CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204325Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 204325
Review #1

Drug Name/Dosage Form	Adzenys ER Amphetamine Extended Release Oral Suspension.
Strength	1.25 mg/ml
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	NEOS THERAPEUTICS INC
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD#:0000	15 Nov 2016	CMC Team Rview
SD#:0003	29 Dec 2016	Drug Substance/Drug Product
SD# 0005	17 Feb 2017	Manufacturing Process and Controls/Drug SubstanceDrug Product
SD# 006	3 Mar 2017	Drug Substance/Drug Product
SD# 009	28 Apr 2017	Drug Substance/Drug Product
SD# 0010	Apr 28 2017	Manufacturing Process and Controls
SD# 0011	11 May 2017	Manufacturing Process and Controls
SD# 0015	26 Jun 2017	Drug Substance
SD 0017	8 August 2017	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Andrei Ponta	Wendy Wilson-Lee
Drug Product	Andrei Ponta	Wendy Wilson-Lee
Process	Chunseng Cai	Akm Khairuzzaman
Microbiology	Elizabeth Bearr	Erika Pfeilerr
Facility	Ruo (Rose) Xu	
Biopharmaceutics	Mei Ou	Ta-Chen Wu
Regulatory Business Process Manager	Grafton Adams	

Application Technical Lead	David Claffey	
Laboratory (OTR)	Jason Rodriguez	
ORA Lead		
Environmental		

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)		Active	03/26/2015	
	Type II			Active	03/26/2015	
	Type III			Active	08/08/2006	
	Type III			Active	07/13/2011	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original IND	IND 110281	
CDER/OPQ/OTR/DPA Report		05/18/17 Lab report on suspension. Cindy Diem Ngo (attached to review).

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

Recommend approval based on the approval recommendation from each of the OPQ review team members.

II. Summary of Quality Assessments

A. Product Overview

The proposed drug product is an extended release oral suspension containing 1.25 mg/ml of amphetamine for the treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older. It is an orange colored suspension with an orange (b) (4) flavor. Amphetamine is present as an enantiomeric mixture of D- and L- isomers in a 3:1 ratio. The drug product is supplied in (b) (4) amber glass bottles with white (b) (4) closure with a (b) (4) seal liner and has tamper-evident and child-resistant closure features.

(b) (4) The drug product contains immediate release drug resinate (b) (4) and delayed release (b) (4) drug resinate. The combination (b) (4) provide an equivalent biphasic dissolution/plasma profile to Adderall XR, the reference listed drug product (NDA 21303). (b) (4)

Data found that typical oral delivery devices (spoon, cup, syringe) reliably delivered typical measured dose. The drug product requires shaking before administration. (b) (4) (b) (4) Data support a 30 day in-use period for the drug product after opening the bottle and a 36 month shelf life for the drug product when stored at controlled room temperature.

An instruction was added to the label to not dilute or mix with food or liquids before administration (b) (4) (b) (4) As the drug product contains FD&C Yellow No. 6 the PI and carton labels will declare its presence as per 21 CFR 201.20(c). In an *in vitro* alcohol-induced dose dumping study, a substantial increase in amphetamine release occurred in the presence of 40% alcohol but not with 5%, 10% and 20% alcohol.

0	⇦ **Total Number of Comparability Protocols (ANDA only)**

Proposed Indication(s) including Intended Patient Population	***Treatment of ADHD in patients 6 years and older***
Duration of Treatment	***Chronic***
Maximum Daily Dose	***12.5 mg, 10 ml***
Alternative Methods of Administration	***None.***

B. Quality Assessment Overview

The proposed drug product is an extended release oral suspension containing 1.25 mg/ml of amphetamine. Amphetamine is present as an enantiomeric mixture of D- and L- isomers in a 3:1 ratio. The drug product contains the following excipients: polystyrene sulfonate, purified water, (b) (4) methacrylic acid, triethyl citrate, citric acid, propylene glycol, methylparaben, propylparaben, xantham gum, vegetable oil, sorbitol solution, orange (b) (4) color (Yellow #6), sucralose, and natural orange (b) (4)

(b) (4) The drug product contains immediate release drug resinate (b) (4) and delayed release (b) (4) drug resinate. The combination of resinates (b) (4) was designed to provide an equivalent biphasic dissolution/plasma profile to Adderall XR, the reference listed drug product (NDA 21303). (b) (4)

(b) (4)

Data found that typical oral delivery devices (spoon, cup, syringe) reliably delivered typical measured dose. The drug product does require shaking. (b) (4)

(b) (4) A study (b) (4) by OPQ OTR (see Attachment) found that the product met assay specification, (b) (4)

(b) (4) Data support a 30 day in-use period for the drug product after opening the bottle. The applicant provided stability data on the registration batches through six months of accelerated storage and 24 months of long-term storage. The results met specification and support the proposed 36 month shelf life for the drug product when stored at controlled room temperature.

The drug product manufacturing process was found adequate. Dr. Cai (process reviewer) participated in the PAI of the manufacturing site (Neos, Texas). (b) (4)

(b) (4)

(b) (4)

The biopharmaceutics review team found the two-stage (pH 1.2 and 6.8) dissolution method acceptable and the data supported the extended release claim. In an *in vitro* alcohol-induced dose dumping study found that a significant increase in amphetamine release occurred in the presence of 40% alcohol but not with 5%, 10% and 20% alcohol. Comparative dissolution studies showed the commercial scale and clinical trial formulation had similar in vitro dissolution behavior. They defer to the OCP review team for results of the in vivo formulation bridging via BA/BE study.

(b) (4) are used for microbial control. The microbiological reviewer found that the preservative and microbiological testing of the stability batches assures the microbiological quality of the drug product and that data support a 30 day in-use period.

The manufacturing sites were found acceptable by OPF on 28 AUG 2017.

Drug substance information was referenced to DMF (b) (4) Both were reviewed in 2015 and found adequate. The claimed categorical exclusion from an EA per 21CFR 25.31 was found acceptable.

