part of the class language for amphetamine products.

6 ADVERSE REACTIONS

- (b) (4) was eliminated from the pediatric (13-17 years old) and adult population tables listing the adverse reactions observed at incidences of 5% or higher. The incidence rates were the same between drug and placebo.
- (b) (4) sudden death and myocardial infarction (b) (4) under Cardiovascular Adverse Reactions Associated with the Use of Amphetamine.

7 DRUG INTERACTIONS

- Updated to table format.

8 USE IN SPECIFIC POPULATIONS
- Conversion of the Adzenys labeling to the Pregnancy and Lactation Labeling Rule (PLLR) format must occur before June 30, 2019. However, applicant voluntarily proposed labeling under Pregnancy section to be consistent with Dyanavel.
- "Safety and effectiveness have been established in pediatric (b) (4) three adequate and well-controlled clinical trials of up to 4 weeks in duration" statement has been updated under section 8.4 Pediatric Use.

11 DESCRIPTION
- Removed table listing amphetamine base content of this product vs. "Mixed Salts of a Single-Entity Amphetamine Product Extended-Release Capsules". The table is now in section 2.5.

12 CLINICAL PHARMACOLOGY
- The section was modified to include clinical studies results conducted with Adzenys XR-ODT.
- Separated PK information into its own subsection in 12.3.
- Food effect and alcohol effect study results are edited for clarity.

14 CLINICAL STUDIES
- Added descriptions of efficacy endpoint measures.
- Added a table for the primary efficacy result.

16 HOW SUPPLIED/STORAGE AND HANDLING
- The embossing will be changed to reflect the labeled strength.

17 PATIENT COUNSELING AND MEDICATION GUIDE
- Updated to reflect changes in the Full Prescribing Information.

10 Conclusions and Recommendations

From a clinical perspective, I recommend approval of Amphetamine XR-ODT (Adzenys XR-ODT) in patients 6 years and older with ADHD. There will be post-marketing requirements to conduct PK, efficacy, and safety studies in patients ages 4 to 5 years old with ADHD.

[See appended electronic signature]
Kavneet Kohli-Chhabra, M.D.
Medical Officer
Division of Psychiatry Products (DPP)

cc: NDA #204326
HFD-130 (Div. File)
TFarchione
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/s/

KAVNEET KOHLI-CHHABRA
01/26/2016

TIFFANY R FARCHIONE
01/26/2016

Cross-Discipline Team Leader Review Memo

Date	*{See Appended Electronic Signature Page}*
From	Ni A. Khin, M.D. Lead Medical Officer Division of Psychiatry Products, HFD-130 Office of Drug Evaluation I, Office of New Drugs (OND) Center for Drug Evaluation and Research (CDER)
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA#	NDA 204326
Applicant Name	Neos Therapeutics Inc.
Date of Submission	December 27, 2012
PDUFA Goal Date	October 28, 2013
Drug Name	Amphetamine (b) (4)
Dosage Forms/Strength	(b) (4) extended release (ER) oral disintegrating tablets (ODT)
Proposed Indication(s)	Attention Deficit Hyperactivity Disorder
Recommended Action:	Complete Response

1. INTRODUCTION

This NDA seeks an approval for an extended release oral formulation of amphetamine (b) (4) in treatment of ADHD. It is formulated as an oral disintegrating tablet with the highest strength containing 18.8 mg amphetamine base which is equivalent to 30 mg of mixed amphetamine salts in the reference listed drug (RLD), Adderall XR. The RLD was initially approved in 2001 for the same indication. Other dosage strengths contain 5, 10, 15, 20 and 25 mg mixed salts of amphetamine. The recommended daily dose is 10 mg for pediatric patients (6-17 yrs) and 20 mg for adults.

For this 505 (b)(2) NDA, the sponsor relies primarily on efficacy and safety data from Adderall XR (NDA 21303). For the proposed drug product, the sponsor asks for both ER and ODT designations. Three bioequivalence/PK studies in healthy adults were conducted and results from these studies were submitted in the NDA. Additionally, the submission also included results from a pediatric PK study in children (ages 6-12 yrs) with ADHD.

