CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204325Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # ***204325***	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: ***Adzenys ER*** Established/Proper Name: ***amphetamine*** Dosage Form: ***extended-release oral suspension*** Strengths: ***1.25 mg/mL***		
Applicant: ***Neos Therapeutics, Inc.***		
Date of Receipt: ***November 15, 2016***		
PDUFA Goal Date: ***September 15, 2017***	Action Goal Date (if different):	
RPM: ***Brendan Muoio, PharmD***		
Proposed Indication(s): ***Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older***		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ ***NO*** ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Adderall XR (NDA 021303)	***Labeling*** - *Nonclinical* - *Clinical efficacy* - *Clinical safety (abuse; drug-drug interactions; clinical pk in special patient populations)*

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

The Sponsor conducted a relative bioavailability study (Study NT0201.1008) comparing equal doses of the to-be-marketed Amphetamine ER Oral Suspension to Adderall XR, the listed drug. The results of the study demonstrated that exposures after administration of Amphetamine ER Oral Suspension and Adderall XR are similar (i.e., meets the Agency's bioequivalent criteria). Therefore, the two products are sufficiently similar to justify reliance on the listed drug.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ ***NO*** ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Adderall XR	***021303***	***Y***

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ ***NO*** ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ ***NO*** ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ ***NO*** ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ ***NO*** ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in dosage form, from capsule to suspension.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ ***NO*** ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ ***YES*** ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): ***Adzenys XR-ODT (NDA 204326), Dyanavel XR (NDA 208147), and Mydayis (NDA 022063), approved generics available***

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): ***Adderall XR/6322819***
Adderall XR/6605300
Adderall XR/RE41148
Adderall XR/RE42096
(each of the 4 patents also has a *PED version)

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ ***21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). If Paragraph IV certification was submitted, proceed to question #15.***

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): ***6322819***
6605300
RE41148
RE42096
(each of the 4 patents also has a *PED version)

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): ***January 30, 2017***

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note *that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information* ***UNLESS*** *the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ ***Patent owner(s) consent(s) to an immediate effective date of approval*** ☒

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

/s/

BRENDAN MUOIO
09/15/2017

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 11, 2017

To: Mitchell Mathis, M.D., Director
Division of Psychiatry Products

Through: Martin S. Rusinowitz, M.D., Senior Medical Officer
Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff

From: Shalini Bansil, M.D., Medical Officer
Controlled Substance Staff

Subject: Amphetamine Extended Release (XR) Oral Suspension (OS).
NDA 204325
Proposed trade name: Adzenys ER
Dosages: 6.3 mg (5 mL) -18.8 mg (15 mL) once daily in the morning
IND Number: 110281
Indication: Attention Deficit Hyperactivity Disorder (ADHD)
Sponsor: Neos Therapeutics, Inc
PDUFA Goal Date: September 15, 2017.

Materials Reviewed:

- 1.11.4 Abuse related information
- 2.3 Quality overall summary
- 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods
- 2.7.4 Summary of Clinical safety
- 5.3.1.1, 5.3.1.2: Clinical study reports

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I. Summary

1. Background

This memorandum responds to a consult request by the Division of Psychiatry Products (DPP) dated Nov 28, 2016, to evaluate abuse-related data submitted byNeos Therapeutics, Inc. in NDA 204325 (developed under IND 110281) for Adzenys ER [Amphetamine Extended Release Oral Suspension (XR-OS)]. This product is an extended-release oral suspension containing 1.25 mg amphetamine base per mL. The drug product is indicated for Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older. For pediatric patients the recommended starting dose is 6.3 mg (5 mL) once daily in the morning. The maximum dose is 18.8 mg (15 mL) daily for patients 6 to 12 years, and 12.5 mg (10 mL) daily for patients 13 to 17 years. In adults the recommended dose is 12.5 mg (10 mL) daily. Amphetamine XR-OS, 18.8 mg/15 mL, is equivalent to 30 mg mixed amphetamine salts/15 mL. In addition to the published literature on the therapeutic applications of amphetamines to describe the efficacy and safety of Amphetamine XR-OS, the Sponsor is relying primarily on efficacy and safety data that formed the basis of the FDA approval for the listed drug, Adderall XR® (extended-release mixed amphetamine salts, Shire Laboratories, Inc., NDA 21303). Psychostimulants (methylphenidate and amphetamines) have been considered the primary line of pharmacotherapy in the treatment of ADHD for many years (initial U.S approval of amphetamine was in 1960). Although the precise mechanism of action by which psychostimulants reduce symptoms of ADHD is currently unknown, these drugs are thought to exert their effect by enhancing synaptic levels of monoamines (dopamine, noradrenaline) in the prefrontal cortex of the brain.