C. Special Product Quality Labeling Recommendations

- Shaking before use
- No mixing with food or liquids before administration
- Presence of Yellow #6.
- In an *in vitro* alcohol-induced dose dumping study, a substantial increase in amphetamine release occurred in the presence of 40% alcohol but not with 5%, 10% and 20% alcohol.

D. Final Risk Assessment (see Attachment)

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LABELING

R Regional Information

1.14 Labeling

Labeling & Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AMPHETAMINE XR-OS (Amphetamine Extended Release Oral Suspension) safely and effectively. See full prescribing information for AMPHETAMINE XR-OS.

AMPHETAMINE XR-OS (Amphetamine Extended Release Oral Suspension), CII
Initial U.S. Approval: (b) (4)

WARNING: ABUSE AND DEPENDANCE
See full prescribing information for complete boxed warning.
- **CNS stimulants, including AMPHETAMINE XR-OS, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. (5.1, 9.3)**
- **Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy (9.2, 9.3)**

INDICATIONS AND USAGE

AMPHETAMINE XR-OS is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older. (1)

DOSAGE AND ADMINISTRATION
- (b) (4) (2.2)
- May be taken with or without food (2.2)
- Pediatric patients (ages 6 to 17 years): Starting dose is 6.3 mg (5 ml) once daily in the morning. Maximum dose is 18.8 mg (15 ml) for patients 6 to 12 years, and 12.5 mg (10 ml) once daily for patients 13 to 17 years. (2.3)
- Adults: 12.5 mg (10 ml) once daily in the morning. (2.4)
- To avoid substitution errors and overdosage, do not substitute for other amphetamine products on a milligram-per-milligram basis because of different amphetamine (b) (4) compositions and differing pharmacokinetic profiles (2.5, 5.8)

DOSAGE FORMS AND STRENGTHS

Extended-release oral suspension containing 1.25 mg amphetamine base per mL (3)

CONTRAINDICATIONS
- Known hypersensitivity to amphetamine products or other ingredients in AMPHETAMINE XR-OS (4)
- Use of monoamine oxidase inhibitor (MAOI) or within 14 days of the last MAOI dose. (4)

WARNINGS AND PRECAUTIONS
- *Serious Cardiovascular Reactions:* Sudden death has been reported in association with CNS stimulant treatment at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, or coronary artery disease. (5.2)
- *Blood Pressure and Heart Rate Increases:* Monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic. (5.3)
- *Psychiatric Adverse Reactions:* May cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use. (5.4)
- *Long-Term Suppression of Growth:* Monitor height and weight in pediatric patients during treatment. (5.5)
- *Peripheral Vasculopathy, including Raynaud's phenomenon:* Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.6)
- *Serotonin Syndrome:* Increased risk when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdosage situations. If it occurs, discontinue AMPHETAMINE XR-OS and initiate supportive treatment (5.7, (b) (4)

ADVERSE REACTIONS
- Pediatric patients ages 6 to 12 years: Most common adverse reactions (≥5% and with a higher incidence than on placebo) were loss of appetite, insomnia, abdominal pain, emotional lability, vomiting, nervousness, nausea, and fever. (6.1)
- Pediatric patients ages 13 to 17 years: Most common adverse reactions (≥5% and with a higher incidence than on placebo) were loss of appetite, insomnia, abdominal pain, weight loss, and nervousness. (6.1)
- Adults: Most common adverse reactions ≥5% and with a higher incidence than on placebo were dry mouth, loss of appetite, insomnia, headache, weight loss, nausea, anxiety, agitation, dizziness, tachycardia, diarrhea, asthenia, and urinary tract infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Neos Therapeutics, Inc. at 1-888-219-1789 (b) (4) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Acidifying and Alkalinizing Agents: Agents that alter urinary pH can alter blood levels of amphetamine. Acidifying agents can decrease amphetamine blood levels, while alkalinizing agents can increase amphetamine blood levels. Adjust AMPHETAMINE XR-OS dosage accordingly. (7.1)

USE IN SPECIFIC POPULATIONS
- *Pregnancy*: Based on animal data, may cause fetal harm. (8.1)
- *Lactation*: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: (b) (4)

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

DOSAGE FORM AND STRENGTH

3 DOSAGE FORMS AND STRENGTHS

Extended-release oral suspension contains 1.25 mg amphetamine (b) (4) per mL.

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

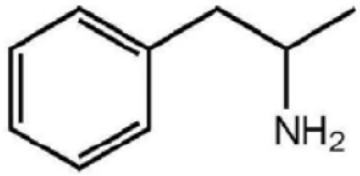
DESCRIPTION

11 DESCRIPTION

AMPHETAMINE XR-OS (amphetamine) extended-release oral suspension contains a 3 to 1 ratio of *d*- to *l*-amphetamine, a central nervous system stimulant.

The labeled strength reflects the amount of amphetamine (b) (4) in AMPHETAMINE XR-OS whereas the strengths of the (mixed salts of a single-entity amphetamine) products are in terms of the amount of amphetamine salts. Table 1 in Section 2.5 details the equivalent amounts of active ingredient in these products.

Structural Formula:



$C_9H_{13}N$ MW 135.21

AMPHETAMINE XR-OS is an extended-release oral suspension containing (b) (4) immediate-release and (b) (4) delayed-release amphetamine.

AMPHETAMINE XR-OS also contains the following inactive ingredients: purified water, sorbitol, propylene glycol, xanthan gum, natural orange flavor, methacrylic acid and methyl methacrylate copolymer, sodium polystyrene sulfonate, vegetable oil, triethyl citrate, methylparaben, citric acid, sucralose, propylparaben, orange color, and polyethylene glycol.

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

HOW SUPPLIED

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

AMPHETAMINE XR-OS (b) (4) has a concentration (b) (4) of 1.25 mg/mL amphetamine (b) (4) and is supplied as light orange to golden, viscous, opaque suspension with orange flavor in bottles of 450 mL (NDC 70165-003-15).

(b) (4) Storage and Handling

Dispense in a tight container with child-resistant closure.

Store at 20° to 25° C (68° to 77° F); excursions permitted from 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature].

