CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204326Orig1s000

CHEMISTRY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 204326

Adzenys XR-ODT

Review #3
(Review #1 of Resubmission)

Established Name	Amphetamine Extended Release Orally Disintegrating Tablets
Strength	3.1, 6.3, 9.4, 12.5, 15.7, and 18.8 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	NEOS Therapeutics Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission	27 JUL 2015	All
Quality Amendment	29 OCT 2015	Drug product and Process
Quality Amendment	10 DEC 2015	Drug product and Drug substance
Quality Amendment	18 DEC 2015	Biopharm

Quality Review Team

DISCIPLINE	REVIEWER
Drug Substance	Andrei Ponta
Drug Product	Andrei Ponta
Process	Akm Khairuzzaman
Microbiology	Akm Khairuzzaman
Facility	Donald Obenhuber
Biopharmaceutics	Gerlie Gieser/Okpo Eradiri
Regulatory Business Process Manager	Dahlia Woody
Application Technical Lead	David Claffey

21 DEC 2015

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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)	acceptable	26-Mar-2015	
	Type II			acceptable	26-Mar-2015	
				acceptable		
				acceptable		

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Listed Drug	NDA 21303	Adderal XR

2. CONSULTS: N/A

Executive Summary

I. Recommendations: Approval

A. Recommendation and Conclusion on Approvability

1. Recommend that this application be approved from an OPQ perspective. The issues that resulted in a CR action in the previous review cycle have been resolved by reformulation of the drug product.
2. The drug product expiry period of 24 months is granted.
3. Recommend that the dosage strengths be expressed in terms of amphetamine base (b) (4)
4. (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. None.

Summary of Quality Assessments

Regulatory background: This document is the OPQ review of the resubmission after a 2013 CR action. CMC deficiencies were the main reason for the previous CR action. Chief amongst the numerous deficiencies cited were that the tablets had hardness, (b) (4) and disintegration failures (b) (4). The applicant reformulated the drug product, therefore this submission contains an entirely revised CMC section. Little of the CMC data from the initial submission were relied upon. The applicant modified the drug product formulation, manufactured new registration drug product lots, and carried out new stability studies in order to address the outstanding deficiencies. It is also noteworthy that although the reformulated product does meet specification, the root causes of the failures of the previous formulation do not appear to have been completely understood.

Dosage form and strengths: This application is a 505(b)(2) for amphetamine extended release orally disintegrating tablet (XR-ODT) referencing Adderall® XR (mixed salts of a single-entity amphetamine product) extended-release capsules (NDA 21303). The strengths, isomer mixture, and release profile are designed to be equivalent to the listed drug. (b) (4) (b) (4) Both products contain amphetamine in the salt form. The (b) (4) in Adderall XR is a mixture of salts (b) (4) (polystyrene sulfonate) is (b) (4) in the proposed product. The proposed drug product contains a 3:1 mixture of d- and l- amphetamine in six dosage strengths: 3.1, 6.3, 9.4, 12.5, 15.7, and 18.8 mg of amphetamine base equivalent which contains the same amount of amphetamine (b) (4) base equivalent as Adderall XR - 5, 10, 15, 20, 25, and 30 mg, respectively.

The applicant proposed debossing the tablets with (b) (4) (b) (4) (b) (4) This will require revision by the applicant. All the strengths are derived from a (b) (4). Tablets are packaged in six-count foil/foil blister cards and placed into secondary cartons along with a rigid, protective travel case.

Composition: [redacted], the drug product contains triethyl citrate [redacted], magnesium stearate [redacted] and crospovidone [redacted], sucralose [redacted], citric acid [redacted], orange flavor and Lake blend orange [redacted] The major difference between the failed formulation in the initial submission and the current commercial formulation is the [redacted]

Drug product control: The drug product formulation development was adequately described, excipients adequately controlled and the drug product specification was found adequate. It contained [redacted] tests and included tests [redacted] including disintegration with the recommended [redacted] acceptance criterion. Three batches of each of the strengths were manufactured. All met specification at release and found no significant changes through the available 18 months stability data. The data support the proposed 24 month drug product expiry period.

Drug product manufacturing: Drug product manufacturing involves [redacted]

Each of the manufacturing and testing facilities was found to be adequate – including the Neos Therapeutics Inc. drug product manufacturing site.

Biopharmaceutics: The biopharmaceutics review team found the application adequate. The dissolution method uses [redacted] Sampling times are at [redacted] The third and final time-point is [redacted] is required. The method was

adequately validated and can discriminate (b) (4) DR:IR ratio. A biowaiver for the lower((b) (4) strengths was granted and dose dumping was found in 40% ethanol media (will be added to label). The extended release claim was found acceptable.

(b) (4)

Drug substance: The drug substances for the sake of this application are nominally (b) (4). Their manufacture is referenced to DMFs which were found adequate. They are (b) (4) (b) (4) a 3:1 d:l amphetamine enantiomeric mixture. (b) (4) (b) (4)

A. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Adzenys XR-ODT
Non Proprietary Name of the Drug Product	Amphetamine extended release orally disintegrating tablets
Non Proprietary Name of the Drug Substance	amphetamine
Proposed Indication(s) including Intended Patient Population	ADHD
Duration of Treatment	chronic
Maximum Daily Dose	
Alternative Methods of Administration	none

B. Biopharmaceutics Considerations

1. BCS Classification: Not applicable since the proposed product is an extended release orally disintegrating tablet (XR ODT)
   - Drug Substance: N/A
   - Drug Product: N/A
2. Biowaivers/Biostudies
   - Biowaiver Requests– A biowaiver was requested for all lower (b) (4) strengths of the to-be-marketed amphetamine XR ODTs.
   - PK studies– Refer to the Clinical Pharmacology review
   - IVIVC- None

The NDA is recommended for approval from a Biopharmaceutics perspective. The following dissolution method and acceptance criteria (agreed to with the Applicant) should be used for routine QC testing of AMP XR ODT tablets.

USP Apparatus	Spindle Rotation	Medium/ Volume/Temperature	Acceptance Criteria
USP Type 2 (Paddles)	75 rpm	Acid Stage (0 - 2 hours): 900 mL of 0.1 N HCl Solution Buffer Stage: at 2 hours, add 100 mL of phosphate buffer to achieve pH 6.8 ± 0.2 medium at 37 ± 0.5 °C	Acid Stage [0.25 hours]: (b) (4) % End of Acid Stage [2.00 hours]: (b) (4) % pH 6.8 Buffer Stage [2.25 hours]: NLT (b) (4) %

C. Novel Approaches

D. Any Special Product Quality Labeling Recommendations

Per the request of the Clinical Pharmacology reviewer, (b) (4) (b) (4) (b) (4) replaced with information from the *in vitro* alcohol induced dose-dumping study using the to-be-marketed formulation. The Biopharmaceutics reviewer recommended labeling edits to this new labeling text are shown below (deleted text = strikethrough; added text = double underscore):

Alcohol Effect

In an (b) (4) *in vitro alcohol-induced dose dumping* (b) (4) *study,* (b) (4) (b) (4) *a substantial increase in amphethamine release occurred in the presence of 40% alcohol* (b) (4) (b) (4) *but not with 5%, 10%, or 20% alcohol.*

Also, recommend that the dosage strengths be expressed in terms of amphetamine base and that the embossing be revised.

E. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

David J. Claffey -S

Digitally signed by David J. Claffey -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300225565, cn=David J. Claffey -S
Date: 2015.12.22 11:29:51 -05'00'

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ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

The Biopharmaceutics review of this NDA Resubmission for the proposed commercial amphetamine (b) (4) extended release orally disintegrating tablets (AMP XR ODT) focuses on the evaluation of (1) the Applicant's biowaiver request for the five lower strengths, (2) the proposed dissolution method and acceptance criteria, (3) results of the *in vitro* alcohol induced dose dumping studies, and (4) the extended release claim for the drug product.

To closely match the systemic d-amphethamine and l-amphethamine exposures of once daily administration of the listed drug (Adderall XR), AMP XR ODT was designed so that approximately 50 (b) (4)% (b) (4) for immediate release (IR), and the remainder is for delayed release (DR). The DR portion of the drug product consists of an (b) (4)

38. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Yes, the proposed two-stage dissolution method is adequate for routine QC testing. This Biopharmaceutics Reviewer is recommending slight modifications to the acceptance criteria, based on the dissolution profiles of the pivotal BE batch and 17 other registration batches at release and over the duration of stability testing.

Dissolution Method
The parameters of the proposed dissolution method for AMP XR ODT are summarized in Table 38-1 below.

(b) (4)

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(b) (4)

[redacted]

39. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

A total of three formulations (preliminary, original and revised) were evaluated during development of AMP XR ODT. The (b) (4) strength of the revised or to-be-marketed formulation was evaluated in a pivotal BE clinical study (using Adderall XR as the reference), in a food-effect study involving healthy subjects, and in an *in vitro* alcohol induced dose-dumping study. All six proposed commercial strengths of the revised formulation manufactured at (b) (4) using the commercial process were included in registration stability studies (e.g., for evaluation of in vitro drug release using the proposed dissolution method); a total of 18 batches (3 batches per strength) including the pivotal clinical batch were evaluated. Based on cumulative *in vitro* and *in vivo* evidence gathered during development, a follow on *in vivo* alcohol induced dose dumping study was not required for the revised formulation.

All six proposed commercial strengths of the to-be-marketed drug product are (b) (4) to each other. All strengths come from a (b) (4) (b) (4) the batch formula is shown in Table 39-1.

Table 39-1. Quantitative Batch Composition of Amphethamine XR-ODT (all strengths)

Ingredient		Quality Standard	Function	Proposed Formulation (kg)	% in Formula
(b) (4)	Levoamphetamine[b]	USP	Active Ingredient		(b) (4)
	Dextroamphetamine[b]	USP	Active Ingredient		
	Polystyrene Sulfonate[c]	USP			(b) (4)
	(b) (4)	USP			
		USP			
		USP			
		USP			
		USP			
(b) (4)	Polyethylene Glycol (b) (4)	NF			(b) (4)
	Methacrylic Acid Copolymer Type A	NF			
	Triethyl Citrate	NF			
	(b) (4)	NF			
	(b) (4)	Supplier			
(b) (4)		Supplier			
Crospovidone		NF			
Sucralose		NF			
Citric Acid (b) (4)		USP			
(b) (4) Orange Flavor (b) (4) (b) (4)		Supplier			
Lake Blend Orange (b) (4)		Supplier			
Magnesium Stearate		NF			
Total Weight and Percentage					

N/A = Not applicable

[a] (b) (4) a 3:1 enantiomer ratio of dextroamphetamine to levoamphetamine.

[b] (b) (4)

[c] Sodium polystyrene sulfonate (b) (4) (b) (4).

[d] (b) (4).

[e] Provided by the supplier (b) (4)

[f] (b) (4) mannitol, fructose, microcrystalline cellulose, crospovidone, and colloidal silicon dioxide.

Source: 3.2.P.3.2 Batch Formula, Table 1

Of note, the revised formulation differs from the original formulation in terms of the following: (b) (4) (b) (4) (b) (4) These formulation changes did not appear to have significantly impacted the *in vitro* drug release of AMP XR ODT, as shown by the comparable

dissolution profiles of the original and the revised formulations in the presence and absence of alcohol in the dissolution media.