Amphetamine is a Schedule II (C-II) substance under the Controlled Substances Act (CSA).

2. Conclusions

- Amphetamine is a Schedule II controlled substance under the CSA.

- The Sponsor is submitting an NDA for Amphetamine XR-OS via the 505(b)(2) pathway, with Adderall XR® (extended-release mixed amphetamine salts) as the listed drug.
- The Sponsor has captured abuse-related adverse events (AEs) during Phase 1 studies. AEs were summarized by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA).
- Amphetamine XR-OS is not significantly different from Adderall XR in terms of bioavailability. The abuse-related AE profile of Amphetamine XR-OS is similar to other approved amphetamine products.
- The product label includes a black box warning regarding abuse and appropriately discusses abuse and dependence in section 9, consistent with other amphetamine-containing drug products.
- The Sponsor does not propose any schedule change to the CII classification of amphetamine in Amphetamine XR-OS.

3. Recommendations

1. Based on the profile of effects in human studies following administration and withdrawal of amphetamine products, including Amphetamine XR-OS, CSS agrees with the Sponsor's request to maintain Amphetamine XR-OS in Schedule II of the CSA.

2. Routine Periodic AdverseEvent Reports (PADERS) are adequate for reviewing and reporting abuse related adverse events.

3. No label changes are recommended for the abuse-related information.

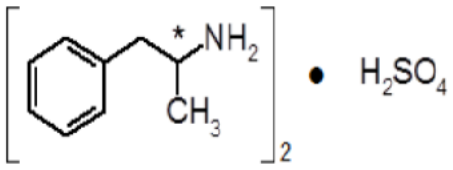
II. Discussion

1. Chemistry

The Amphetamine XR-OS formulation contains dextroamphetamine and levoamphetamine

(b) (4)

Molecular Structure of Amphetamine Sulfate and General Properties (Sponsor's Submission 2.3 S)



General Properties	Amphetamine sulfate is a white, odorless crystalline powder with a slightly bitter taste. It is freely soluble in water and slightly soluble in alcohol.
Stereochemistry	Amphetamine sulfate is a racemic mixture of *R* and *S* enantiomers issuing from a stereogenic center located on the α carbon of the aminopropyl sidechain. The drug substance is optically inactive as it is a racemic mixture.
Molecular Name	(±)-(2S)-1-phenyl-2-propanamine; sulfuric acid
Molecular Weight	368.49 g/mol
Description	White to off-white solid
Melting Point	> 300°C
Solubility	Freely Soluble

1.1 Substance Information

Amphetamine XR-OS (18.8 mg of amphetamine base per 15 mL suspension or 1.25 mg of amphetamine base per mL of suspension) was formulated to contain an equivalent active composition of amphetamine in the free base form to the mixed amphetamine salts (dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine sulfate and

amphetamine aspartate) in Adderall XR. Amphetamine Sulfate, USP and Dextroamphetamine Sulfate, USP are the active pharmaceutical ingredients (APIs) in the Amphetamine (AMP) XR-OS formulation.