The review team consists of:

Material Reviewed/Consulted	Name of discipline reviewers
Clinical Reviewer, DPP	Cara Alfaro, Pharm.D.
ONDQA: CMC Reviewers Biopharmaceutics Reviewer	David Claffey, Ph.D. Kavita Vyas, Ph.D., Okponanabofa Eradiri, Ph.D.
DPP Pharmacologist/Toxicologist	Shiny Mathew, Ph.D.
OCP: Clinical Pharmacology Reviewer	Praveen Balimane, Ph.D.
Consultants: OSE/DMEPA OMP/DMPP OC: Manufacturing/Facility Review	Loretta Holmes, BSN, Pharm D. Sharon Willaims, RN, MSN Mahesh Ramanadham, PharmD
Project Managers: Project Manager, DPP ONDQA Project Manager	Kofi Ansah, Pharm.D. Teshara Bouie, MSA

2. BACKGROUND

The IND development program of NT0202, amphetamine [redacted] was initiated under IND#112991 by Neos in September 2011.

3.0 CHEMISTRY, MANUFACTURING & CONTROL (CMC)

Dr. Claffey conducted the CMC product review of this NDA (review dated 5/1/13). Dr. Kavita Vyas conducted the manufacturing process review (review dated 5/3/13). Dr. Ramanadham provided an initial compliance review of manufacturing process and facilities (review dated 5/17/13).

The sponsor made cross-reference to DMFs [redacted] and [redacted] for the manufacture of the drug substance, [redacted]. DMF [redacted] was found inadequate to support the application. The drug product is a tablet containing 3:1 mixture of d- and l- amphetamine [redacted] in 6 dosage strengths. Development studies determined that this product containing [redacted] similar to those of the RLD. The product specification is noted to be [redacted]. The limit for [redacted] was set [redacted] and disintegration time was set [redacted] The registration lots did not meet the disintegration acceptance criterion [redacted]. No release or stability criteria were provided for the registration lots of the intermediate strengths [redacted] as they are not yet manufactured. No certificate of analysis provided. The batch analysis data provided is incomplete. The 12 month stability data was also incomplete. Dr Claffey noted the fact that significant changes were observed [redacted] where results generally failed to meet drug product acceptance criteria, especially for the [redacted] product.

A disciplinary review letter outlining extensive deficiencies related to the product quality, stability as well as manufacturing process was sent to the sponsor on 5/29/13 (see letter for details). In this letter, ONDQA asked the sponsor to provide in process, release, and stability data for at least 3 consecutive drug product batches for all strength. The sponsor was also asked to provide adequate data to bridge the quality of these drug product batches with those in the human BE study.

On August 1, 2013, the sponsor submitted response on August 1, 2013 in which the sponsor stated that they plan to have a consistent production process justified by development data showing the drug product meets acceptable quality attributes. They intend to produce in-process release and stability data for three additional lots. They also plan to conduct a new BE study to demonstrate bioequivalence between their product using revised CMC process and the RLD at the highest [redacted] mg strength.

Sponsor's response was reviewed (amended CMC review dated 9/12/13). Several items were determined adequate. The major CMC deficiencies have not yet been adequately addressed by the sponsor. The CMC reviewers recommended a complete response action as the sponsor has not yet manufactured an acceptable quality drug product or the proposed process has the capability to commercially manufacture a quality drug product.

The Office of Compliance also made a withhold recommendation (memo dated 8/29/13) indicating that additional inspections of the manufacturing process and testing facilities for the drug product would be conducted when the sponsor is able to manufacture supportive batches using a revised manufacturing process. Deficiencies identified at the Neos and the (b) (4) facilities also need to be resolved.