Reviewer's Assessment:

Proposed Commercial Drug Product

With the development of the revised formulation per FDA advice, the dissolution method was redeveloped and revalidated, and new clinical and registration stability studies were conducted. Note that pivotal clinical Lot 4E042E is one of the three registration lots for the (b) (4) strength of AMP XR ODT.

Since the highest proposed strength of the to-be-marketed formulation of AMP XR ODT was evaluated in pivotal *in vivo* BE and food effect studies, as well as in an *in vitro* alcohol-induced dose dumping study, a bridging study between the previous formulations and the proposed commercial formulation (highest strength) is not necessary. Accordingly, the Biopharmaceutics review did not focus on the *in vitro* and clinical data presented for the preliminary and the original formulations of AMP XR ODT. It is important to note that the original formulation was used in the trial (NT0202.1004) that evaluated the oral bioavailability of AMP XR ODT in pediatric patients 6 to 12 years old.

Furthermore, for all proposed strengths of the to-be-marketed AMP XR ODT formulation there is *in vitro* evidence of comparable drug release profiles and/or drug release data conforming to specifications during batch release and/or stability testing.

Extended Release Claim

Collectively, the following information support the extended release claim for the proposed drug product: (1) In *in vitro* dissolution studies, complete release of the active ingredients only occurs following (b) (4) (b) (4) (b) (4). As observed for the reference product, Adderall XR, (b) (4) is released immediately during the (b) (4) of dissolution testing (b) (4) whereas the (b) (4) released (b) (4) of the medium. (2) Following oral administration of the (b) (4) AMP XR ODT tablet to healthy subjects, the median plasma Tmax of both d-amphethamine and l-amphethamine was approximately 5 hours (i.e., comparable to the Tmax values observed with Adderall XR (single dose or once daily), and prolonged compared to the reported Tmax of Adderall immediate release given twice daily). In the pivotal BE study conducted by the Applicant, the C_{max}, the C_{last}, and the plasma concentration-time profiles of the active ingredients were almost superimposable, suggesting a similar fluctuation index between AMP XR ODT and Adderall XR. Note that in registration studies for Adderall XR [NDA 21-203], the plasma Tmax for both APIs was prolonged by 3 hours, and the plasma Cmax-to-Cmin ratio or fluctuation index for both APIs was lower for Adderall XR given once daily compared to Adderall IR given twice daily.

This Reviewer agrees that the proposed product is an extended release formulation consisting of both immediate release and delayed release components, and an orally disintegrating tablet.

Orally Disintegrating Tablet Classification
Based on the rapid *in vitro* disintegration time (NMT [redacted] (b) (4) along with the manner by which it was administered to the participants of the pivotal BE study, the proposed tablet could be categorized as an orally disintegrating tablet (ODT).

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:
The contents of the NDA resubmission adequately address the Biopharmaceutics related deficiencies in the Complete Response and Discipline Review Letters issued for the original submission of NDA 204-326.

The proposed dissolution method is acceptable.

Based on the dissolution data of the batch of AMP XR ODT (b) (4) that was shown to be bioequivalent to the listed drug (Adderall XR 30 mg) in the pivotal BA/BE study (as well as the registration stability batches of all proposed strengths of AMP XR ODT), this Reviewer recommends the following acceptance criteria for dissolution testing of all six proposed commercial strengths of AMP XR ODT at release and through the duration of stability testing. The revised drug product Specifications table should be submitted.

Acid Stage [0.25 hours]:	(b) (4)%
End of Acid Stage [2.00 hours]:	(b) (4)%
pH 6.8 Buffer Stage [2.25 hours]:	NLT (b) (4)%

In response to the FDA Information Request dated 12/17/2015, the sponsor agreed to revise the acceptance criteria for dissolution testing of AMP XR ODT tablets at release and through the duration of stability testing as recommended.

The Applicant's biowaiver request for the lower strength tablets is granted. The Division of Biopharmaceutics recommends APPROVAL of NDA 204326.

12/17/2016
Gerlie Gieser, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics/OPQ

Secondary Review Comments and Concurrence:

I concur with Dr. Gieser's APPROVAL recommendation for NDA 204326.

12/17/2015
Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics/OPQ

ASSESSMENT OF MICROBIOLOGY

40. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: The drug product is not a sterile product. (b) (4) (b) (4) are (b) (4) as a part of in process test as described under the section, 3.2.P.3 and above (under Q # 33) in this review. Additionally, the drug product specification includes this test for batch release as follows:

(b) (4)

Reviewer's Assessment:Acceptable.

2.3.P.7 Container/Closure System

41. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure (b) (4) and change control program in terms of validation?

Applicant's Response: The drug product is not a sterile product. The proposed marketing configuration is a (b) (4) blister card package comprised of a (b) (4) (b) (4). Since the drug product class is sensitive to (b) (4), this (b) (4) foil (b) (4) package provides a significant barrier to (b) (4). Each blister card holds 6 Amphetamine XR-ODTs, and the blister card cavity sizes are designed for the six different tablet sizes (b) (4) (b) (4)). Five printed blister cards will be then packaged into a printed secondary carton along with a package insert and a rigid.

Reviewer's Assessment: Acceptable.

There is no [redacted] (b) (4) for the container closure system. Both long term and short term stability studies on the finished product with the proposed container closure system showed that the microbial tests always met the limit. Therefore, there is no concern on the proposed container/closure system to function as a barrier to microbial ingress for the drug product.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

42. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

There are none used.

Reviewer's Assessment: Adequate

43. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: NA

Reviewer's Assessment: NA

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

Secondary Review Comments and Concurrence:

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

44. Is the applicant's claim for categorical exclusion acceptable?

45. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

Pursuant to 21 CFR 25.30, Neos Therapeutics, Inc. claims a categorical exclusion from the requirement of an Environmental Assessment for [redacted] (b) (4), which is a new dosage form that is directly substitutable for an already approved product (Adderall XR®) and would not be considered to increase the use of the active moiety.

Reviewer's Assessment: Adequate

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

Andrei Ponta 18-Nov-2015

Secondary Review Comments and Concurrence:

Labeling & Package Insert

1. **Package Insert**

(b) (4)

[redacted]

Item	Information Provided in NDA		Reviewer's Assessment
Product title, Drug name (201.57(a)(2))			
Proprietary name and established name	Proprietary: Adzenys XR-ODT Established Name: Amphetamine		The label and information provided in NDA are in agreement.
Dosage form, route of administration	Form: Extended release oral disintegrating tablets	Route: Oral (b) (4) (b) (4)	The label and information provided in NDA are in agreement.
Controlled drug substance symbol (if applicable)	Adzenys XR-ODT contains amphetamine, a Schedule II controlled substance.		The controlled substance symbol designating the schedule in which the controlled substance is listed is included.
Dosage Forms and Strengths (201.57(a)(8))			
A concise summary of dosage forms and strengths	Extended release orally disintegrating tablet: (b) (4) (b) (4)		The label and information provided in NDA are in agreement. (b) (4) (b) (4)

Conclusion: Inadequate

The label is consistent with the information provided in the NDA. (b) (4) [redacted]

(b) "Full Prescribing Information" Section

<u># 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))</u>

3. DOSAGE FORMS AND STRENGTHS

ADZENYS XR-ODT (b) (4) [redacted] mg Amphetamine Extended Release Orally Disintegrating Tablet: round, orange to light orange mottled (debossed (b) (4) [redacted] on one side)

ADZENYS XR-ODT (b) (4) [redacted] mg Amphetamine Extended Release Orally Disintegrating Tablet: round, orange to light orange mottled (debossed (b) (4) [redacted] on one side)

ADZENYS XR-ODT (b) (4) [redacted] mg Amphetamine Extended Release Orally Disintegrating Tablet: round, orange to light orange mottled (debossed (b) (4) [redacted] on one side)

ADZENYS XR-ODT (b) (4) [redacted] mg Amphetamine Extended Release Orally Disintegrating Tablet: round, orange to light orange mottled (debossed (b) (4) [redacted] on one side)

ADZENYS XR-ODT (b) (4) [redacted] mg Amphetamine Extended Release Orally Disintegrating Tablet: round, orange to light orange mottled (debossed (b) (4) [redacted] on one side)

ADZENYS XR-ODT (b) (4) [redacted] mg Amphetamine Extended Release Orally Disintegrating Tablet: round, orange to light orange mottled (debossed (b) (4) [redacted] on one side)

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablet	The label and information provided in NDA are in agreement.
Strengths: in metric system	(b) (4) [redacted]	The label and information provided in NDA are in agreement. (b) (4) [redacted] (b) (4) [redacted]
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Amphetamine XR-ODT is supplied as orange to light orange mottled tablets debossed with (b) (4) [redacted] (b) (4) [redacted].	The label and information provided in NDA are in agreement.

Conclusion: Inadequate

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

(b) (4) [redacted]

(b) (4)

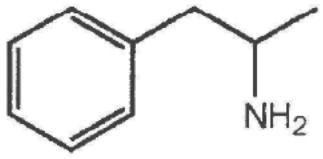
#11: Description (21CFR 201.57(c)(12))

11. DESCRIPTION

ADZENYS XR-ODT (amphetamine) extended-release orally disintegrating tablet contains (b) (4) to 1 ratio of d- to l-amphetamine.

(b) (4)

Structural Formula:



$C_9H_{13}N$ MW 135.21

ADZENYS XR-ODT is an extended-release orally disintegrating tablet containing 50% immediate-release and 50% extended-release amphetamine.

ADZENYS XR-ODT also contains the following inactive ingredients: Mannitol, Crospovidone, Microcrystalline Cellulose, Methacrylic Acid Copolymer Type A, Sodium Polystyrene Sulfonate, Citric Acid, Fructose, Orange Flavor, Colloidal Silicon Dioxide, Triethyl Citrate, Sucralose, Lake Blend Orange, Magnesium Stearate, and Polyethylene Glycol.