2. Nonclinical Pharmacology

The Sponsor has not conducted specific studies to assess the abuse potential of amphetamine XR OS. It is an extended-release oral suspension formulation of amphetamine that is being submitted as a 505(b)(2) application, using Adderall XR® (Shire LLC) as the listed drug product. The Sponsor anticipates that AMP XR-OS will be dosed in AMP base equivalents containing the same amount of AMP base and the same dose range (based on AMP base) as the reference drug. Moreover, the abuse potential of the active moiety in AMP XR-OS is presumed to be similar to that of Adderall XR given its bioequivalent plasma concentration-time profile when compared with Adderall XR for both d- and l-amphetamine.

Abuse potential data included in this NDA are derived from a review of the literature conducted by the Sponsor and an in vitro ethanol dissolution study with the commercial-scale (to-be-marketed) formulation of AMP XR-OS.

Results of Searches: Since amphetamine was first used medically, there have been reports of drug abuse. This class of drugs has a high potential for abuse, dependence, and misuse that has been well-documented in the literature. The current literature continues to report nonmedical use of stimulants, especially in adults aged 18 to 25 years old. This is likely a result of an increased use in college students to enhance academic performance. Moore (2014) and Burgard (2013) both reported a trend toward higher uses of Adderall and Ritalin on college campuses during times of stress: first week of classes, midterms and finals.The trend was stronger for Adderall than for Ritalin. In both articles, campus waste water was collected and analyzed for the metabolites of Ritalin. Burgard compared self-reports of the non-prescriptive use of Adderall and Ritalin to the level of metabolites in the waste water. Results indicated an under-reporting of the non-prescriptive use of Adderall and Ritalin, thus indicating that the use of non-prescriptive Adderall and Ritalin may be higher than current estimates. Based on the literature searches, it is expected that AMP XR-OS will have a similar abuse profile to other AMP products, including Adderall XR.

In Vitro Alcohol Dissolution Study: The commercial scale AMP XR-OS (30 mg/15 mL) formulation and the reference product, Adderall XR (30 mg capsule), were evaluated in an in vitro alcohol dissolution study to ascertain the performance of the formulation when administered with varying amounts of alcohol. The in vitro alcohol study used dissolution media with concentrations of ethanol of 0%, 5%, 10%, 20% and 40% v/v. Sample acquisition time points at 0.25, 0.5, 1.0, 2.0, 2.25 and 2.5 hours were tested for each dissolution. The following tables show the results of the alcohol dissolution study (Sponsor's submission 1.11.4) comparing

AMP XR-OS (Sponsor's Table 1) with Adderall XR (Sponsor's Table 3).

Table 1: Amphetamine XR-OS (Lot 4E057B) – Formulation Dissolution Results in Media with Various Concentrations of Ethanol

Time (hours)	Alcohol Concentration (v/v) of Dissolution Media				
	% Released in 0% Ethanol	% Released in 5% Ethanol	% Released in 10% Ethanol	% Released in 20% Ethanol	% Released in 40% Ethanol
0.25	56.3%	56.7%	57.2%	56.7%	78.6%
0.50	57.1%	57.5%	57.9%	59.6%	84.7%
1.00	58.0%	58.5%	59.0%	61.4%	92.5%
2.00	59.1%	59.8%	60.3%	63.8%	97.0%

Table 3: Adderall XR Dissolution Results in Media with Various Concentrations of Ethanol

Time (hours)	Alcohol Concentration (v/v) of Dissolution Media				
	% Released in 0% Ethanol	% Released in 5% Ethanol	% Released in 10% Ethanol	% Released in 20% Ethanol	% Released in 40% Ethanol
0.25	48.8%	49.3%	49.6%	50.1%	74.5%
0.50	50.1%	50.7%	51.7%	64.4%	92.2%
1.00	51.3%	51.8%	56.4%	80.9%	97.9%
2.00	52.1%	53.9%	68.4%	95.5%	99.3%

The *in vitro* alcohol-induced dose dumping study revealed a substantial increase in amphetamine release from AMP XR OS in the presence of 40% alcohol but not with 5%, 10% or 20% alcohol. Adderall XR shows a similar degree of amphetamine release in various concentrations of alcohol.