4.0 BIOPHARMACEUTICS

According to the initial Biopharmaceutic review by Dr. Eradiri (dated 5/1/2013), although the principle and basis for selection of the (b) (4) dissolution method are acceptable, a systematic approach was not seemed to be taken in the selection of the equipment and dissolution conditions. Additional issues included: 1) no supportive data for their choice of the paddle speed, 2) an inadequate a priori investigation regarding the choice of the acceptance criteria sampling timepoints for QC release testing, 3) lack of the individual vessel dissolution data (b) (4) (b) (4) The sponsor was asked to provide additional data to resolve the issues identified. No dissolution acceptance criteria could be established. Based on the provided information, the biowaiver request for the lower strengths could not be considered at this time.

Sponsor's response was reviewed (addendum dated 9/11/13). The sampling proposal for collecting dissolution data sets on the new clinical and registration batches are found acceptable. The supportive data submitted in the response supports for 75 rpm as the optimal paddle speed, (b) (4) (b) (4) The experiments conducted for the selection of the apparatus and rotation did not seem to be adequate to evaluate the discriminating capability of the selected method. The sponsor has not yet provided individual vessel dissolution data for (b) (4) for setting the acceptance criteria. These biopharmaceutics deficiencies remain outstanding.

5.0 NON-CLINICAL PHARMACOLOGY/TOXICOLOGY

As noted by Dr. Mathew in her review dated 8/22/13, no impurities, degradants or novel excipients in NT0202 that would require additional toxicological characterization have been identified.

6.0 CLINICAL PHARMACOLOGY

Dr. Balimane wrote a brief memo (dated 8/29/2013) noting that although data from the pivotal BE study appears to demonstrate bioequivalence between the sponsor's product and the RLD, the 4 submitted bioequivalence/PK studies (including an *in-vivo* alcohol dose dumping study) were not reviewed in detail as the results were based on the existing formulation with significant CMC deficiencies. As the sponsor plans to manufacture new batches of the product to address for the manufacturing and quality product issues and also plans for an additional BE study, he provided some comments from OCP perspective as to what parameters the sponsor should focus on in conduct of additional BE and PK/food effect studies. Dr. Balimane also indicated that the sponsor would not necessarily need to conduct another *in-vivo* alcohol dose dumping study, instead, from OCP perspective, an *in-vitro* study would be sufficient to study any dose dumping effect with alcohol for their new batch of drug product.

7.0 CLINICAL

Dr. Alfaro reviewed the safety data from a total of 112 subjects participated in 4 BE/PK studies in which single 30 mg doses of NT0202 were administered. The first study (Study NT0202.1001) was a single dose, three-period, three-treatment, three-way crossover BE study of two controlled release tablet formulation of amphetamine polistirex to 30 mg mixed amphetamine salts and ADDERALL XR 30 mg under fasted conditions. The second study NT0202.1002 was the food effect study on the PK. The sponsor also conducted an in-vivo study to investigate the effect of alcohol on the PK (NT0202.1003). These 3 studies were conducted in healthy adults. In addition, the sponsor conducted a pediatric PK study (NT0202.1004) in children aged 6-12 years diagnosed with ADHD.

There were no reports of deaths or serious adverse events. No subjects discontinued the trials due to adverse events. No safety findings in these trials that would raise new safety concern with the drug.

8.0 OTHER RELEVANT REGULATORY ISSUES

8.1 Other Discipline Consults

We consulted OSE/DMEPA to evaluate the proposed trade name. Following the teleconference between DMEPA and the sponsor on 9/10/13, the sponsor withdrew their application for the proposed propriety name, (b) (4) XR-ODT on 9/13/13. We also consulted OMP/DMPP to evaluate the proposed Med Guide. As DPP does not plan to take an approval action of this NDA in this cycle, the Patient Labeling Reviewer deferred the Med Guide review.

9.0 OSI INSPECTIONS

OSI inspection was requested for study NT0202.1001. According to the inspection report by (b) (4). (b) (4) dated (b) (4), data from both clinical and analytical sites, (b) (4) (b) (4), found acceptable.