Item	Information Provided in NDA		Reviewer's Assessment
Proprietary name and established name	Proprietary: Adzenys XR-ODT Established Name: Amphetamine		The label and information provided in NDA are in agreement.
Dosage form and route of administration	Form: Extended release oral disintegrating tablets	Route: Oral (b) (4) (b) (4)	The label and information provided in NDA are in agreement.
Active moiety expression of strength with equivalence statement for salt (if applicable)	The drug product contains amphetamine base: 3.13, 6.27, 9.40, 12.5, 15.7, and 18.8 mg of amphetamine which is the equivalent (b) (4) base content of Adderall XR - 5, 10, 15, 20, 25, and 30 mg, respectively.		The applicant includes a strength equivalence table.
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Poly styrene sulfonate, triethyl citrate, magnesium stearate, (b) (4), methacrylic acid copolymer type A, (b) (4) orange flavor (b) (4), crospovidone, citric acid, and (b) (4),		**The label and information provided in NDA are in agreement.** (b) (4) (b) (4) **Additionally, the**

	fructose, microcrystalline cellulose, crospovidone, and colloidal silicon dioxide).	**applicant lists poly ethylene glycol but does not indicate the MW.**
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ therapeutic class	A central nervous system (CNS) stimulant indicated	Adequate
Chemical name, structural formula, molecular weight	The drug product contains a 3:1 mixture of d- and l-amphetamine. Their molecular formula is $C_9H_{13}N$ and molecular weights are 135.21.	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa, solubility, or pH)	Amphetamine is a (b) (4) soluble in water.	Adequate

Conclusion: Inadequate

(b) (4)

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

15. HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ADZENYS XR-ODT (b)(4) mg Extended Release Orally Disintegrating Tablet: round, orange to light orange mottled (debossed (b)(4) on one side), carton containing 5 blister cards of 6 tablets each, for a total of 30 tablets, NDC (b)(4)-005-30

ADZENYS XR-ODT (b)(4) mg Extended Release Orally Disintegrating Tablet: round, orange to light orange mottled (debossed (b)(4) on one side), carton containing 5 blister cards of 6 tablets each, for a total of 30 tablets, NDC (b)(4)-010-30

ADZENYS XR-ODT (b)(4) mg Extended Release Orally Disintegrating Tablet: round, orange to light orange mottled (debossed (b)(4) on one side), carton containing 5 blister cards of 6 tablets each, for a total of 30 tablets, NDC (b)(4)-015-30

ADZENYS XR-ODT (b)(4) mg Extended Release Orally Disintegrating Tablet: round, orange to light orange mottled (debossed (b)(4) on one side), carton containing 5 blister cards of 6 tablets each, for a total of 30 tablets, NDC (b)(4)-020-30

ADZENYS XR-ODT (b)(4) mg Extended Release Orally Disintegrating Tablet: round, orange to light orange mottled (debossed (b)(4) on one side), carton containing 5 blister cards of 6 tablets each, for a total of 30 tablets, NDC (b)(4)-025-30

ADZENYS XR-ODT (b)(4) mg Extended Release Orally Disintegrating Tablet: round, orange to light orange mottled (debossed (b)(4) on one side), carton containing 5 blister cards of 6 tablets each, for a total of 30 tablets, NDC (b)(4)-030-30

Storage

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

Store ADZENYS XR-ODT blister packages in the rigid, plastic travel case provided after removal from the carton. To obtain additional travel cases, patients and health care professionals can call Neos Therapeutics, Inc., at 1-XXX-XXX-XXXX.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Extended release orally disintegrating tablet: (b) (4) (b) (4)	The label and information provided in NDA are in agreement. (b) (4) (b) (4)
Available units (b) (4) (b) (4)	Tablets are available in blister packs (6 per pack), 5 packs per carton.	The label and information provided in NDA are in agreement.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Amphetamine XR-ODT is supplied as orange to light orange mottled tablets debossed with (b) (4) (b) (4)	The label and information provided in NDA are in agreement.
Special handling (e.g., protect from light, do not freeze)	The drug product is stable to short term excursions between 15°C and 30°C.	The label and information provided in NDA are in agreement.
Storage conditions	Store at 25° C (77° F) [see USP controlled room temperature].	The label and information provided in NDA are in agreement.

Manufacturer/distributor name listed at the end of PI, following Section #17

Manufactured by Neos Therapeutics, LP., Grand Prairie, TX 75050. Made in USA.

For more information call 1-888-319-1789.

Pharmacist: Medication Guide to be dispensed to patients

ADZENYS XR-ODT is a registered trademark of Neos Therapeutics, Inc.

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Drug product manufacturing, packaging, testing, and release are performed by Neos Therapeutics, LP at their Grand Prairie, TX site.	The label and information provided in NDA are in agreement.

Conclusion: Inadequate

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

(b) (4)

2. Container and Carton Labeling

1) Immediate Container Label

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

(b) (4)

[redacted]

Reviewer's Assessment:

Item	Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary: Adzenys XR-ODT Established Name: Amphetamine	Adequate

Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Extended release orally disintegrating tablet: (b) (4)	Adequate
Route of administration 21.CFR 201.100(b)(3))	Oral	Adequate
Net contents* (21 CFR 201.51(a))	The number of tablets is included on the label.	Adequate
Name of all inactive ingredients 21CFR 201.100(b)(5)**	NA	NA
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.	Inadequate
Storage (not required)	The storage conditions are not 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)	The NDC number is present on the label.	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	The bar code appears on the label.	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	The manufacture is listed on the label.	Adequate
Others	NA	Adequate

*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.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate

The label information is accurate.

2) Carton Labeling

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(b) (4)

[redacted]

Item	Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Proprietary: Adzenys XR-ODT Established Name: Amphetamine	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	Extended release orally disintegrating tablet: (b) (4) (b) (4)	**Strength is based on base equivalent**

Net contents (21 CFR 201.51(a))	5 blisters containing 6 tablets each	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
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Poly styrene sulfonate, triethyl citrate, magnesium stearate, (b) (4) (b) (4) methacrylic acid copolymer type A (b) (4) orange flavor (b) (4), crospovidone, citric acid, and (b) (4) mannitol, fructose, microcrystalline cellulose, (b) (4), and colloidal silicon dioxide).	The label and information provided in NDA are in agreement. However, the applicant lists the contents of (b) (4), (b) (4) Additionally, the applicant lists poly ethylene glycol but does not indicate the MW.
Sterility Information (if applicable)	NA	NA
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	The label bears the "Rx only" statement.	Adequate
Storage Conditions	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)	The NDC number is present on the label.	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	The bar code appears on the label.	Adequate
Name of manufacturer/distributor	The manufacture is listed on the label.	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Statement appears on the label.	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	NA	NA
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	NA	NA

Conclusion: Adequate

The label information is accurate.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

Secondary Review Comments and Concurrence:

I. List of Deficiencies To Be Communicated

None

II. Attachments

A. Lifecycle Knowledge Management

Not formally carried out as this is a resubmission.

Lifecycle reviewers should be cognizant of changes which can impact the physical properties of the tablet ((b) (4), hardness, (b) (4), etc) as these were issues in the initial submission. They are not present in the reformulated product but the root causes of these issues were not determined hence there is a risk that they could arise again.

NDA 204326

Tradename XR ODT

Amphetamine Extended Release Orally Disintegrating Tablets

Neos Therapeutics Inc.

Quality Review #2

David J. Claffey, PhD & Kavita A. Vyas, PhD
ONDQA

Mahesh Ramanadham, PharmD/MBA
CDER OC

Table of Contents

Chemistry Review Data Sheet

1. NDA 204326

2. REVIEW #: 2

3. REVIEW DATE: 5 SEP 2013

4. REVIEWERs: David J Claffey, Kavita Vyas & Mahesh Ramanadham

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N-000	28 DEC 2012
Product Review	1 MAY 2013
Manufacturing Process Review	17 MAY 2013
Manufacturing Facility Review	3 MAY 2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Response to DR letter	1 AUG 2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Neos Therapeutics Inc
Address:	Grand Prairie, TX
Representative:	Dorothy Engelking
Telephone:	972-408-1312

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: [redacted] (b) (4)
b) Non-Proprietary Name (USAN): amphetamine [redacted] (b) (4) extended release orally disintegrating tablet
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: ADHD

11. DOSAGE FORM: extended release orally disintegrating tablets

12. STRENGTH/POTENCY: 3.13, 6.27, 9.40, 12.5, 15.7, & 18.8 mg amphetamine base (5, 10, 15, 20, 25, 30 mg equivalent of mixed amphetamine salts)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____x_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

The drug substance is described as being a [redacted] (b) (4).

It is present in the drug product as a 3:1 mixture of amphetamine [redacted] (b) (4)

[redacted] (b) (4)

[redacted] (b) (4)

Molecular Formula

[redacted] (b) (4)

Relative Molecular Mass

[redacted] (b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted] (b) (4)	II	[redacted] (b) (4)		1	Adequate	1 MAY 2013 (David Claffey)	
	II			3	Adequate	22 AUG 2013 (David Claffey)	
	II			3	Adequate (by Neeru Takiar)	4/14/2011	
				4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Product Review	Application deficient	1 May 2013	David Claffey
Manufacturing Process Review	Application deficient	3 May 2013	Kavita A. Vyas
Manufacturing Facility Review	Application deficient	17 May 2013	Mahesh Ramanadham
EES	Withhold	30 AUG 2013	
Pharm/Tox	Pending		
Biopharm	Pending	1 May 2013	Okpo Eradiri
LNC	Consulted regarding labeled strength and established name. Labeled strength should be based on (b) (4) base		

The Chemistry Review for NDA 204326

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend a Complete Response from a product quality perspective as the applicant has not adequately addressed all product quality deficiencies identified in the Discipline Review letter (dated 5/29/2013). Further, CDER Office of Compliance issued a withhold recommendation regarding the proposed manufacturing and testing sites.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable Not Applicable.

II. Summary of Chemistry Assessments

This review covers the following (i) the applicant's responses (dated August 1, 2013) to the quality discipline review letter (dated May 29, 2013) and (ii) updates on the acceptability of the manufacturing sites, specifically, the firm's responses to Inspection 483 for the proposed sites. A detailed manufacturing facility assessment is included on page 45 of this document.

The applicant proposes to manufacture new registration drug product lots and carry out new stability and clinical studies in order to address the outstanding deficiencies. At this time the quality review team expects that quality reviewers for any future resubmission will consider data from the initial registration lots to be developmental rather than supportive in nature. The new stability and clinical studies will need to demonstrate that the applicant is capable of manufacturing a product that consistently maintains its quality through the proposed expiry period.

A. Description of the Drug Product(s) and Drug Substance(s)

A1. Drug Substance

Refer to Review #1.

Update:

Details of the manufacture of drug substances were provided in DMFs (b) (4) and (b) (4). DMF (b) (4) was previously found inadequate to support this application, however it was amended on 9 APR 2013 and was found adequate to support this application (David Claffey, 23 AUG 2013).

A2. Drug Product

Refer to Review #1.

Update:

Responses to deficiencies 4, 5b, 6a, 6b, 6l, 7, 9, 10, 13, 16, 17 18 and 19 were adequate. The remaining deficiencies have not been adequately addressed.

The applicant proposes to manufacture new registration drug product lots and carry out new stability and clinical studies in order to address the deficiencies #1, 2, 3, 5a, 5c, 6c, 6d, 6e, 6f, 6g, 6i, 6j, 6k, 6m, 11a, 11b, 15 in the 1 MAY 2013 DR letter.

Due to the strength-specific stability profiles observed in the previous registration lots the applicant was advised in the DR letter that the previous (b) (4) was inappropriate (b) (4)

Further the applicant's response to deficiency #8 was found to be inadequate as they proposed (b) (4) (b) (4) The applicant will be advised in the CR letter to validate the drug product methods with drug product (unless a surrogate has been adequately qualified).

In response to deficiency #6h where a CoA for the clinical lot was requested, it was unclear whether this lot underwent full testing before its use in the clinic. Testing for related substances, metals and (b) (4) were carried out on the clinical lot after the applicant's receipt of the DR letter. The original CoA will again be requested and the applicant will be advised that we expect lots to undergo full testing to ensure that they meet the drug product specification before their use in the clinic.

Additional data regarding the drug product specified upper acceptance criterion for (b) (4) (b) (4) particle size (deficiencies 11c and 12, respectively) will be requested. Response to #14 will be included in a future submission.

In response to deficiency #17, the applicant has agreed to remove the term (b) (4) from the proposed established name.

A3. Drug Product Manufacturing Process

Refer to reviews by Kavita Vyas (dated 5/3/13) and Mahesh Ramanadham (dated 5/17/2013).

Update:

Questions 1, and 20-33 summarized major issues with the development program, manufacturing process, and quality of drug product. As such, there are 3 aspects to the deficiencies. None are addressed satisfactorily by the applicant.