The pharmacist should provide an oral dosing (b) (4) or other suitable measuring device.

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

Immediate Container Label

(b) (4)

Reviewer's Assessment:

Item	Information Provided in NDA	Conclusions
Proprietary name,	The established name follows the proprietary	Adequate

established name (font size and prominence (21 CFR 201.10(g)(2))	name. The font size of the established name is at least half of the most prominent proprietary name font size.	
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The quantity of the active ingredient provided is accurate.	Adequate
Net contents (21 CFR 201.51(a))	The number of tablets is not included on the label.	Adequate
Lot number per 21 CFR 201.18	There is a designated space for the lot number.	Adequate
Expiration date per 21 CFR 201.17	There is a designated space for the expiration date.	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	The label does not bear the "Rx only" statement.	Adequate
Storage (not required)	The storage conditions are included	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	There is a designated space for the NDC number.	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	The bar code appears on the label.	Adequate
Name of manufacturer	The manufacture is listed on the label.	Adequate
Others	NA	NA

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

Conclusion:

The label is accurate and consistent with the information provided in the NDA.

List of Deficiencies: Not Applicable

Primary Labeling Reviewer Name and Date: Andrei Ponta 31-Jul-2017

Andrei Ponta

Digitally signed by Andrei Ponta
Date: 8/01/2017 09:16:15AM
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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 8/01/2017 09:19:04AM
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BIOPHARMACEUTICS

Product Background:

NDA: 204325 [505(b)(2)]

Drug Product Name / Strength: Amphetamine Extended-Release Oral Suspension, 1.25 mg/mL

Route of Administration: Oral

Applicant Name: Neos Therapeutics, Inc.

Review Summary:

The Applicant submitted NDA 204325 on 11/15/2016 in seeking approval for the proposed Amphetamine Extended-Release Oral Suspension (Amphetamine XR-OS) 1.25 mg/mL, indicating for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older. The list drug (LD) products are the extended-release ADDERALL® XR approved under NDA 021303.

The proposed Amphetamine XR-OS formulation contains (b) (4)

The Biopharmaceutics review evaluates: 1) in vitro dissolution method and acceptance criteria, 2) in vitro alcohol dose dumping studies, 3) the extended release claim for the proposed drug product, and 4) bridging of formulations.

(1) In Vitro Dissolution Method and Acceptance Criteria

The proposed in vitro dissolution method: USP Apparatus II paddle, 75 rpm; acid stage is 900 mL of 0.1 N HCl (pH 1.2); buffer stage is 1000 mL of phosphate buffer (pH 6.8). The proposed acceptance criteria are: (b) (4)% drug release at 0.25 hours, (b) (4)% drug release at 2.00 hour, and NLT (b) (4)% drug release at 2.50 hours. Both in vitro dissolution method and the acceptance criteria are acceptable.

(2) In Vitro Alcohol-Induced Dose Dumping

The in vitro dose dumping potential was observed with the highest 40% alcohol, but not the lower % alcohol, in acidic dissolution medium for the proposed drug product, Amphetamine XR-OS. The in-vivo dose-dumping potential is not expected in view of the lack of in-vivo dose dumping for Amphetamine XR-ODT (b) (4)

(3) The Extended Release Claim

The submitted information, including the Pharmacokinetic properties and bioavailability profiles, met the requirements as described in *21 CFR 320.25(f)* and thus supported the extended release (ER) claim for the proposed drug product, Amphetamine XR-OS.

(4) Bridging of Formulations

The comparative dissolution studies showed the commercial scale formulation and the clinical trial formulation of the proposed Amphetamine XR-OS having similar in vitro dissolution behavior. Defer to the OCP review team for results of the in vivo formulation bridging via BA/BE study.

RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 204325 for Amphetamine Extended-Release Oral Suspension, 1.25 mg/mL, is recommended for APPROVAL.

The approved dissolution method and acceptance criterion are summarized as follows:

USP Apparatus	II (Paddle)
Dissolution Media and Volume	Acid Stage (0-2 hours): 0.1 N HCl (pH 1.2), 900 mL Buffer Stage (After 2 hours): Phosphate buffer (pH 6.8), 1000 mL
Agitation speed	75 rpm
Temperature	37°C ± 0.5°C
Sampling time points	0.25, 0.5, 2, 2.25, 2.5, 3 and 4 hours
Sample volume	15 mL
Acceptance criteria	Acid stage: (b) (4) % at 0.25 hours % in 2.00 hours Buffer stage: NLT (b) (4) % in 2.50 hours

Note: in M.3.2.P.5.1, the proposed dissolution specification did not specify the acid stage or buffer stage, however, the dissolution analytical procedure (method # TM-082) submitted in M.3.2.P.5.2 stated that sample acquisition time at acid stage (prior to pH change) is 0.25, 0.5 and 2.0 hour, and the sample acquisition time at buffer stage (after pH change) is 2.25 and 2.5 hour.

The Applicant will be requested to (1) clarify the acid and buffer stages in specification table of the proposed drug product and (2) to acknowledge the FDA recommended acceptance criteria.

BCS Designation

Reviewer's Assessment:

The Applicant did not submit a formal request for BCS Class 1 or Class 3 designation or relevant information/data for the drug substance or drug product.