10.0 LABELING

The sponsor's proposed labeling changes are based on the currently approved labeling language from the (b) (4) with some labeling edits to reflect their formulation. Sudden cardiac death, elevated blood pressure, psychosis, mania, and abuse/dependence are included as part of the warnings/precautions. Since we are issuing a complete response action, we decided not to negotiate final labeling language with the sponsor in this review cycle.

11.0 RECOMMENDATION/RISK BENEFIT ASSESSMENT

As noted in the CMC and biopharmaceutics reviews, the sponsor's response is deemed inadequate as major deficiencies noted in the ONDQA disciplinary letter remain unaddressed. The review team recommends that the Division issue a complete response (CR) letter. We will reiterate outstanding CMC deficiencies in the CR letter. As the sponsor also plans to conduct additional pivotal BE study with their newly manufactured product using revised manufacturing process, we should include OCP comments regarding this new BE study as well as the alcohol effect study in the CR letter.

cc: HFD-130/Mathis/Alfaro/Ansah

File: NK/NDA/Memo_N204326_ 09172013.doc

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/s/

NI A KHIN
09/17/2013

Review and Evaluation of Clinical Data
NDA 204326

Sponsor: Neos Therapeutics, Inc.

Drug: Amphetamine (b) (4) extended release orally disintegrating tablet (NT0202)

Material submitted: 505(b)(2) New Drug Application

Indication: Treatment of Attention Deficit Hyperactivity Disorder (adults/pediatrics)

Submit Date: 12/27/2012

Received Date: 12/28/2012

PDUFA Goal Date: 10/28/2013

Clinical Reviewer: Cara Alfaro, Pharm.D.

Review Completion Date: 08/19/2013

I. Regulatory Background

Neos Therapeutics, Inc., has developed NT0202, an extended release oral formulation of amphetamine (b) (4) an oral disintegrating tablet equivalent to 18.8 mg amphetamine base which is equivalent to 30 mg of mixed amphetamine salts in the reference listed drug, ADDERALL XR. Additional tablet strengths (b) (4) (b) (4) have also been developed. NT0202 contains amphetamine (b) (4) (b) (4) – these total tablet weights correspond to 18.8 mg and 3.13 mg amphetamine (b) (4) base, respectively. When compared to ADDERALL XR, the 18.8 mg amphetamine (b) (4) base equates to 30 mg amphetamine in its mixed salts form and the 3.13 mg amphetamine base to 5 mg amphetamine mixed salts.

For this 505(b)(2) application, Neos Therapeutics is relying primarily on efficacy data that formed the basis of the FDA approval for ADDERALL XR (extended-release mixed amphetamine salts, Shire Laboratories, Inc., NDA 21303) and the published literature on the therapeutic applications of amphetamines to describe the efficacy of NT0202. The following meetings were held between the Sponsor and the Division of Psychiatry Products:

- January 13, 2011 Pre-IND meeting
  Plans to submit a 505(b)(2) application that references NDA 21-303 ADDERALL XR. The Sponsor proposed a single dose bioequivalence study comparing the controlled release *suspension* to the reference listed drug ADDERALL XR 30 mg under fasting and fed conditions in adults (≥ 18 years of age) and a pharmacokinetic study in a pediatric population (6-12 years and 11 months). The Division suggested conducting the adult study prior to the pediatric study and that the latter should study the full spectrum of age strata (e.g. 6-7, 8-9,

10-12) with at least 4 completers per stratum. The Sponsor was advised that in addition to the AUC and Cmax metrics, they must provide data demonstrating that the PK time-course of the drug product matches the PK time-course of ADDERALL XR. The Division also noted that if bioequivalence is established, the Sponsor would not need to perform separate studies in patients with impaired renal function.

- August 1, 2011 IND 110,281 filed with Division (mixed amphetamine resin controlled release oral liquid *suspension*)

- August 1, 2011 IND 112,991 filed with Division (mixed amphetamine resin orally disintegrating *tablet*/enteric-release coating)

- October 14, 2011 End of Phase 1 meeting (IND 112,991) Sponsor proposing a single dose fed-fasting PK study and a single dose pediatric bioavailability study and sought concurrence on NDA fileability. The Division also provided feedback regarding the study design for a study to evaluate potential dose-dumping when the drug product is coadministered with alcohol.