Manufacturing process related deficiencies #20, 30, 31 and 32 were adequately addressed. The applicant proposes to manufacture new registration drug product lots and carry out stability and clinical studies on the product made using the new process to address deficiencies #1, 21, 22, 23a, 23b, 23c, 25, 26, 27, 28, 29, 33. Therefore these deficiencies remain outstanding and will be addressed in the next review cycle. In response to deficiency #20 the applicant agreed to (b) (4) and (b) (4). The response to deficiency #24 does not address concern with the capability of the equipment.

A4. Manufacturing Facilities

Refer to review by Mahesh Ramanadham (dated 5/1/2013).

Update:

The NEOS and (b) (4) manufacturing facilities listed in the NDA have been issued withhold recommendations due lack of readiness for a pre-approval inspection. (b) (4) (b) (4) has been removed from the application by the applicant. (b) (4) responsibilities will be transferred to NEOS and (b) (4). Please see the 'withhold concurrence' memos entered into DARRTS for further clarification.

A detailed manufacturing facility assessment in included on page 45 of this document.

Chemistry Assessment Section

Establishment Name	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Most Recent Milestone and Status
						(b) (4)	OC RECOMMENDATION - Acceptable
							OC RECOMMENDATION - Acceptable
							OC RECOMMENDATION - Acceptable
							WITHDRAWN (4/19/13)
							OC RECOMMENDATION - Acceptable
							OC RECOMMENDATION - WITH HOLD
NEOS THERAPEUTICS, INC.	3000205839	DAL	USA	Finished drug product manufacturing, packaging, release and stability testing	TTR	05/23/2011-05/27/2011 56002 - VAI (no TTR coverage)	OC RECOMMENDATION - WITH HOLD

B. Description of How the Drug Product is Intended to be Used

Refer to Review #1.

C. Basis for Quality Recommendation

A complete response is recommended [redacted (b) (4)] Also, CDER OC issued an overall recommendation of "Withhold" for this application.

Biopharmaceutics deficiencies also remain outstanding (see review by Okpo Eradiri dated SEP 2013).

We recommend that the following be included in the CR letter:

Responses to deficiencies 4, 5b, 6a, 6b, 6c, 6l, 7, 9, 10, 13, 16, 17, 18, 19, 20, 30, 31, and 32 were adequate. The remaining deficiencies have not been adequately addressed.

Deficiencies were identified at the Neos Therapeutics Inc and the [redacted (b) (4)] facilities. Satisfactory resolution of these deficiencies is required before this application may be approved.

We request that you:

1 Provide full responses to the remaining deficiencies in the DR letter and provide all modified data such as drug product and drug substance specifications, stability protocols, analytical methods etc.

2 Provide a detailed summary of changes made to each section – preferably in a tabular format.

3 [redacted (b) (4)]

4 Similarly, considering the differences in manufacturing process, controls and packaging we recommend that you manufacture three lots [redacted (b) (4)] of each tablet strength, although [redacted (b) (4)] manufactured will be considered.

5 Provide the original CoA for lot 1E040A in response to deficiency #6h (a recent revision was provided in the 1 AUG 2013 response). We expect that lots undergo full testing to ensure that they meet the drug product specification before their use in the clinic.

6 In response to deficiency #8 you propose to (b) (4) (b) (4). This approach is unacceptable (b) (4) (b) (4)

7 Regarding the response to deficiency #11c: we request that these studies be carried out (b) (4). In addition, we request stability data for these lots as most of the issues being investigated were not detected (b) (4)

8 Regarding the response to deficiency #12: in order to evaluate the particle size specification for the (b) (4), the requested data from the (b) (4) lots used in the drug product lots manufactured thus-far will be required. Although this is a compendial excipient, (b) (4)

9 Regarding the response to Deficiency #24: The response discusses the (b) (4) (b) (4) The response (b) (4) (b) (4) Please address this in your response.

III. Administrative

A. Reviewer's Signature

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EES REPORT

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 204326/000	**Sponsor:**	NEOS THERAP INC
Org. Code:	130		2940 NORTH HWY 360 STE 100
Priority:	5		GRAND PRAIRIE, TX 75050
Stamp Date:	28-DEC-2012	**Brand Name:**	AMPHETAMINE (b) (4) EXTENDED-RELEASE
PDUFA Date:	28-OCT-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	29-AUG-2013	**Product Number; Dosage Form; Ingredient; Strengths**	001; TABLET; AMPHETAMINE; (b) (4) 002; TABLET; AMPHETAMINE; 003; TABLET; AMPHETAMINE; 004; TABLET; AMPHETAMINE; 005; TABLET; AMPHETAMINE; 006; TABLET; AMPHETAMINE;

FDA Contacts:	D. CLAFFEY	Prod Qual Reviewer	3017961343
	T. BOUIE	Product Quality PM	3017961649
	K. ANSAH	Regulatory Project Mgr	3017964158
	C. TELE	Team Leader	3017961762

Overall Recommendation:	WITHHOLD	on 30-AUG-2013	by M. RAMANADHAM	(HFD-320)	3017963272
	WITHHOLD	on 31-JAN-2013	by EES_PROD		
	PENDING	on 23-JAN-2013	by EES_PROD		
	PENDING	on 23-JAN-2013	by EES_PROD		

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/s/

DAVID J CLAFFEY
09/11/2013

MAHESH R RAMANADHAM
09/11/2013

KAVITA A VYAS
09/11/2013

VIPULCHANDRA N DHOLAKIA
09/12/2013

RAMESH K SOOD
09/12/2013

Memorandum

Date 8/29/13

From Mahesh Ramanadham
Team Leader (Acting)
CDER/OC/OMPQ/DGMPA/NDMAB

Kavita Vyas
Chemist
CDER/OPS/ONDQA/DNDQAI/BRIII

Subject Concurrence with [redacted] Withhold Recommendation for NDA 204326/000, Amphetamine [redacted] ER ODT [redacted])

Thru Don Henry
Branch Chief (Acting)
CDER/OC/OMPQ/DGMPA/NDMAB

Ramesh Sood
Branch Chief
CDER/OPS/ONDQA/ DNDQAI/BRI

To Memo-To-File NDA 204326/000

Applicant: NEOS THERAPEUTICS INC
2940 NORTH HWY 360 STE 100
GRAND PRAIRIE TX 75050

Establishment: [redacted]

CDER/OC/OMPQ/DGMPA and CDER/OPS/ONDQA/DNDQAI have completed a review of an establishment inspection report (EIR) covering a pre-approval inspection (PAI) and GMP inspection conducted by [redacted] investigators from [redacted] at the [redacted] facility. DGMPA has also reviewed the firm's [redacted] written response to the FDA Form-483 observations. This inspection was initiated by [redacted] to provide pre-approval coverage of listed operations in support of NDA 204326/000. This was the first FDA inspection of this facility. This site is responsible for performing [redacted]

DGMPA and DNDQAI concur with the [redacted] withhold recommendation for NDA 204326/000. [redacted] recommended withholding approval of this application due to the firm not being ready for the pre-approval inspection and subsequent product specific deficiencies.

The inspection revealed that the firm has not fully implemented a quality system or corresponding operations conforming to CGMP requirements as this site historically performs (b) (4) (b) (4) and was not aware that work performed for NEOS would be used to support an NDA. Site representatives therefore asserted that any work performed for NEOS was not performed under CGMP. (b) (4) representatives also clarified that the firm was in the process of adopting a CGMP quality system to support drug operations, but had not yet done so as they were unaware of being named in an application product (see page 6/22 of the EIR). Additionally, site representatives stated that they believed (b) (4) would be performing (b) (4) operations in support the NDA, though they are unsure what operations would be performed (see page 6/22 of the EIR).

Firm representatives asserted that 1) they were not informed by NEOS that (b) (4) work was being used to support an NDA and 2) the site was not ready for an inspection in support of this NDA as any work performed was not conducted under CGMP. Due to the firm's assertions during the inspection, (b) (4) elected to suspend the pre-approval inspection, inform (b) (4) (b) (4) that they were considered 'not ready' in support of this application, and conduct a general CGMP audit of the facility. Therefore the 483 included observations on general CGMP.

The following deficiencies specific to (b) (4) operations in support of NDA 204326/000, Amphetamine (b) (4) ER ODT (b) (4) were documented in the EIR:

(b) (4)

- (b) (4)

This follow up communication further illustrates that (b) (4) is not ready to perform commercial operations in support of NDA 204326.

CDER/OC/OMPQ/DGMPA and CDER/OPS/ONDQA/DNDQAI Recommendation:

Based on the above assessment of the inspection findings, the firm's assertion that work was not performed and is not ready to be performed under CGMP, product specific deficiencies noted in the EIR, and follow up communication between (b) (4) and the firm, DGMPA and DNDQAI concur with the (b) (4) recommendation to withhold approval of NDA 204326/000, Amphetamine (b) (4) ER ODT (b) (4)). DGMPA and DNDQAI concur that this site is 'not ready' for a pre-approval inspection in support of NDA 204326/000.

If you have any questions, please contact me at (301) 796-3272 or by email at Mahesh.Ramanadham@fda.hhs.gov

Mahesh Ramanadham, PharmD/M.B.A., RPh.
LCDR, USPHS
Team Leader (acting)
CDER/OC/OMPQ/DGMPA/NDMAB

(b) (4)
NDA 204326 Amphetamine (b) (4) ER ODT

cc:

(b) (4)

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/s/

MAHESH R RAMANADHAM
08/30/2013

KAVITA A VYAS
08/30/2013

DON L HENRY
08/30/2013

RAMESH K SOOD
08/30/2013

Memorandum

Date 8/29/13

From Mahesh Ramanadham
Team Leader (Acting)
CDER/OC/OMPQ/DGMPA/NDMAB

Kavita Vyas
Chemist
CDER/OPS/ONDQA/DNDQAI/BRIII

Subject Concurrence with Dallas District Office (DAL-DO) Withhold Recommendation for NDA 204326/000, Amphetamine (b) (4) ER ODT (b) (4))

Thru Don Henry
Branch Chief (Acting)
CDER/OC/OMPQ/DGMPA/NDMAB

Ramesh Sood
Branch Chief
CDER/OPS/ONDQA/DNDQAI/BRI

To Memo-To-File NDA 204326/000

Applicant: NEOS THERAPEUTICS INC
2940 NORTH HWY 360 STE 100
GRAND PRAIRIE TX 75050

Establishment: NEOS THERAPEUTICS INC
2940 NORTH HWY 360 STE 100
GRAND PRAIRIE TX 75050
FEI: 3010138966

CDER/OC/OMPQ/DGMPA and CDER/OPS/ONDQA/DNDQAI have reviewed NEOS' NDA 204326/000 and responses to FDA's May 29, 2013 discipline review letter under the CDER/office of product quality (OPQ) (b) (4). During review of the NDA, it was determined that the manufacturer had not demonstrated it was capable of manufacturing drug product of consistent and uniform quality. Batches manufactured in support of the application routinely failed to meet quality specifications. Additionally the review of the executed and proposed manufacturing processes identified a lack of development and scientifically justified manufacturing operations. Major deficiencies with the quality section of the NDA were communicated to NEOS in the May 29, 2013 discipline review letter. A decision was made to hold the pre-approval inspection of the finished drug product manufacturing facility until an acceptable response to these deficiencies was received.