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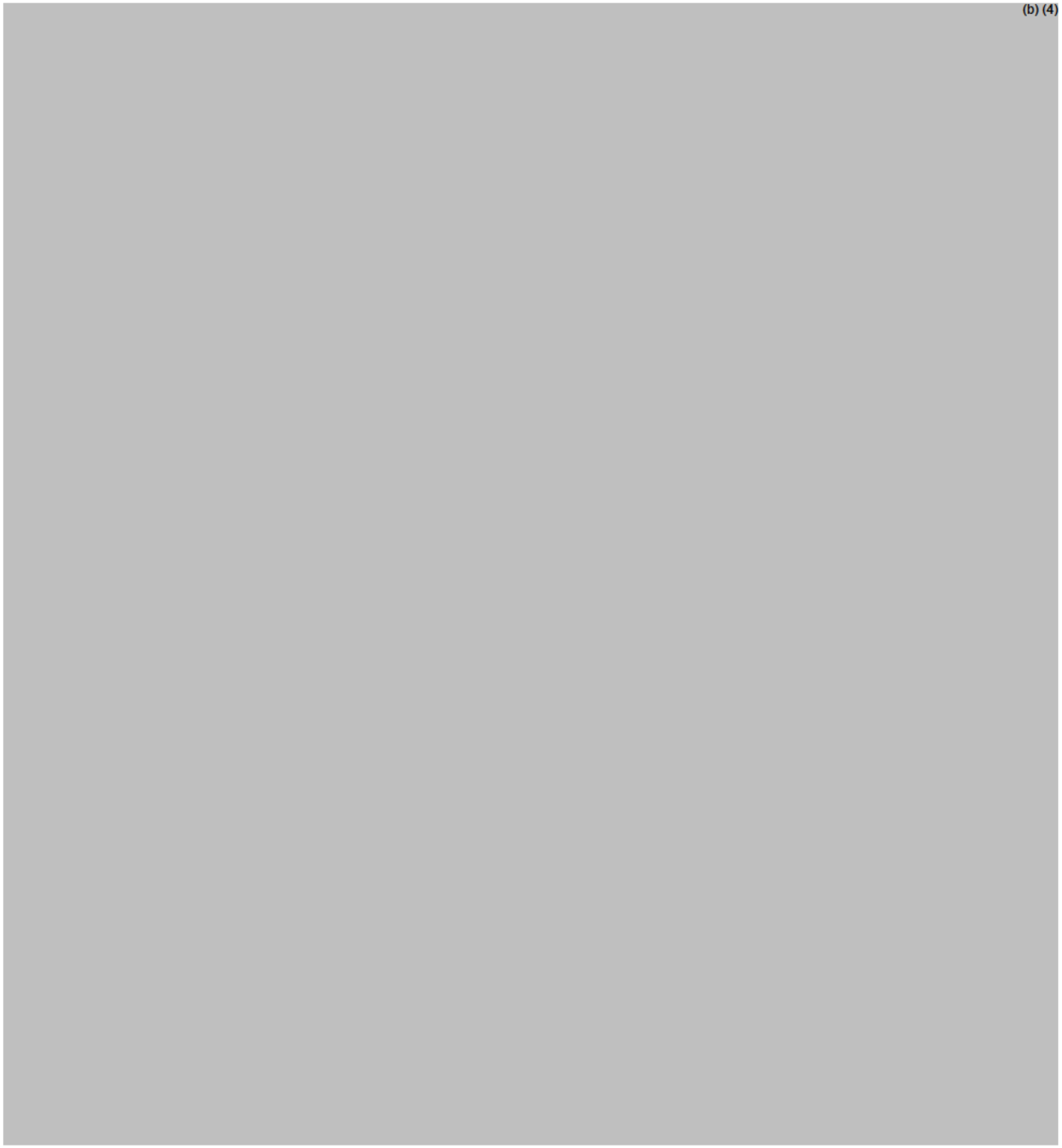
(b) (4)



MODIFIED RELEASE ORAL DRUG PRODUCTS – In-Vitro Alcohol Dose Dumping

Reviewer's Assessment:

The alcohol-induced dose dumping potential of the proposed Amphetamine XR-OS was investigated in 0.1 N HCl with 0, 5, 10, 20 and 40% (v/v) of ethanol, using the proposed dissolution method, with samples being collected at 0.25, 0.5, 1, 2, 2.25 and 2.5 hours (Study SR14-022 in M.5.3.1.3). In addition, comparisons were made comparing results from this study

to those previously obtained from the approved drug product, Amphetamine XR-ODT 30 mg, and the LD product, ADDERALL® XR 30 mg (Studies SR14-019 and SD14-022 in M.5.3.1.3). The dissolution profile data are presented in Table 20 and Figure 7. Results of the similarity factor (*f2*) calculation are summarized in Table 21.

Table 20: In Vitro Dissolution Data of Amphetamine XR-OS (Lot 4E057) in Varying Concentrations of Ethanol from 0% to 40%

	Time (Hours)			
	0.25	0.50	1.00	2.00
0% Alcohol	56.3%	57.1%	58.0%	59.1%
5% Alcohol	56.7%	57.5%	58.5%	59.8%
10% Alcohol	57.2%	57.9%	59.0%	60.3%
20% Alcohol	56.7%	59.6%	61.4%	63.8%
40% Alcohol	78.6%	84.7%	92.5%	97.0%

Figure 7: In Vitro Dissolution Profiles of Amphetamine XR-OS (Lot 4E057) in Varying Concentrations of Ethanol from 0% to 40%

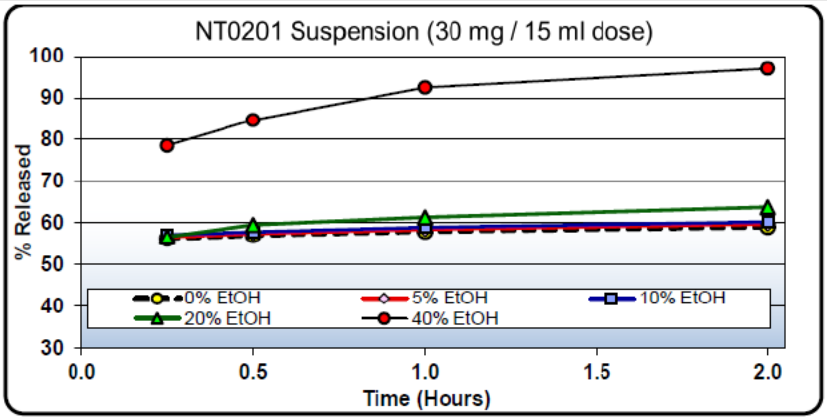


Table 21: Similarity Factor (*f2*) Comparisons of Amphetamine XR-OS in Varying Concentrations of Ethanol to Control (0% Ethanol)

	Similarity Factor (F2) Compared to Control (0% Ethanol)
	0.25 hr to 2.0 hr
5% Alcohol	97.4%
10% Alcohol	92.6%
20% Alcohol	74.0%
40% Alcohol	25.3%

hr = hour(s)

Significant increase in drug release from Amphetamine XR-OS was observed in the presence of 40% ethanol. For comparison, Amphetamine XR-ODT 30 mg and ADDERALL® XR 30 mg showed the similar alcohol dose dumping potential in 40% ethanol, given in Figure 8-9. The individual data were provided in study report (SR14-019) in M.5.3.1.3 (Application 204325 - Sequence 0000 - Report SR14-019).