- September 13, 2012 Pre-NDA meeting. Discussion of content and timing of planned 505(b)(2) NDA filing for the mixed amphetamine resins controlled-release orally disintegrating tablets.

II. Materials Reviewed

Submission Date	Materials
12/28/2012	Clinical Study Reports: Study NT0202.1001 Study NT0202.1002 Study NT0202.1003 Study NT0202.1004 Data Listings Debarment Certification Financial Disclosure Certification Patent Certification Request for Waiver of Pediatric Studies Draft Labeling (PLR)
1/4/2013	Proprietary Name Request for Review
1/11/2013	Amendment to Patent Certification
3/26/2013	Amended Draft Labeling (PLR)
4/19/2013	Amended Draft Labeling (PLR)
6/28/2013	Proprietary Name Request for Review

All the clinical trials conducted with NT0202 were Phase 1 bioequivalence/PK studies. NT0202.1001, NT0202.1002 and NT0202.1003 were conducted in healthy adults and study NT0202.1004 was conducted in children with ADHD (6 to 12 years of age). In all of these clinical trials, single 30 mg doses of NT0202 were administered.

NT0202.1001 "A single-dose, three-period, three-treatment, three-way crossover bioequivalence study of two controlled release tablet formulations of mixed amphetamine polistirex equivalent to 30 mg mixed amphetamine salts and ADDERALL XR 30 mg (mixed amphetamine salts) under fasted conditions"

NT0202.1002 "The effect of food on the pharmacokinetics of a controlled release oral disintegrating tablet formulation of amphetamine polistirex (equivalent to 30 mg mixed amphetamine salts) in healthy subjects"

NT0202.1003 "A two-cohort, single-dose, four-period, four-treatment, four-way crossover study of the effect of alcohol on the pharmacokinetics of NT0202, a controlled release orally disintegrating tablet formulation of amphetamine polistirex (equivalent to 30 mg mixed amphetamine salts), in healthy subjects"

NT0202.1004 "A single-dose, single-period, one-treatment, pharmacokinetic study of a controlled release formulation of mixed amphetamine resins oral disintegrating tablets (equivalent to 30 mg mixed amphetamine salts) under fasted conditions to children (ages 6-12) with attention-deficit hyperactivity disorder"

III. Financial Disclosures

On 12/27/2012, Dorothy J. Engelking, Vice President Regulatory Affairs for Neos Therapeutics, Inc., certified that Neos Therapeutics, Inc., had not entered into any financial arrangement with the listed clinical investigators (Zamora, Bostrum, Riesenberg) whereby the value of compensation to the investigator could be affected by the outcome of the study. She also certified that each listed clinical investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in the product or a significant equity interest; no interests were disclosed. She further certified that no listed investigator was the recipient of significant payments of other sorts.

Table 1. Clinical Studies and Investigators

Clinical Study	Principal Investigator
NT0202.1001 NT0202.1002 NT0202.1003	Cynthia A. Zamora, M.D. Worldwide Clinical Trials Drug Development Solutions San Antonio, TX
NT0202.1004	Samantha Bostrum, M.D. Westside Medical Clinton, Utah Robert A. Riesenberg, M.D. Atlanta Center for Medical Research Atlanta, GA

IV. Review of Clinical Safety Data

Given the extensive safety experience to date with ADDERALL and ADDERALL XR and marketed generic amphetamine products and the brief duration of the bioequivalence/pharmacokinetic studies, the studies conducted with NT0202 are unlikely to

produce meaningful new safety data that could be extrapolated to the clinical use of amphetamine products. Therefore, this safety review will focus on the more serious adverse experiences from the 3 bioequivalence studies conducted in healthy adult subjects. Since study NT0202.1004 included children (6 to 12 years of age) with ADHD, a more detailed review of all safety data will be discussed.