DGMPA and DNDQAI have reviewed NEOS' August 1, 2013 response to FDA's May 29, 2013 discipline review letter and have found that the response to the identified deficiencies does not justify the use of FDA resources in conducting a pre-approval inspection. NEOS' response

acknowledges the deficiencies identified and proposes to manufacture supportive batches using a revised manufacturing process. NEOS has not yet manufactured these batches and does not inform the Agency in the response as to when they intend to manufacture. Additionally, NEOS does not identify what changes will be made to the manufacturing process or when these changes will be implemented. Due to an absence of acceptable supportive batches and a developed manufacturing process, FDA finds that NEOS is not ready for an FDA pre-approval inspection in support of this NDA. DGMPA and DNDQAI conferred with DAL-DO regarding NEOS' discipline review response and DAL-DO concurred that the site is considered 'not ready' for a pre-approval inspection. Therefore DAL-DO entered a 'with-hold' recommendation for this facility.

DGMPA and DNDQAI concurs with DAL-DO's withhold recommendation for NDA 204326 as FDA is unable to verify NEOS' 1) readiness to manufacture, 2) conformance to application commitments and 3) the integrity of data presented in the application.

CDER/OC/OMPQ/DGMPA and CDER/OPS/ONDQA/DNDQAI Recommendation:

Based on the DGMPA and DNDQAI assessment of NDA 204326/000, deficiencies conveyed in FDA's May 29, 2013 deficiency review letter, and assessment of NEOS' August 1, 2013 response, DGMPA and DNDQAI concur with the DAL-DO's recommendation to withhold approval of NDA 204326/000, Amphetamine (b) (4) ER ODT (b) (4). OMPQ and ONDQA concur that this site is 'not ready' for a pre-approval inspection in support of NDA 204326/000.

If you have any questions, please contact me at (301) 796-3272 or by email at Mahesh.Ramanadham@fda.hhs.gov

Mahesh Ramanadham, PharmD/M.B.A., RPh.
LCDR, USPHS
Team Leader (acting)
CDER/OC/OMPQ/DGMPA/NDMAB

cc:

DAL - District Pre-Approval Manager (PAM), Jose Martinez
NDMAB Acting Team Leader
CMS case #: 70503

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/s/

MAHESH R RAMANADHAM
08/30/2013

KAVITA A VYAS
08/30/2013

DON L HENRY
08/30/2013

RAMESH K SOOD
08/30/2013

NDA 204-326
Manufacturing Process / Facility Review

(b) (4)

Amphetamine Extended Release Orally Disintegrating Tablets

(b) (4)

Sponsor: Neos Therapeutics Inc.

Mahesh Ramanadham, PharmD/M.B.A.
CDER/OC/OMPQ/DGMPA/NDMAB

Table of Contents

A. The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend **Complete Response** in its present form from a CMC point of view due to deficiencies identified in the drug product, manufacturing process and facility sections, Biopharm sections, and supporting drug substance DMF (b) (4). An overall Office of Compliance recommendation is pending (an initial withhold recommendation exists for a (b) (4) site).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No recommendations from the CMC or OMPQ point of view.

II. Summary of Quality Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

A1. Drug Substance

See review by David Claffey (5/1/2013). The drug substance is a (b) (4) (b) (4) (b) (4) are used to produce the target (b) (4).

A2. Drug Substance Manufacturing Process/Facility

Details of the manufacture of (b) (4) are cross referenced to DMFs (b) (4) and (b) (4) respectively. DMF (b) (4) was found adequate to support this application and DMF (b) (4) is inadequate to support this application (see reviews dated 5/1/2013 by David Claffey, and 6/25/2012 by Zhigang Sun respectively).

A3. Drug Product

See review by David Claffey (dated 5/1/2013). The drug product was developed as an extended-release orally-disintegrating tablet of six strengths packaged in blisters. The strengths, isomer mixture and release profile were designed to be equivalent to the reference listed drug (RLD), Adderall XR. The tablets contain a 3:1 mixture of d- and l- amphetamine in six dosage strengths which contain 3.13, 6.27, 9.40, 12.5, 15.7 and 18.8 mg equivalents of amphetamine (b) (4) base. The strengths were designed to have the same equivalent (b) (4)-base content as Adderall XR 5, 10, 15, 20, 25 and 30 mg, respectively. Both products contain amphetamine in the salt form. The (b) (4) in the RLD is a mixture of salts (b) (4) (b) (4) polystyrene sulfonate (b) (4) in the proposed product. The applicant proposes expressing the strengths primarily in terms of amphetamine (b) (4)-base with their equivalent to Adderall XR also being listed in labels and labeling.

Tablets of each strength are orange in color (b) (4) (b) (4). They are embossed with (b) (4) (b) (4)

The drug product specification is typical of an orally administered tablet. The limit for (b) (4) is set at a (b) (4)% and disintegration time is set at (b) (4) (b) (4) recommended by the Agency ODT guidance. Dissolution acceptance criteria require (b) (4) and NLT (b) (4) (b) (4) Incomplete batch analysis data were provided for three (b) (4) registration lots each of the smallest (1E051E, 1E086E, 1E089E) and largest (1E088E, 1E090E, 1E098E) dosage strength. One (b) (4) strength lot was also used in the pivotal bioequivalence studies. The lots generally met the proposed acceptance criteria – except for disintegration where the results generally (b) (4) (b) (4) acceptance limit. Batch analysis data were not provided for the four intermediate strengths - only partial data on one (b) (4) 'demonstration lot' of each strength derived from a (b) (4) were provided. Incomplete stability data were provided for these

six lots through the 12-month time point. Significant changes were observed in tablet hardness, (b) (4) and disintegration over time where results generally failed to meet drug product acceptance criteria – especially for the (b) (4) strength product. No release or stability data were provided for the intermediate strength products.

In summary, the drug product does not meet specification (b) (4) (b) (4) to the point that an expiry period can not be assigned.

A4. Drug Product Manufacturing Process

See reviews by Kavita Vyas (dated 5/1/13) and Mahesh Ramanadham (dated 5/1/2013). The drug product used in the clinical trials and registration stability studies was manufactured using a (b) (4) process involving the following (b) (4) steps.

(b) (4)

The applicant provided details of the manufacturing process development, manufacturing process, and in process controls results for 6 (b) (4) batches of tablets (2 lots were used in clinical trials and all lots in registration stability). These data (b) (4) the extreme strengths (b) (4) (b) (4) No manufacturing data were provided for the intermediate strengths.

The applicant proposes (b) (4) (b) (4)

A5. Manufacturing Facilities

See review by Mahesh Ramanadham (dated 5/1/2013). The drug product is manufactured at Neos Pharmaceuticals, Grand Prairie, TX. A pre-approval inspection is pending. The following table captures the current status of the manufacturing facilities listed in support of the application:

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

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

/s/

MAHESH R RAMANADHAM
05/17/2013

TARA R GOOEN
05/17/2013

JOSEPH D DOLESKI
05/17/2013

NDA 204326

(b) (4)

Amphetamine Extended Release Orally Disintegrating Tablets

Neos Therapeutics Inc.

Process Review

Kavita A. Vyas, PhD
ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA 204326

2. REVIEW #:1

3. REVIEW DATE: 30 APR 2012

4. REVIEWER: Kavita A. Vyas, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N-000	28 DEC 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Neos Therapeutics Inc
Address:	Grand Prairie, TX
Representative:	Dorothy Engelking
Telephone:	972-408-1312

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): amphetamine (b) (4) extended release orally disintegrating tablet
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: ADHD

11. DOSAGE FORM: extended release orally disintegrating tablets

12. STRENGTH/POTENCY: 3.13, 6.27, 9.40, 12.5, 15.7, & 18.8 mg amphetamine base (5, 10, 15, 20, 25, 30 mg equivalent of mixed amphetamine salts)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

____x_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
The drug substance is described as being a (b) (4).
It is present in the drug product as a 3:1 mixture of amphetamine (b) (4) (b) (4)

(b) (4)

Molecular Formula

(b) (4)

Relative Molecular Mass

(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	1 MAY 2013 (David Claffey)	
	II			3	Inadequate	21 JUN 2012 (Zigang Sun)	
	II			3	Adequate (by Neeru Takiar)	4/14/2011	
				4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Manufacturing Product Review	Application remains deficient	1 May 2013	David J. Claffey
Manufacturing Facility Review	Application remains deficient	1 May 2013	Mahesh Ramanadham
EES	Pending		
Pharm/Tox	Pending	1 May 2013	Okpo Eradiri
Biopharm	Pending		
LNC	Consulted regarding labeled strength and established name.		

The Chemistry Review for NDA 204326

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application can not be recommended for approval from quality perspective in its present form due to deficiencies outlined in the Discipline Review letter (dated 5/1/2013).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

A1. Drug Substance

The drug substance is a [(b) (4)] [(b) (4)] are used to produce the target [(b) (4)]

A2. Drug Substance Manufacturing Process/Facility

Details of the manufacture of [(b) (4)] are cross referenced to DMFs [(b) (4)] and [(b) (4)] respectively. DMF [(b) (4)] was found adequate to support this application and DMF [(b) (4)] is inadequate to support this application (see reviews dated 5/1/2013 by David Claffey, and 6/25/2012 by Zhigang Sun respectively).

A3. Drug Product

Refer to review by David J. Claffey (dated 5/1/13). The drug product was developed as an extended-release orally-disintegrating tablet of six strengths packaged in blisters. The strengths, isomer mixture and release profile were designed to be equivalent to the reference listed drug (RLD), Adderall XR. The tablets contain a 3:1 mixture of d- and l- amphetamine in six dosage strengths which contain 3.13, 6.27, 9.40, 12.5, 15.7 and 18.8 mg equivalents of amphetamine [(b) (4)] base. The strengths were designed to have the same equivalent [(b) (4)]-base content as Adderall XR 5, 10, 15, 20, 25 and 30 mg, respectively. Both products contain amphetamine in the salt form. The [(b) (4)] in the RLD is a mixture of salts [(b) (4)] polystyrene sulfonate [(b) (4)] in the proposed product. The applicant proposes expressing the strengths primarily in terms of amphetamine [(b) (4)]-base with their equivalent to Adderall XR also being listed in labels and labeling.

Tablets of each strength are orange in color [(b) (4)] [(b) (4)]

(b) (4)

[redacted]

The drug product specification is typical of an orally administered tablet. The limit for (b) (4) is set at a (b) (4)% and disintegration time is set at (b) (4) (b) (4) recommended by the Agency ODT guidance. Dissolution acceptance criteria require (b) (4) and NLT (b) (4) (b) (4) respectively, in a more neutral medium (pH 6.8). Incomplete batch analysis data were provided for three (b) (4) registration lots each of the smallest (1E051E, 1E086E, 1E089E) and largest (1E088E, 1E090E, 1E098E) dosage strength. One (b) (4) strength lot was also used in the pivotal bioequivalence studies. The lots generally met the proposed acceptance criteria – except for disintegration where the results generally (b) (4) acceptance limit. Batch analysis data were not provided for the four intermediate strengths - only partial data on one (b) (4) 'demonstration lot' of each strength derived from a (b) (4) were provided. Incomplete stability data were provided for these six lots through the 12-month time point. Significant changes were observed in tablet hardness, (b) (4) and disintegration over time where results generally failed to meet drug product acceptance criteria – especially for the (b) (4) strength product. No release or stability data were provided for the intermediate strength products.