Figure 8: In Vitro Dissolution Profiles of Amphetamine XR-ODT 30 mg (NT0202; revised Formulation, Lot 4E042E) in Varying Concentrations of Ethanol from 0% to 40%

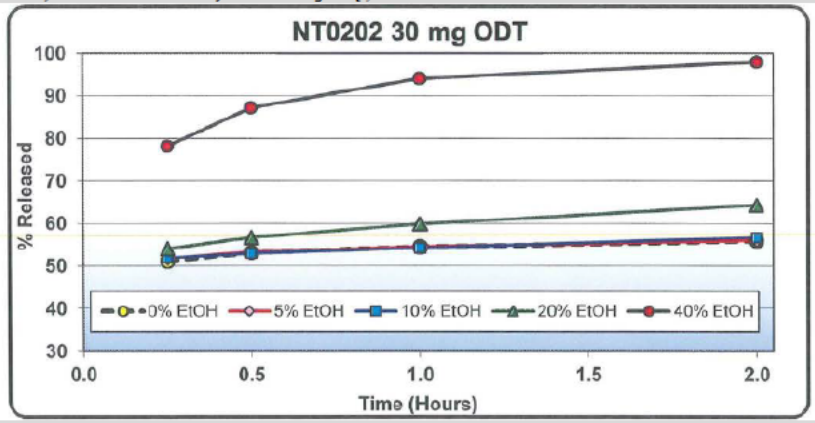
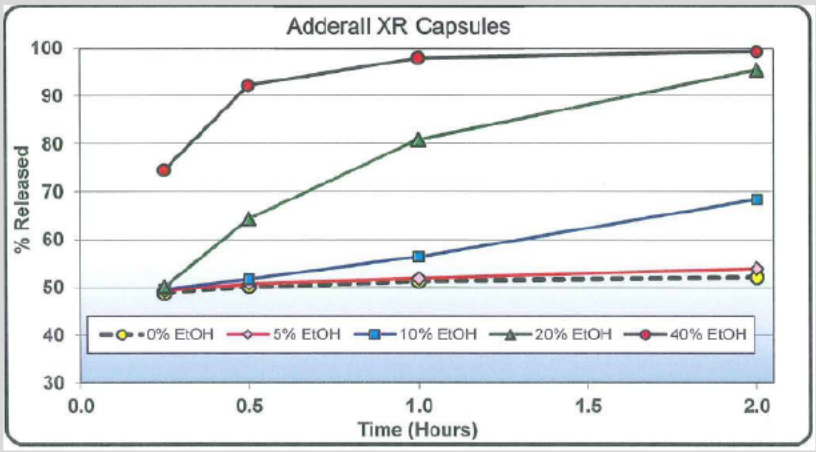


Figure 9: In Vitro Dissolution Profiles of ADDERALL® XR 30 mg (Lot A90382A) in Varying Concentrations of Ethanol from 0% to 40%



Reviewer's Comment:

Note that, despite the in vitro observation, results of an in-vivo study (Protocol NT0202.1003) did not reveal an alcohol-induced dose-dumping potential with up to 40% alcohol in humans for Amphetamine XR-ODT. This Reviewer expects that the Amphetamine XR-OS would act similarly with Amphetamine XR-ODT in vivo in the presence of alcohol (b) (4)

The acceptability of the Applicant's proposed labeling statement and the clinical implications, based on the findings of the in vitro and in vivo results, will be deferred to Clinical and Clinical Pharmacology review teams.

EXTENDED RELEASE DOSAGE FORMS – Extended Release Claim

Reviewer's Assessment:

The submitted information supported the extended release (ER) claim for the proposed drug product, Amphetamine XR-OS for the following reasons:

Meeting requirements described in *21 CFR 320.25(f)*:
(1) Following oral administration of the commercial scale formulation of Amphetamine XR-OS to healthy subjects, the bioequivalence for d- and l-amphetamine was established based on the geometric mean ratios and the 90% confidence intervals for the log-transformed C_{max}, AUC_{0-5}, AUC_{5-last}, and AUC_{inf}, against the LD product ADDERALL® XR under fasted conditions, being within the 80 to 125% BE acceptance range (pivotal BE study NT0201.1008) (Table 22). The median T_{max} of both d- and l-amphethamine in plasma after oral administration for both Amphetamine XR-OS and ADDERALL® XR was similar at approximately 5 hours. The plasma concentration-time profiles of the active moieties from both drug products were almost superimposable, as illustrated in Figures 10-11.

Table 22: Analysis of d-amphetamine and l-amphetamine comparing the commercial scale formulation of Amphetamine XR-OS to ADDERALL XR under fasted conditions following single dose oral administration, Study NT0201.1008

Parameter	Geometric Mean Ratio (%)[a]		90% Confidence Interval[b]	
	d-amphetamine	l-amphetamine	d-amphetamine	l-amphetamine
$\ln(C_{max})$	94.09	97.71	92.32, 95.90	95.91, 99.55
$\ln(AUC_{0-5})$	97.69	100.91	92.02, 103.71	95.07, 107.11
$\ln(AUC_{5-last})$	94.54	98.29	91.27, 97.92	94.83, 101.87
$\ln(AUC_{inf})$	94.23	97.70	91.50, 97.04	94.54, 100.96