A total of 112 subjects participated in the 4 clinical trials: 36 subjects in NT0202.1001, 16 subjects in NT0202.1002, 32 subjects in NT0202.1003 and 28 subjects in NT0202.1004. Study NT0202.1004 was conducted in children (6 to 12 years of age) with the following numbers per age strata: 6 subjects 6-7 years of age; 11 subjects 8-9 years of age and 11 subjects 10-12 years of age. NT0202 was dosed as 30 mg single doses in all of the studies. NT0202 30 mg tablet was placed on the tongue and allowed to disintegrate. Subjects could use normal mouth movements to facilitate disintegration. A mouth check was performed to ensure that the tablet was completely disintegrated and all medication had been swallowed. If the tablet was not ingested completely, the subject was instructed to continue with the process as described until complete ingestion had occurred. The tablet was not to be crushed or chewed.

A. Deaths

No deaths were reported in the three Phase 1 clinical studies conducted in healthy adults and the one Phase 1 clinical study conducted in children (6 to 12 years of age) with ADHD.

B. Non-Fatal Serious Adverse Events

No serious adverse events were reported in the three Phase 1 clinical studies conducted in healthy adults and the one Phase 1 clinical study conducted in children (6 to 12 years of age) with ADHD.

C. Adverse Events Resulting in Dropouts

No subjects discontinued the clinical trials due to adverse events.

The numbers of subjects discontinuing each study and the reason for discontinuation:
NT0202.1001 – 3 subjects discontinued (2- lost to follow-up, 1- positive urine drug screen)
NT0202.1002 – no discontinuations, all subjects completed
NT0202.1003 – 5 subjects discontinued (3-withdrew consent, 2- positive urine drug screen)
NT0202.1004 - no discontinuations, all subjects completed

D. Significant Adverse Events

The Sponsor noted "other significant adverse events" for study NT0202.1001 only (Table 2). Of note, most of these events were identified on examination of clinical labs which were obtained at screening and EOS (end of study) only in this 3-way cross-over trial. The Sponsor did not note "other significant adverse events" for the other three clinical trials.

Table 2. Significant Adverse Events noted by Sponsor for Study NT0202.1001.

Subject	Adverse Event	Onset of AE	Severity	Outcome
#212 21YOHM	Urinary tract infection	Noted at EOS labs	Mild	Resolved
#219 22 YOHM	AST increased (24 to 74 U/L)	Noted at EOS labs	Mild	Resolved
#220 63 YOHM	Rash	Period 3, following NT0202	Mild	Resolved within 24 hours
#226 24 YOM	Elevated blood glucose (94 to 163 mg/dL)	Noted at EOS labs	Mild	Resolved
#233 21 YOBM	Neutropenia (present at screening)	Noted at EOS labs	Mild	Resolved

A review of clinical laboratory assessments noted an increase in ALT and AST in a subject in study NT0202.1003 (subject #122). This subject had ALT/AST WNL at screening with elevations noted at end of study (at ~7 weeks): ALT = 158 U/L, AST = 61 U/L; total bilirubin was WNL. Repeat labs obtained one week later showed a trend for decreasing LFTs: ALT = 76 U/L, AST = 41 ULN. No further data available.

It is difficult to interpret the LFT findings in isolation and without a placebo- or other comparator group. Additionally, the study designs also make inferences regarding causality to NT0202 more difficult. For example, clinical labs in Study NT0202.1001 were obtained at screening and end of study, not at the end of each cross-over treatment. Alcohol was administered in Study NT0202.1003 to evaluate dose-dumping of NT0202. Increases in ALT and/or AST are not in currently approved product labeling for ADDERALL XR.