The Sponsor states that in order to evaluate the abuse potential of a drug product, chemical and dissolution aspects must be considered, including the effect of external factors such as pH on the rate of release of the drug. To determine the effect of these variables on the release of amphetamine from AMP XR-OS, in vitro dissolution profiles for different dosage quantities were generated in the presence of varying pH levels, (b) (4) In this comparative dissolution study, the clinical trial formulation and the commercial scale formulation of AMP XR-OS were used. (b) (4)

(b) (4). Overall, these in vitro data indicate that the AMP XR-OS used in clinical trials and as the commercial formulation retains the expected amphetamine release profile at varying pHs. The results of the studies suggest that if AMP XR-OS is misused, either intenionally or unintentionally, minimal changes would take place in the rate of release of amphetamine from the XR-OS product.

3. Clinical Pharmacology

The Sponsor conducted five Phase 1 studies investigating the bioavailability/bioequivalence of AMP XR-OS, four in healthy adult volunteers (NT0201.1005, NT0201.1006, NT0201.1007, and NT0201.1008) and one in children (6-12 years of age) with ADHD (NT0201.1004). The clinical trial formulation was used in studies NT0201.1004, NT0201.1005, and NT0201.1006. The PK profile of the commercial scale formulation of AMP XR-OS was compared to that of the clinical trial formulation in study NT0201.1007 and to that of Adderall XR in study NT0201.1008.
The results of NT0201.1007 and NT0201.1008 indicate that the commercial-scale formulation of AMP XR-OS is bioequivalent to the clinical trial formulation of AMP XR-OS and Adderall XR.

The Sponsor's Table 31 (Sponsor's submission 2.7.1) compares the PK profile of the commercial-scale formulation of AMP XR-OS to Adderall XR:

Table 31: Analysis of d-Amphetamine and l-Amphetamine Comparing the Commercial Scale Formulation of Amphetamine XR-OS to ADDERALL XR under Fasted Conditions Following Single Dose Oral Administration, Study NT0201.1008

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

[a] Ratio (%) = geometric mean for Commercial Formulation Amphetamine XR-OS /geometric mean for ADDERALL XR

3.1 Drug/Product Interactions

The PK results of studies NT0201.1006 and NT0201.1007 demonstrated that there are no significant differences in PK parameters in the fed or fasted state following administration of the clinical trial formulation or the commercial-scale formulation.

The Sponsor's Table 29 (Sponsor's submission 2.7.1) compares the PK profile of the commercial-scale formulation of AMP XR-OS in the fed or fasted state:

Table 29: Analysis of d-Amphetamine and l-Amphetamine under Fed and Fasted Conditions Following Single Dose Oral Administration of the Commercial Scale Formulation of Amphetamine XR-OS, Study NT0201.1007

Parameter	Geometric Mean Ratio (%)[a]		90% Confidence Interval[b]	
	d-amphetamine	l-amphetamine	d-amphetamine	l-amphetamine
$\ln(C_{max})$	88.65	88.55	86.34, 91.02	86.11, 91.05
$\ln(AUC_{last})$	97.66	96.33	94.44, 100.99	92.92, 99.85
$\ln(AUC_{inf})$	97.67	96.10	94.30, 101.15	92.39, 99.96
$\ln(AUC_{0-5})$	90.77	91.12	85.34, 96.54	85.50, 97.10
$\ln(AUC_{5-last})$	98.66	96.86	94.68, 102.79	92.81, 101.09

[a] Ratio (%) = geometric mean for Commercial Formulation Amphetamine XR-OS (fed)/geometric mean for Commercial Formulation Amphetamine XR-OS (fasted)

4. Clinical Studies

4.1 Adverse Event Profile Through all Phases of Development

NT0201.1004 (Phase 1): A single-dose, single-period, one-treatment, PK study of an XR formulation of amphetamine oral suspension (equivalent to 30 mg mixed amphetamine salts/15 mL) under fasted conditions in children (ages 6-12) with ADHD.