[a] Ratio (%) = geometric mean for Commercial Formulation Amphetamine XR-OS /geometric mean for ADDERALL XR
[b] To be labeled as bioequivalent, the 90% confidence interval for the geometric mean ratio must fall between 80% to 125%.
$\ln(AUC_{0-5})$ = log-transformed area under the concentration time curve from time zero to 5 hr; $\ln(AUC_{5-last})$ = log-transformed area under the concentration time curve from time zero to the time of the last quantifiable concentration; $\ln(AUC_{inf})$ = log-transformed area under the plasma concentration time curve from time zero extrapolated to infinity; $\ln(C_{max})$ = log-transformed peak concentration in plasma
Source: NT0201.1008: Table 11.4.3.5 and 11.4.3.6

Figure 10: Mean *d*-amphetamine Concentration-Time Profiles after administration of AMP XR-OS (Treatment A) and Adderall XR (Treatment B)

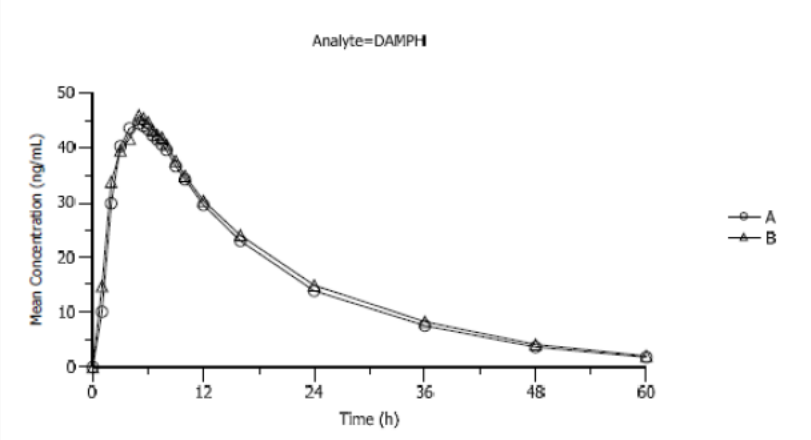
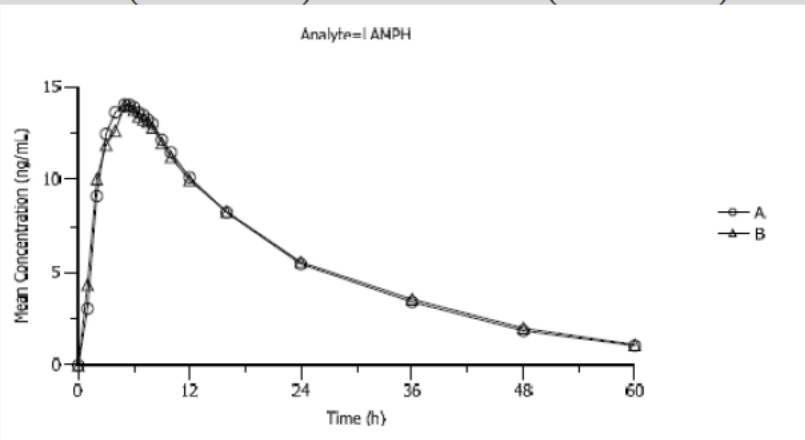


Figure 11: Mean *l*-amphetamine Concentration-Time Profiles after administration of AMP XR-OS (Treatment A) and Adderall XR (Treatment B)



(2) The commercial scale formulation and clinical trial formulation of Amphetamine XR-OS were also shown to be the bioequivalent with respect to d- and l-amphetamine under fasted or fed condition (BA/BE study NT0201.1007). The clinical trial formulation of Amphetamine XR-OS was also shown to be bioequivalent to the LD product ADDERALL® XR under fasted conditions (BA/BE study NT0201.1005). The plasma concentration-time profiles of the active ingredients of the commercial scale formulation and the clinical trial formulation of Amphetamine XR-OS were also superimposable against the LD product.

(3) The drug product's steady-state performance was shown to be equivalent to a currently marketed extended release LD product, ADDERALL® XR (approved under NDA 21203), that contains the same active drug ingredient or therapeutic moiety.

(4) Same dosing benefit/frequency (once daily, taken with or without food) as the LD extended-release products.

(5) Dose dumping potential can be ruled out for the Amphetamine XR-OS in the presence of food or alcohol, as described in the above sections.

Supportive in-vitro dissolution information:
Similar drug release profiles are shared by both the proposed Amphetamine XR-OS and LD product ADDERALL® XR (b) (4)

Bridging of Formulations

Reviewer's Assessment:

As recommended by the FDA (Pre-NDA meeting dated June 19, 2014), a bioequivalence study to bridge the commercial to the clinical product, as well as comparative multipoint dissolution

data in support of the proposed changes in the commercial product relative to the clinical product will be necessary for the Applicant's planned NDA.

To support the approval for the proposed drug product, the Applicant conducted a BA/BE study (NT0201.1007) to evaluate the comparative pharmacokinetic profiles of API between commercial scale formulation and clinical trial formulation following a single dose in healthy adults. The PK parameters C_{max}, AUC_{last}, and AUC_{inf} of the active moieties were reported being within the accepted 80 to 125% range. The review of this in vivo BE study will defer to the OCP review team.

In addition, the in vitro comparative dissolution studies were performed between the commercial scale formulation (Lot 4E057B) and the clinical trial formulation (Lot 2E083E2) (b) (4)

(b) (4)

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(b) (4)

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Reviewer's Comment:

Results of comparative dissolution profile data and the *f2* calculation show that both commercial scale formulation and the clinical trial formulation of the proposed Amphetamine XR-OS have similar in vitro dissolution behaviors. No additional formulation bridging is needed from the Biopharmaceutics perspective. Note that the acceptability of the bridge between these two formulations in vivo in the pivotal BA/BE study will be assessed by the OCP.

List of Deficiencies: N/A

Primary Biopharmaceutics Reviewer Name and Date:

Mei Ou, Ph.D. *03/30/2017*
Biopharmaceutics Reviewer
Division of Biopharmaceutics Branch III (DBIII)
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality (OPQ)

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Ta-Chen Wu, Ph.D. *08/18/2017*
Activing Biopharmaceutics Lead
Division of Biopharmaceutics Branch I (DBI)
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality (OPQ)

Ta-Chen Wu

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Mei Ou

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Date: 8/21/2017 09:10:08AM
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MICROBIOLOGY

Product Background: -

NDA: 204325

Drug Product Name / Strength: Amphetamine Extended-Release Oral Suspension

Route of Administration: Oral

Applicant Name: Neos Therapeutics, Inc.