E. Safety Summary NT0202.1004

NT0202.1004 "A single-dose, single-period, one-treatment, pharmacokinetic study of a controlled release formulation of mixed amphetamine resins oral disintegrating tablets (equivalent to 30 mg mixed amphetamine salts) under fasted conditions to children (ages 6-12) with attention-deficit hyperactivity disorder"

Adverse Events

In this single-dose study, the Sponsor defined treatment-emergent adverse events as any adverse event that began within 7 days of the dose of study drug. Eleven (39.3%) subjects experienced 34 adverse events. Table 3 lists the adverse events by preferred term, most frequent to least frequent. Many of the adverse events are consistent with stimulants (e.g. tachycardia, blood pressure increased). This study did not include a placebo group as a comparator which limits the overall interpretability of these findings. Per the Sponsor, the majority of the adverse events were considered to be mild and 3 were of moderate severity

(rhinitis, headache, presyncope). The contusion adverse events were antecubital bruising, likely related to the blood sampling in this pharmacokinetic study; none of these patients had decreases in platelets (see Clinical Labs).

Table 3. Adverse Events Occurring in Study NT0202.1004

	NT0202 ODT (N = 28) n (%)
Contusion	4 (14.3)
Presyncope	3 (10.7)
Heart rate increased	2 (7.1)
Headache	2 (7.1)
Anxiety	1 (3.6)
Back pain	1 (3.6)
Blood pressure increased	1 (3.6)
Body temperature increased	1 (3.6)
Insomnia	1 (3.6)
Peripheral coldness	1 (3.6)
Rash	1 (3.6)
Rhinitis	1 (3.6)
Skin reaction	1 (3.6)
Vasoconstriction	1 (3.6)

Clinical Labs

Clinical labs were obtained at screening and at visit 5 (~Day 7). The majority of clinical labs obtained during the study were unremarkable. Two patients (both in the 6 to 7 year old cohort) had decreases in platelet counts; one from 221 to 135 x 10^3/uL and the other from 317 to 127 x 10^3/uL. Two patients (both in the 10 to 12 year old cohort) had increases in total bilirubin; one from 0.8 to 1.6 mg/dL and the other from 0.9 to 1.2 mg/dL. The patient with the increase in total bilirubin to 1.6 mg/dL also had a slight increase in ALT from 17 to 35. No follow-up labs were obtained in any patients. Neither of these findings is currently in product labeling for the RLD, ADDERALL XR. Lack of a placebo group in this study limits the interpretability of these findings.

V. Pediatric Plan

The Sponsor is seeking a partial waiver from performing pediatric bioavailability studies of its amphetamine (b) (4) extended release orally disintegrating tablet in infants, children (b) (4) (b) (4) – ages 0 to 5 years and 11 months, (b) (4). Neos Therapeutics has performed a single-dose pharmacokinetic study in children (6 to 12 years of age) with ADHD.

The Sponsor requests the waiver for the 0 to (b) (4) year and 11 months age group is based on a paucity of data around the safety and efficacy of stimulant medications in preschool children such that stimulant medications are not advocated as a first-line treatment in this age group.

(b) (4)

The Sponsor is requesting approval for labeling identical to that of ADDERALL XR, the reference listed drug. Labeling for ADDERALL XR provides for dosing recommendations for treatment of ADHD in children (6 to 12 years), adolescents (13 to 17 years) and adults. In prior meetings (1/13/11, 9/13/12), the Division of Psychiatry Products indicated that it would be appropriate to request a waiver of the requirement to conduct a bioavailability study in adolescents as long as the adult healthy volunteer bioequivalence study showed NT0202 to be bioequivalent to ADDERALL XR in the established metrics of C_{max}, AUC_{inf} and specified pAUC values.

Since a Complete Response action is being recommended based on significant CMC deficiencies, a Pediatric Review Committee (PeRC) meeting was not held. Further evaluation of proposed product labeling was not conducted.

VI. OSI Inspection

The Division of Bioequivalence and GLP Compliance conducted inspections of the clinical and analytical portions of study NT0202.1001. The report was finalized on 8/4/2013. The analytical portion of the inspection was performed at (b) (4) (b) (4) in (b) (4) by (b) (4) (b) (4) The clinical portion of the inspection was performed at Worldwide Clinical Trials Drug Development Solutions, Clinical Research Services in San Antonio, TX in June/July 2013 by R. Todd Lorenz. No objectionable conditions were observed and a Form FDA-483 was not issued for either site.