In summary, the drug product does not meet specification (b) (4) (b) (4) to the point that an expiry period can not be assigned. The main product-related deficiencies are outlined in Section C1, below.

A4. Drug Product Manufacturing Process

Covered in this review and in review by Mahesh Ramanadham (dated 5/2/2013). The drug product used in the clinical trials and registration stability studies was manufactured using a (b) (4) process involving the following (b) (4) steps.

(b) (4)

[redacted]

(b) (4)

The applicant provided details of the manufacturing process development, manufacturing process, and in process controls results for 6 (b) (4) batches of tablets (2 lots were used in clinical trials and all lots in registration stability). These data (b) (4) (b) (4) (b) (4) No manufacturing data were provided for the intermediate strengths.

The applicant proposes (b) (4) (b) (4) Major issues were identified with the (b) (4) and the proposed (b) (4) (see section C2 of this Executive Summary for details)

A5. Manufacturing Facilities

Refer to review by Mahesh Ramanadham (dated 5/1/2013). The drug product is manufactured at Neos Pharmaceuticals,Grand Prairie,TX. A pre-approval inspection is pending. The following table captures the current status of the manufacturing facilities listed in support of the application:

Establishment Name	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Most Recent Milestone	Most Recent EER Compliance Status
(b) (4)							OC RECOMMENDATION	AC
							OC RECOMMENDATION	AC
							OC RECOMMENDATION	AC
							DO RECOMMENDATION	WH
							OC RECOMMENDATION	AC
							ASSIGNED NSPECTION TO IB	PN
NEOS THERAPEUTICS, INC.	3000205839	DAL	USA	Finished drug product manufacturing, packaging, release and stability testing	TTR	05/23/2011-05/27/2011 56002 - VAI (no TTR coverage)	SUBMITTED TO DO	PN

B. Description of How the Drug Product is Intended to be Used

The proposed product is intended for the treatment of ADHD. It is proposed that patients [redacted] can be switched to [redacted] dose equivalent of the proposed product taken once daily. A table for determining the [redacted] proposed product when switching from the extended release mixed amphetamine salts (e.g. Adderall XR) is provided in the labeling. [redacted] can be taken with or without food.

The tablet should remain in the blister pack until the patient is ready to take it. It should not be pushed through the foil and should be placed with dry hands on the patients tongue. [redacted]

C. Basis for Quality Recommendation

C1. Deficiencies related to Product

The highest risk product-related deficiencies relate to the drug product batch analysis and stability data:

Main batch analysis deficiencies:

- The registration lots did not meet the disintegration acceptance criterion [redacted].
- No data from the registration lots of the intermediate strengths [redacted] were provided (not yet manufactured).
- Incomplete batch analysis data [redacted] and no certificates of analysis were provided for the drug product registration lots.
- The source of the drug product release data is unclear – it appears that some data [redacted]
- Data indicates that the [redacted] acceptance range.

Main Stability deficiencies:

- Disintegration time consistently [redacted] acceptance criterion – in several time points [redacted].
- Tablet hardness [redacted] % were recorded.
- [redacted]

- Other deficiencies include inconsistent and missing data and uncertainty on whether data (b) (4) (b) (4)
- The data indicate that the drug product will not meet its quality attributes to the point that an expiry period can not be assigned.

These and other deficiencies relating to the drug product and excipient specifications and tests will be relayed to the applicant in the discipline review letter.

C2. Deficiencies related to Drug Product Manufacturing Process

(b) (4)

C3. Deficiencies related to Drug Product Manufacturing Facilities

Pre-approval inspections for Neos Therapuetics, (b) (4) (b) (4) are required to support this application:

- Neos Therapeutics has no inspectional history for solid oral dosage form manufacturing operations to verify compliance with CGMP. Given the deficiencies observed with the manufacturing process, a pre-approval inspection *may* not be considered until the applicant has demonstrated they have a viable manufacturing process.

- [redacted] (b) (4) has no FDA inspection history to verify compliance with CGMP. An inspection is pending.
- [redacted] (b) (4) has been inspected in support of this application. [redacted] (b) (4) has recommended to withhold this application based on this inspection due to the use of uncontrolled, unofficial notebooks and un-validated analytical methods. The EIR, 483, and firm response to the 483 will be evaluated by the Office of Compliance to determine the final recommendation for this application.

C4. Deficiencies related to Other Disciplines

Biopharm has identified deficiencies (see review by Okpo Eradiri dated 5/1/2013).

C5. Overall Assessment

Evaluation of this application is divided between several reviews. The individual elements that constitute a control strategy are therefore distributed in three review documents. The following attempts to summarize a combined contribution of each element to the control strategy, and therefore to the quality of drug product and reliability of manufacturing process. (see detailed discussion in review by Kavita A. Vyas dated 5/1/2013).

1. [redacted] (b) (4)
2.
3.
4.
5.
6.
7.

Overall, the applicant's control strategy appears to fail at two critical points, at the product quality level and process quality level. Therefore, this application can not be recommended for approval from quality perspective in its present form.

III. Administrative

A. Reviewer's Signature

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/s/

KAVITA A VYAS
05/02/2013

RAMESH K SOOD
05/03/2013

NDA 204326

(b) (4)

Amphetamine Extended Release Orally Disintegrating Tablets

Neos Therapeutics Inc.

Product Review

David J. Claffey, PhD
ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA 204326

2. REVIEW #:1

3. REVIEW DATE: 30 APR 2012

4. REVIEWER: David J Claffey, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N-000	28 DEC 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Neos Therapeutics Inc
Address:	Grand Prairie, TX
Representative:	Dorothy Engelking
Telephone:	972-408-1312

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): amphetamine (b) (4) extended release orally disintegrating tablet
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: ADHD

11. DOSAGE FORM: extended release orally disintegrating tablets

12. STRENGTH/POTENCY: 3.13, 6.27, 9.40, 12.5, 15.7, & 18.8 mg amphetamine base (5, 10, 15, 20, 25, 30 mg equivalent of mixed amphetamine salts)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

____x_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
The drug substance is described as being a (b) (4).
It is present in the drug product as a 3:1 mixture of amphetamine (b) (4) (b) (4).

(b) (4)

Molecular Formula

(b) (4)

Relative Molecular Mass

(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	1 MAY 2013 (David Claffey)	
	II			3	Inadequate	21 JUN 2012 (Zigang Sun)	
	II			3	Adequate (by Neeru Takiar)	4/14/2011	
				4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Manufacturing Process Review	Application remains deficient	1 May 2013	Kavita A. Vyas
Manufacturing Facility Review	Application remains deficient	1 May 2013	Mahesh Ramanadham
EES	Pending		
Pharm/Tox	Pending	1 May 2013	Okpo Eradiri
Biopharm	Pending		
LNC	Consulted regarding labeled strength and established name.		

The Chemistry Review for NDA 204326

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application can not be recommended for approval from quality perspective in its present form due to deficiencies outlined in the Discipline Review letter (dated 5/1/2013).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable Not Applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

A1. Drug Substance

The drug substance is a [redacted] are used to produce the target [redacted]

A2. Drug Substance Manufacturing Process/Facility

Details of the manufacture of [redacted] are cross referenced to DMFs [redacted] and [redacted] respectively. DMF [redacted] was found adequate to support this application and DMF [redacted] is inadequate to support this application (see reviews dated 5/1/2013 by David Claffey, and 6/25/2012 by Zhigang Sun respectively).

A3. Drug Product

The drug product was developed as an extended-release orally-disintegrating tablet of six strengths packaged in blisters. The strengths, isomer mixture and release profile were designed to be equivalent to the reference listed drug (RLD), Adderall XR. The tablets contain a 3:1 mixture of d- and l- amphetamine in six dosage strengths which contain 3.13, 6.27, 9.40, 12.5, 15.7 and 18.8 mg equivalents of amphetamine [redacted] base. The strengths were designed to have the same equivalent [redacted]-base content as Adderall XR 5, 10, 15, 20, 25 and 30 mg, respectively. Both products contain amphetamine in the salt form. The [redacted] in the RLD is a mixture of salts [redacted] polystyrene sulfonate [redacted] in the proposed product. The applicant proposes expressing the strengths primarily in terms of amphetamine [redacted]-base with their equivalent to Adderall XR also being listed in labels and labeling.

Tablets of each strength are orange in color [redacted]

(b) (4)

[redacted]

The drug product specification is typical of an orally administered tablet. The limit for (b) (4) is set at a (b) (4)% and disintegration time is set at (b) (4) (b) (4) recommended by the Agency ODT guidance. Dissolution acceptance criteria require (b) (4) and NLT (b) (4) (b) (4) Incomplete batch analysis data were provided for three (b) (4) registration lots each of the smallest (1E051E, 1E086E, 1E089E) and largest (1E088E, 1E090E, 1E098E) dosage strength. One (b) (4) strength lot was also used in the pivotal bioequivalence studies. The lots generally met the proposed acceptance criteria – except for disintegration where the results generally (b) (4) acceptance limit. Batch analysis data were not provided for the four intermediate strengths - only partial data on one (b) (4) 'demonstration lot' of each strength derived from a (b) (4) were provided. Incomplete stability data were provided for these six lots through the 12-month time point. Significant changes were observed in tablet hardness, (b) (4) and disintegration over time where results generally failed to meet drug product acceptance criteria – especially for the (b) (4) strength product. No release or stability data were provided for the intermediate strength products.

In summary, the drug product does not meet specification (b) (4) (b) (4) to the point that an expiry period can not be assigned. The main product-related deficiencies are outlined in Section C1, below.

A4. Drug Product Manufacturing Process

Refer to reviews by Kavita Vyas (dated 5/1/13) and Mahesh Ramanadham (dated 5/1/2013). The drug product used in the clinical trials and registration stability studies was manufactured using a (b) (4) process involving the following (b) (4) steps.

(b) (4)

[redacted]

(b) (4)

The applicant provided details of the manufacturing process development, manufacturing process, and in process controls results for 6 (b) (4) batches of tablets (2 lots were used in clinical trials and all lots in registration stability). These data (b) (4) (b) (4) (b) (4) No manufacturing data were provided for the intermediate strengths.

The applicant proposes (b) (4) (b) (4) Major issues were identified with the (b) (4) and the proposed (b) (4) (see section C2 of this Executive Summary for details)

A5. Manufacturing Facilities

Refer to review by Mahesh Ramanadham (dated 5/1/2013). The drug product is manufactured at Neos Pharmaceuticals,Grand Prairie,TX. A pre-approval inspection is pending. The following table captures the current status of the manufacturing facilities listed in support of the application:

Establishment Name	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Most Recent Milestone	Most Recent EER Compliance Status
(b) (4)								AC
								AC
								AC
								WH
								AC
								PN
NEOS THERAPEUTICS, NC.	3000205839	DAL	USA	Finished drug product manufacturing, packaging, release and stability testing	TTR	05/23/2011-05/27/2011 56002 - VAI (no TTR coverage)	SUBMITTED TO DO	PN

B. Description of How the Drug Product is Intended to be Used

The proposed product is intended for the treatment of ADHD. It is proposed that patients [redacted] can be switched to [redacted] dose equivalent of the proposed product taken once daily. A table for determining the [redacted] proposed product when switching from the extended release mixed amphetamine salts (e.g. Adderall XR) is provided in the labeling. [redacted] can be taken with or without food.