Manufacturing Site: Neos Therapeutics, LP, 2940 North Highway 360, Suite 100, Grand Prairie, TX 75050

Method of Sterilization: Not applicable, non-sterile

Review Summary: The submission is recommended for approval on the basis of sterility assurance.

List Submissions being reviewed: 11/15/2016; 02/17/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

Supporting/Related Documents: N/A

Remarks Section: The submission dated 02/17/2017 contains the applicant's response to the 74 day letter comments and 24 months of stability data.

S Drug Substance – N/A, non-sterile

P.1 Description of the Composition of the Drug Product

- Description of drug product – Non-sterile drug-resinate (b) (4) suspension for oral administration. The drug product includes a (b) (4) 450 mL (b) (4) bottle.

- Drug product composition –

Ingredient	Quality Standard	Function	% w/w	mg/mL dose
(b) (4) (b) (4)	USP			(b) (4)
	USP			
	USP			
	USP			
Levoamphetamine	USP			
Dextroamphetamine	USP			
Polystyrene Sulfonate	USP			
Polyethylene Glycol (b) (4)	NF			
Methacrylic Acid and Methyl Methacrylate Copolymer	NF			
Triethyl Citrate	NF			
Purified Water[b]	USP			
(b) (4)				
Purified Water[a]	USP			
Citric Acid (b) (4)	USP			
Propylene Glycol	USP			
Methylparaben	NF			
Propylparaben	NF			
Xanthan Gum	FCC			
Vegetable (b) (4) Oil	FCC			
Sorbitol (b) (4)	USP			
Orange (b) (4) Color	FCC			
Natural Orange (b) (4)	Supplier			
Sucralose	NF			
(b) (4)				
b (b) (4)				
(b) (4)				

- Description of container closure system –

Component	Description	Manufacturer
Bottle	(b) (4) mL Glass bottles (b) (4), amber (b) (4) glass	(b) (4)
Closure	Child-Resistant Closure, (b) (4), white-ribbed, with tamper evident ring and sealing line	

Reviewer's Assessment: The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain microbiological quality.

Acceptable

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity – N/A, non-sterile

Antimicrobial Effectiveness Testing

Antimicrobial effectiveness testing was performed according to USP <51> on lot # RD09-S009-90, which was formulated with the (b) (4) preservatives at the lower limit ((b) (4) %) of the finished product release specification and stability specification.

Note to Reviewer: (b) (4)

he submission dated 11/15/2016 indicates that the lot used for AET (#RD09-S009-90) is formulated with the preservatives at the lower limit of the release and stability specification, (b) (4) The drug product reviewer issued the following deficiency in the 74 Day Letter dated 01/26/2017.

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).

The applicant provided the drug product composition of lot #RD09-S009-90. The composition of the lot used for AET is the same as the commercial composition, except that it contains (b) (4)% of the commercial levels of (b) (4)

Results

The actual plate counts were not provided. The submission provided the initial population and the log reduction over 28 days. The results are summarized in the table below.

Organism	Log Population		
	Day 0	Day 14	Day 28
A. niger (ATCC 16404)	5.23	2.68	2.56
C. albicans (ATCC 10231)	5.01	2.77	< 1
E. coli (ATCC 8739)	5.51	< 1	< 1
S. aureus (ATCC 6538)	5.38	< 1	< 1
P. aeruginosa (ATCC 9027)	5.56	< 1	< 1

Lot # RD09-S009-90 met the USP <51> Category 3 acceptance criteria for antimicrobial effectiveness.

Reviewer's Assessment: The applicant has shown that the drug product formulated at the lower limit of the release and stability specification for each preservative meets the USP <51> Category 3 criteria for antimicrobial effectiveness.

Acceptable

P.3 Manufacture

P.3.1 Manufacturers

Neos Therapeutics, LP, 2940 North Highway 360, Suite 100, Grand Prairie, TX 75050. Responsible for the manufacturing, packaging, testing, release and stability testing of the finished drug product.

Drug product

Release/stability testing (as applicable) – N/A

P. 3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

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(b) (4)

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P.7 Container Closure – See P.1

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(Section 3.2.P.8.1, Stability Summary)

Proposed Expiry: (b) (4)

The stability testing schedule is as follows:

Stability storage conditions: 25°C ± 2°C/ 60% RH

Test	Time (Months)								
	0	3	6	9	12	15	18	24	36
(b) (4) Assay	H/U	H/U	H/U	H/U	H/U		H/U	H/U	NP
Assay	H/U	H/U	H/U	H/U	H/U		H/U	H/U	NP
Total Aerobic Microbial Counts (TAMC)	H/U				U			U	NP
Total Yeast and Mold Count (TYMC)	H/U				U			U	NP
Absence of *S. aureus*	H/U				U			U	NP
Absence of *Salmonella* species	H/U				U			U	NP
Absence of *E. coli*	H/U				U			U	NP
Absence of *P. aeruginosa*	H/U				U			U	NP
Absence of *B. cepacia* Complex (BCC)							U	U	U
Antimicrobial effectiveness					U			U	NP

H = Horizontal; U = upright; NP = Not provided

Reviewer's Assessment: The stability testing schedule is adequate to support the proposed expiry.