VII. Other Significant Issues Identified By Other Disciplines During Review Cycle

A Discipline Review (DR) Letter was sent to the Sponsor on 5/29/2013. This letter outlined significant deficiencies regarding the quality and stability of the drug product. Details regarding these deficiencies are included in the DR letter as well as the chemistry review (5/1/2013; David J. Claffey, Ph.D.). Additional deficiencies were noted and outlined in the manufacturing process and facility review (5/17/2013; Mahesh Ramanadham, Pharm.D/MBA).

The Sponsor responded to the DR letter in a response submitted 8/1/2013. The Sponsor plans to provide data with new lots of finished drug product manufactured using a consistent process at the (b) (4) The Sponsor will also perform a bioequivalence study with this new drug lot.

(b) (4)

The following is the amphetamine base strength and the equivalent corresponding Mixed Amphetamine Salt (MAS):

Amphetamine base equivalent	**3.1 mg**	**6.3 mg**	**9.4 mg**	**12.5 mg**	**15.7 mg**	**18.8 mg**
Each dose contains MAS equivalent:	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg

These issues will be further addressed once the Sponsor has submitted data responding to all CMC deficiencies as well as additional bioequivalence clinical data.

VIII. Labeling Review

A labeling review was not conducted since a CR action was recommended due to significant CMC issues identified.

IX. Conclusions and Recommendations

CMC has recommended that a Complete Response action be taken based on significant deficiencies noted in the NDA submission. This reviewer concurs with that recommendation.

Cara Alfaro, Pharm.D.
Clinical Analyst
Division of Psychiatry Products

08/19/2013

cc: HFD-130/Khin
Ansah
Mathis
Alfaro

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/s/

CARA L ALFARO
08/19/2013

NI A KHIN
08/20/2013
See CDTL memo for additional comments.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204326 **Applicant: Neos Therapeutics** **Stamp Date: 12/28/2012**

Drug Name: (b) (4) **NDA/BLA Type: NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?		X		In the preNDA meeting, the Division agreed with the Sponsor's plan to utilize the Summary of Clinical Safety in lieu of a separate ISS.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			This application is a 505(b)(2). The reference listed drug is ADDERALL XR (amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product			X	The Sponsor is relying on bioequivalent

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	(*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:				studies to bridge the efficacy data to the reference listed drug, ADDERALL XR.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	The Sponsor is not conducting any placebo-controlled studies to determine efficacy. This application is a 505(b)(2).
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	This application is a 505(b)(2).
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	This application is a 505(b)(2).
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	This application is a 505(b)(2) and will rely on data from the reference listed drug. QT studies were not required for the reference listed drug.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			The Sponsor has provided a literature search for 2001 (the date of the ADDERALL XR approval) through April 2012.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	This application is a 505(b)(2).
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	This application is a 505(b)(2) and will rely on data from the innovator product. The proposed formulation has been administered to 78 healthy adult subjects and 28 children (ages 6 to 12) with ADHD – all administered as a single dose.
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	This application is a 505(b)(2). The Sponsor is relying on data from the reference listed drug.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	No serious adverse events (including death) or discontinuations due to adverse events occurred in the clinical trials.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	No special studies/data were requested.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The Sponsor has requested a partial waiver from performing pediatric bioavailability studies in infants/children (0 to < (b) (4) years) (b) (4)

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					(b) (4)
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			This application is a 505(b)(2). The Sponsor is relying on data from the reference listed drug which is classified as a Schedule II drug. Since this drug is an orally disintegrating tablet, *in vitro* studies were conducted to evaluate abuse potential.
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	No serious adverse events (including death) or discontinuations due to adverse events occurred in the clinical trials. No case report forms required to be submitted.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	No additional case report forms were requested by the Division.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No review issues identified at this time.

Cara Alfaro, Pharm.D.
Clinical Analyst
Division of Psychiatric Products

02/11/2013

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

/s/

CARA L ALFARO
02/11/2013

NI A KHIN
02/13/2013