The tablet should remain in the blister pack until the patient is ready to take it. It should not be pushed through the foil and should be placed with dry hands on the patients tongue. [redacted]

C. Basis for Quality Recommendation

C1. Deficiencies related to Product

The highest risk product-related deficiencies relate to the drug product batch analysis and stability data:

Main batch analysis deficiencies:

- The registration lots did not meet the disintegration acceptance criterion [redacted]
- No data from the registration lots of the intermediate strengths [redacted] were provided (not yet manufactured).
- Incomplete batch analysis data [redacted] and no certificates of analysis were provided for the drug product registration lots.
- The source of the drug product release data is unclear – it appears that some data [redacted]
- Data indicates that the [redacted] acceptance range.

Main Stability deficiencies:

- Disintegration [redacted] acceptance criterion – in several time points [redacted]
- Tablet hardness [redacted] % were recorded.
- [redacted]

- Other deficiencies include inconsistent and missing data and uncertainty on whether data (b) (4) (b) (4).
- The data indicate that the drug product will not meet its quality attributes to the point that an expiry period can not be assigned.

These and other deficiencies relating to the drug product and excipient specifications and tests will be relayed to the applicant in the discipline review letter.

C2. Deficiencies related to Drug Product Manufacturing Process

(b) (4)

C3. Deficiencies related to Drug Product Manufacturing Facilities

Pre-approval inspections for Neos Therapuetics, (b) (4) (b) (4) are required to support this application:

- Neos Therapeutics has no inspectional history for solid oral dosage form manufacturing operations to verify compliance with CGMP. Given the deficiencies observed with the manufacturing process, a pre-approval inspection *may* not be considered until the applicant has demonstrated they have a viable manufacturing process.

- [redacted] (b) (4) has no FDA inspection history to verify compliance with CGMP. An inspection is pending.
- [redacted] (b) (4) has been inspected in support of this application. [redacted] (b) (4) has recommended to withhold this application based on this inspection due to the use of uncontrolled, unofficial notebooks and un-validated analytical methods. The EIR, 483, and firm response to the 483 will be evaluated by the Office of Compliance to determine the final recommendation for this application.

C4. Deficiencies related to Other Disciplines

Biopharm has identified deficiencies (see review by Okpo Eradiri dated 5/1/2013).

C5. Overall Assessment

Evaluation of this application is divided between several reviews. The individual elements that constitute a control strategy are therefore distributed in three review documents. The following attempts to summarize a combined contribution of each element to the control strategy, and therefore to the quality of drug product and reliability of manufacturing process. (see detailed discussion in review by Kavita A. Vyas dated 5/1/2013).

1. [redacted] (b) (4)
2.
3.
4.
5.
6.
7.

Overall, the applicant's control strategy appears to fail at two critical points, at the product quality level and process quality level. Therefore, this application can not be recommended for approval from quality perspective in its present form.

III. Administrative

A. Reviewer's Signature

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

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

/s/

DAVID J CLAFFEY
05/01/2013

RAMESH K SOOD
05/01/2013

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I (Branch I)

Initial Quality Assessment
NDA: 204326

OND Division:	Division of Psychiatry Products
Applicant:	Neos Therapeutics, Inc.
NDA Filing Category:	505(b)(2)
Letter Date:	27-DEC-12
Stamp Date:	28-DEC-12
PDUFA Date:	28-OCT-13
Proposed Trade Name:	(b) (4)
Established Name:	Amphetamine (b) (4) Extended-Release Orally Disintegrating Tablets
Dosage Form:	Tablet
Strengths:	Equivalent to 5, 10, 15, 20, 25 and 30 mg mixed amphetamine salt (equivalent to 3.1, 6.3, 9.4, 12.5, 15.7, and 18.8 mg amphetamine base, respectively)
Route of Administration:	Oral
Indication:	Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
Assessor:	Chhagan G. Tele, Ph.D.
ONDQA Fileability:	Yes

Background

Neos Therapeutics, Inc. (Neos) has developed a new extended release oral formulation of amphetamine (b) (4), an oral disintegrating tablet (ODT) for the treatment of attention deficit hyperactivity disorder (ADHD). For this 505(b)2 application, Neos is relying primarily on efficacy data that formed the basis of the FDA approval for the reference listed drug (RLD) ADDERALL XR® (extended-release mixed amphetamine salts, Shire Laboratories, Inc., NDA 21-303, approved 11-OCT-2001) and the published literature on the therapeutic applications of amphetamines to describe the efficacy. Reports of abuse and potential for abuse liability have been consistently associated with amphetamine use. Amphetamine and its salts are classified as a Schedule II drug and the product label of ADDERALL XR contains warnings regarding the high potential of abuse. Extended release forms of amphetamines release drug more slowly compared to their immediate release counterparts, and appear to have less drug abuse potential. Electronic submission (e-CTD format) is provided for the CMC information for the review. The applicant provided Quality Overall Summary in the submission. The applicant had face-to-face Pre-IND meeting (13-JAN-2011), End of Phase 1 meeting (19-OCT-2011), and Pre-NDA meeting (13-SEP-2012) with the clinical division to discuss CMC, biopharmaceutics, clinical pharmacology, and clinical issues. Minutes of these meetings can be found in DARRTS and should be read by the respective reviewers. No CMC specific meetings have been held with the sponsor; however the reviewers need to bridge any changes and agreements evolved from these meetings, amendments, and annual reports submitted during the drug development. The labeling proposed for the Neos Therapeutics, Inc. drug product is the same as the labeling for the listed drug except for changes required because (1) the drugs are produced and distributed by different manufacturers, (2) differences in package configurations, (3) inactive ingredients are not identical, and (4) differences in the tablet descriptions. Neos proposed (b) (4) trade name for the drug product for review and acceptance. However, the naming format will be evaluated by the Division of Medication Error Prevention and Analysis (DMEPA).

The applicant requested a waiver of the requirement to conduct *in vivo* bioavailability studies on all strengths of the product requested for approval. The request of a waiver of the requirement to conduct bioequivalence (BE) and/or bioavailability (BA) studies will be reviewed by ONDQA Biopharmaceutics and/or Office of Clinical Pharmacology Division.

Drug Substance

(b) (4)

Drug Product

Amphetamine (b) (4) Extended Release Orally Disintegrating Tablet (ODT) is an extended release, non-sterile, oral formulation composed of an immediate release (b) (4) combined with a (b) (4), delayed release (b) (4). The applicant developed six strengths of amphetamine (b) (4) extended release ODT, with potency expressed in milligram equivalents to the mixed amphetamine salts: (5 mg-equivalent [3.13 mg base] (b) (4) 10 mg equivalent [6.27 mg base] (b) (4) 15 mg-equivalent [9.40 mg base] (b) (4), 20 mg-equivalent [12.5 mg base] (b) (4), 25 mg-equivalent [15.7 mg base] (b) (4), and 30 mg-equivalent [18.8 mg base] (b) (4) (b) (4) with the only difference being the tablet size, weight and debossing. All tablet strengths have been manufactured by (b) (4)

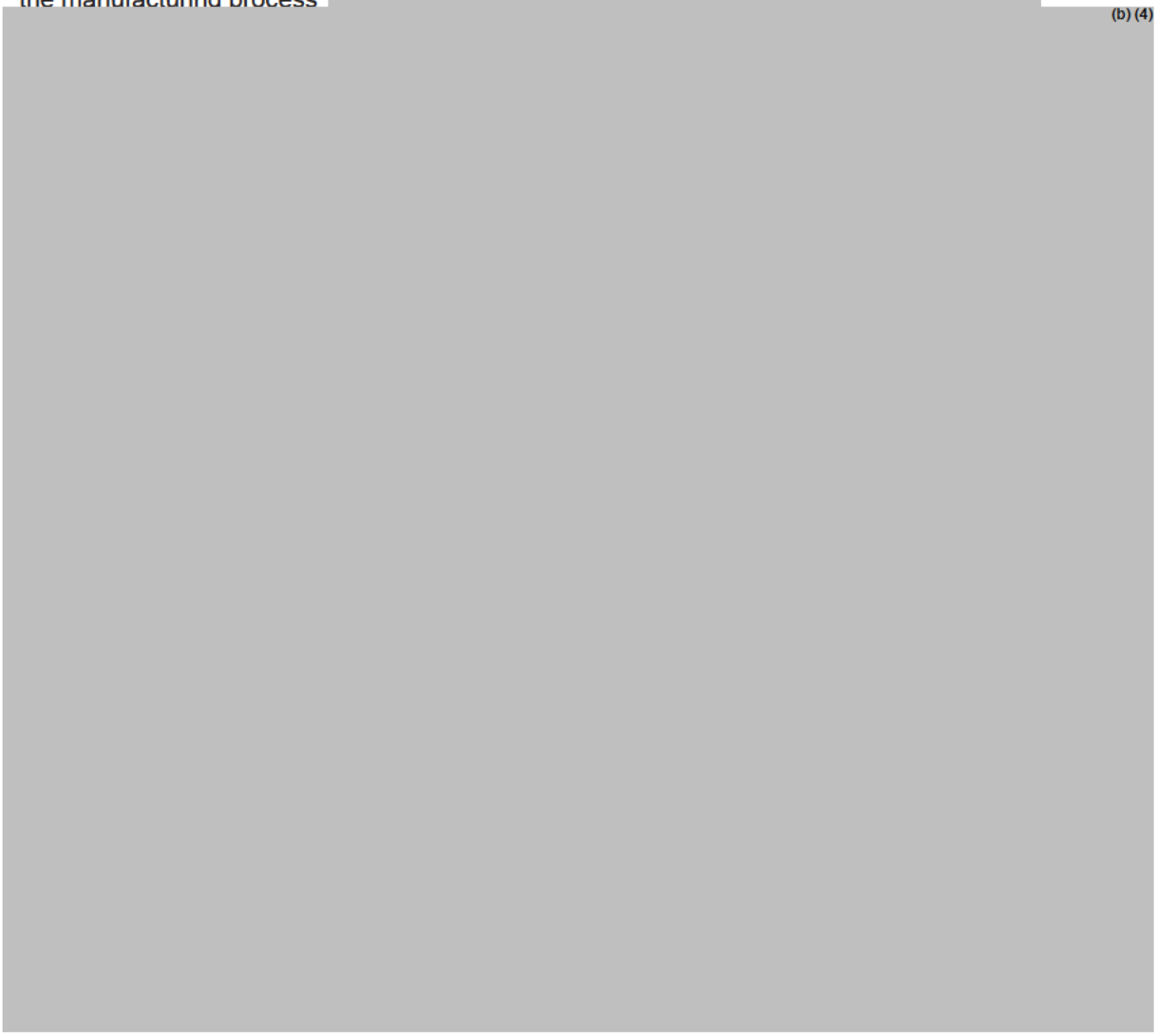
(b) (4)