Acceptable

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(Section 3.2.P.8.1, Stability Summary; Section 3.2.P.8.2, Post-Approval Stability Protocol and Commitment; Section 3.2.P.5.1, Specification(s))

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
(b) (4) Assay	HPLC	(b) (4) %
Assay	HPLC	%
Total Aerobic Microbial Counts (TAMC)	USP <61>	NMT (b) (4) CFU/g
Total Yeast and Mold Count (TYMC)	USP <61>	NMT (b) (4) CFU/g
Absence of *E. coli*	USP <62>	Absent in 1 mL
Absence of *B. cepacia* Complex (BCC)	Microbial identification and enumeration	Absent in 1 mL

Note to Reviewer: The applicant performed tests for absence of *Salmonella* species (absent/10 mL), *S. aureus* (absent/1 mL), and *P. aeruginosa* (absent/1 mL) per USP <62> on registration lots through 12 months of long-term storage at 25ºC/60% RH and 6 months of accelerated storage at 40ºC/75% RH. The applicant concluded from the results that no significant trend was observed. Testing for absence of *Salmonella* species, *S. aureus*, and *P. aeruginosa* (b) (4) See Section 3.2.P.2, Microbiological Attributes.

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 25ºC / 60% RH, upright orientation

Test	Time (Months)								
	0	3	6	9	12	15	18	24	36
(b) (4) Assay	X	X	X	X	X		X	X	X
Assay	X	X	X	X	X		X	X	X
Total Aerobic Microbial Counts (TAMC)	X				X			X	X
Total Yeast and Mold Count (TYMC)	X				X			X	X
Absence of *E. coli*	X				X			X	X
Absence of *B. cepacia* Complex (BCC)	X								

Post Approval Stability Commitment

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Reviewer's Assessment: The stability specification and post-approval stability protocol and commitment are adequate to assure maintenance of the drug product's microbiological quality

Acceptable

P.8.3 Stability Data

The results of microbiological testing of lot #4E057A, #4E057B, #4E058A, #4E058B, #4E059A, and #4E059B stored under long-term conditions in the upright orientation were provided. All lots met the specification for (b) (4) TAMC, TYMC, and absence of *S. aureus*, *Salmonella* species, *E. coli*, and *P. aeruginosa* at the time points indicated in the stability testing schedule described in Section P.8.1 of this review. All lots met the specification for absence of BCC organisms at the 18 and 24 month time points. The lots will undergo testing for absence of BCC organisms at 36 months, but the data is not yet provided. The lots were tested for antimicrobial effectiveness at 12 and 24 months and conformed to the USP <51> acceptance criteria for a Category 3 Product.

Reviewer's Assessment: The preservative and microbiological testing of the stability batches assures the microbiological quality of the drug product stored under long-term conditions up to the (b) (4) month proposed expiry.

Acceptable

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: Not applicable

A.2.1 Materials of Biological Origin

Reviewer's Assessment: Not applicable

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: Not applicable

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: Not applicable

A.2.4 Viral Clearance Studies

Reviewer's Assessment: Not applicable

R Regional Information

Executed Batch Records

Executed batch records are provided for lot #(s): 4E057A, 4E057B, 4E058A, 4E058B, 4E059A, 4E059B.

Note to Reviewer: No manufacturing steps required validation to assure microbiological quality.

Reviewer's Assessment: Not applicable

Comparability Protocols – No CP was included in the application.

Reviewer's Assessment: Not applicable

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

(Section 1.14.1.3, Draft Labeling Text – PDF; Section 3.2.P.2, Container Closure System)

Storage temperature: 20 – 25ºC, excursions permitted from 15 – 30ºC. ; Route of administration: oral; Container: (b) (4) The drug product is not reconstituted or further diluted.

An in-use period is not specified in the package insert. (b) (4)

(b) (4)

Note to Reviewer: Thirty days is not substantially longer than the 28 day time period for which the subject drug product has been shown to be antimicrobial.

Reviewer's Assessment: The labeling instructions are adequate to support the microbiological quality of the subject drug product.

Acceptable

Post-Approval Commitments: N/A

Lifecycle Management Considerations

Reviewer's Assessment: Changes to the post-approval stability protocol would require review.

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date: Elizabeth Bearr, 03/09/2017
Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Elizabeth Bearr

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Erika Pfeiler

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FDA/CDER/OPQ/OTR
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis MO 63110
P: 314.539.2135

METHOD VERIFICATION REPORT SUMMARY

Date: May 18, 2017

To: Andrei Ponta, Drug Product Reviewer
Grafton Adams, RBPM

Through: Jason Rodriguez, Ph.D., Acting Lab Chief, Branch I, CDER/OPQ/OTR/DPA

From: Cindy Diem Ngo, Chemist, CDER/OPQ/OTR/DPA
Laura C. Pogue, Ph.D., Method Verification Coordinator, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 204325: Amphetamine ER Oral Suspension 1.25 mg/mL

The following methods were evaluated and are *acceptable* for quality control and regulatory purposes:

1. TM-052: Assay and Uniformity of Dosage Units-Amphetamine Extended Release Oral Suspension
2. Additional observations and analysis per reviewer suggestions

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to the methods:

1. All method analyses passed specifications. Additional studies and observations to investigate the precipitation or separation of particulates did not result in any significant concerns. As expected, the use of a dosing cup with viscous suspensions will lead to the remainder of drug product on the walls of a dosing cup (values reported below). The use of a syringe could minimize this effect as suggested by DPA analysis.

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Jason Rodriguez

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RISK ASSESSMENT

Review Assessment				
Attribute/ CQA	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
	H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	L	Release and stability testing	Acceptable	
Physical stability (b) (4)	L		Acceptable	(b) (4)
Viscosity	L	(b) (4)	Acceptable	

		suspension		
Physical stability (b) (4)	M	(b) (4)	Acceptable	(b) (4)
Dosing accuracy	H	Data were provided to demonstrate that typical dosing devices can reliably deliver typical doses. Data were provided to support the in-use periods. Study by OTR in St Louis found product could be dosed accurately.	Acceptable	
Palatability	M	Did not appear to be an issue during clinical studies.	Acceptable	

		(b) (4)		
Microbial Limits	L	Found to be acceptable by the micro review team.	Acceptable	
Leachables	M	Data on articles tested found no issues with leachables.	Acceptable	
Dissolution for Suspension only	M	(b) (4)	Acceptable	

		method		
Alcohol dose dumping	H	Dose dumping found at highest in vitro alcohol levels (40%). (b) (4)	Acceptable	(b) (4)

David Claffey

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