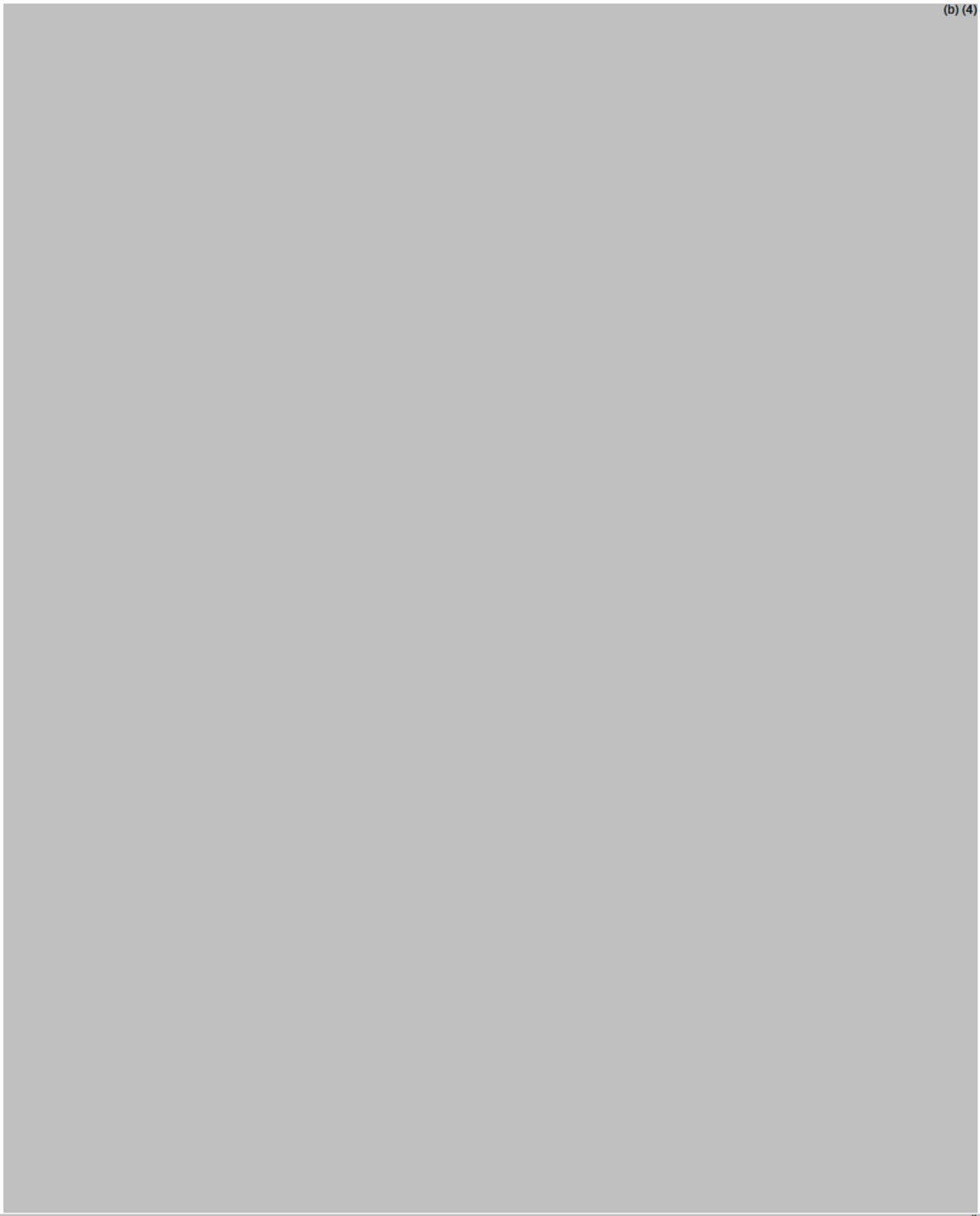
(b) (4) The reviewer needs to evaluate the safety and appropriateness of levels of these materials used in the commercial formulation.

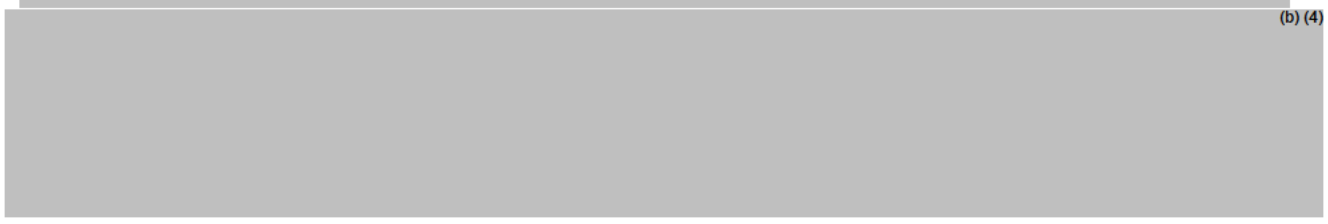
Inactive ingredients used for the Amphetamine (b) (4) Extended Release Orally Disintegrating tablets are Sodium Polystyrene Sulfonate USP (b) (4) Polyethylene Glycol NF, Methacrylic Acid Copolymer Type A NF, Triethyl Citrate (b) (4) (Mannitol, Fructose, Microcrystalline Cellulose, Crospovidone, Colloidal Silicon Dioxide, (b) (4) (b) (4) Sucralose FCC, Citric Acid USP (b) (4) Orange Flavor (b) (4) Lake Blend Orange (b) (4) (b) (4) Magnesium Stearate NF. (b) (4) (b) (4) (b) (4)

(b) (4)

Manufacturing, processing, packaging, labeling and handling of Amphetamine (b) (4) Extended Release Orally Disintegrating tablets will take place at the manufacturing facility, Neos Therapeutics, LP; Grand Prairie, TX. Several in-process tests are performed in manufacturing of tablets. The reviewer needs to evaluate these in-process parameters to ensure the robustness of the manufacturing process (b) (4)




(b) (4)


(b) (4)

(b) (4)

The Amphetamine (b) (4) Extended Release Orally Disintegrating Tablets are packaged into blister packs (b) (4).

(b) (4)

(b) (4)

There are six different strengths of tablets that will be commercially available, however only the (b) (4) DTs has been placed on the current stability program. (b) (4) with the size, weight and debossing of the tablet being the only differences between the different strengths. The ODT batches of (b) (4) and (b) (4) were chosen to perform (b) (4)

(b) (4)

The stability studies include three batches of Amphetamine (b) (4) Extended Release Orally Disintegrating Tablets (ODT) (b) (4) and three batches of Amphetamine (b) (4) Extended Release Orally Disintegrating Tablets (b) (4) (b) (4) The ODT (b) (4) were packaged in six (6)-count blister packaging (as described in Section 3.2.P.7) and have been exposed to long-term stability conditions for 12 months and accelerated conditions for 6 months. There were no trends observed for the ODT (b) (4) through the 6-month accelerated time point or the 12-month long-term stability condition. Based on the available stability data as well as the stress studies, an initial expiration date of 24 months is proposed for commercial Amphetamine (b) (4) Extended Release Orally Disintegrating Tablets manufactured by Neos Therapeutics, LP and packaged in six-count blister packs.

Critical Issues for Review

Drug Substance

- The NDA applicant references [redacted] DMF # [redacted] and [redacted] DMF # [redacted] for the CMC information. These DMFs will need to be evaluated and found acceptable to support this NDA.

Drug Product

- The compatibility of the excipients used in the drug product will need to be evaluated.
- [redacted]

- The applicant identified Critical Quality Attributes [redacted] for the [redacted] process. The reviewer needs to evaluate the data for these critical quality attributes of the [redacted] process to ensure a consistent product is produced that meets the specified attributes including particular controls [redacted] The reviewer also need to evaluate the data to confirm the holding time for the [redacted] tablets.
- The reviewer need to evaluate the container closure suitability.
- The adequacy of the dissolution method and specification limits will need to be determined in conjunction with the ONDQA biopharm reviewer.
- Stability data [redacted]: 6 months accelerated and 12 months long-term data, [redacted]: 6 months accelerated and 12 months long-term data) is provided in the NDA submission packaged in commercial configuration at commercial packaging site. The reviewer need to evaluate stability data to confirm the expiry date.
- NDA submission contains no nanoscale materials. However, the reviewer should indicate that no nanoscale materials are present (see MAPP 5015.9 entitled, "Reporting Format for Nanotechnology—Related Information in CMC Review.")
- The reviewer need to confirm consistency in chemical structure, chemical name, molecular formula, and molecular weight of the drug substance with the current USP dictionary and USAN in the Description section of the labeling. Additionally reviewer need to confirm that all the excipients used in the drug product formulation are included.

Comments and Recommendation:

The NDA is fileable from a CMC perspective. The NDA does not appear to incorporate elements of QbD. NDA submission contains [redacted]. [redacted] information is cross-referenced to DMF # [redacted] and Dextroamphetamine Sulfate information is cross-referenced to DMF # [redacted] regarding chemistry, manufacture, control, reference standards, stability, and packaging. The applicant provided a LoAs dated 16-MAY-12 to refer both DMFs for the drug substance CMC information. Both DMF # [redacted] and [redacted] will need to be reviewed and found adequate to support NDA. Assignment of the NDA to a single reviewer is recommended. The dissolution part of the submission should be consulted to the ONDQA biopharm group. Biopharmceutics reviewer has been assigned yet.

A claim for categorical exclusion under 21 CFR §25.31(b) is provided in Module 1. In accordance with 21 CFR §25.31, Neos Therapeutics, Inc. requested a categorical exclusion [25.31(a)] from the requirement for an Environmental Assessment as approval of [redacted], which is a new dosage form that is directly substitutable for an already approved product (ADDERALL® XR), and would not be considered to increase the use of the active moiety.

The list of manufacturing, testing, and packaging sites for drug substance and drug product is provided to enter into EES. The ONDQA PM need to submit all testing, packaging, and manufacturing sites into EES. The reviewer will need to confirm that these sites are correct and that there are no additional sites that need to be entered.

PRODUCT QUALITY: CMC AND BIOPHARMACEUTICS
FILING REVIEW FOR NDA

NDA Number: 204326	**Applicant:** Neos Therapeutics, Inc.	**Stamp Date:** 28-DEC-12
Drug Name: Amphetamine (b) (4) Extended-Release Orally Disintegrating Tablets	**NDA Type:** Standard	**Filing:**

CMC Reviewer: David Claffey, Ph. D.
Biopharmaceuticals Reviewer: not assigned yet

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion requested

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?			Biopharmaceutics reviewer's input needed
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		X	

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
34.	Does the application contain dissolution data?	X		
35.	Is the dissolution test part of the DP specifications?	X		
36.	Does the application contain the dissolution method development report?	X		
37.	Is there a validation package for the analytical method and dissolution methodology?	X		
38.	Does the application include a biowaiver request?			Biopharmaceutics reviewer need to review the information if provided in the application
39.	Does the application include a IVIVC model?			Biopharmaceutics reviewer need to review the information if provided in the application
40.	Is information such as BCS classification mentioned, and supportive data provided?		X	
41.	Is there any in *vivo* BA or BE information in the submission?			Biopharmaceutics reviewer's input needed

K. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
42.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
43.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			NA
44.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Biopharmaceutics reviewer's input needed
45.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	

Chhagan Tele 07-JAN-12

Name of CMC Lead Date
Division of Pre-Marketing Assessment #1
Office of New Drug Quality Assessment

Ramesh Sood

Name of Branch Chief Date
Division of Pre-Marketing Assessment #1
Office of New Drug Quality Assessment

APPEARS THIS WAY ON ORIGINAL

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

/s/

CHHAGAN G TELE
01/08/2013
IQA Memo

RAMESH K SOOD
01/08/2013