This study was designed to evaluate PK and safety in children with ADHD who received one single-dose 15 mL administration of NT0201 (AMP XR-OS), equivalent to 30 mg mixed amphetamine salts (MAS)/15 mL) following an overnight fast of at least 10 hours.

A total of 29 male and female children, aged 6 to 12 years, were enrolled in this study. All 29 subjects received treatment, completed the PK sampling schedule, and completed the study. There were no dropouts or withdrawals. No abuse related AEs were reported.

NT0201.1005 (Phase I): A Single-Dose, Four-Period, Four-Treatment, Four-Way Crossover Bioequivalence Study of Three Formulations of NT0201 Amphetamine Polistirex Extended Release Oral Liquid Suspension (Equivalent to 30 mg Mixed Amphetamine Salts/15 mL) and Adderall XR® 30 mg Capsule under Fasted Conditions

This was a single-dose, open-label, randomized, four-period, four-treatment crossover study in which 44 healthy adult subjects received separate single-dose administrations of three different test formulations of NT0201 Amphetamine Polistirex XR Oral LS and a single separate dose of Adderall XR® 30 mg capsule. All doses were administered under fasted conditions.

The objective of this study was to compare the rate of absorption and oral bioavailability of three different formulations of Amphetamine Polistirex XR Oral LS (equivalent to 30 mg

MAS /15 mL) to an equivalent 30 mg oral dose of the commercially available reference product, Adderall XR.

Thirty nine (39) subjects completed all 4 study periods. One subject was withdrawn for protocol non-compliance at Period 2 check-in (positive urine drug screen). Four other subjects did not complete the study for non abuse related events. Euphoric mood was reported in 2.4% of individuals receiving the test product and in 2.4 % of those receiving Adderall. One subject reported increased energy with the test product (2.4%)

NT0201.1006 (Phase I): A Single-Dose, Three-Period, Three-Treatment, Three-Way Crossover Food Effect Study of an Investigational Formulation of Amphetamine Polistirex Extended Release Oral Liquid Suspension (Equivalent to 30 mg Mixed Amphetamine Salts/15 mL) and Adderall XR® 30 mg Capsule

This was a single-dose, open-label, randomized, three-period, three-treatment crossover study in which 30 healthy adult subjects received one dose of NT0201 Amphetamine Polistirex XR OLS (equivalent to 30 mg mixed amphetamine salts/15 mL) under fasted conditions, one dose of NT0201Amphetamine Polistirex XR OLS under fed conditions, and one dose of Adderall XR® under fed conditions. A total of 30 subjects participated in the study and 29 subjects completed all three study periods.
One Subject withdrew consent from the study due to an AE of multiple episodes of vomiting. Agitation and euphoria were reported by 3.3% of the subjects who received the study drug and by none who received Adderall.

NT0201.1007 (Phase I): A Single-Dose, Three-Period, Three-Treatment, Three-Way Crossover Bioavailability Study of a Commercial Scale Formulation of Amphetamine Extended-Release Oral Suspension (AMP XR OS, equivalent to 30 mg MAS/15 mL) under Fed and Fasted Conditions and a Clinical Trial Formulation of AMP XR OS (equivalent to 30 mg Mixed Amphetamine Salts/15 mL) under Fasted Conditions.

In this study 48 healthy adult subjects received a dose of AMP XR OS (formulation 1) under fed conditions in one period, a dose of AMP XR OS (formulation 1) under fasted conditions in another period, and a dose of AMP XR OS (formulation 2) under fasted conditions in a different period. Euphoric mood was reported in 2-4% of subjects. The most commonly reported AE was euphoric mood (n = 5).

NT0201.1008 (Phase I): A Single-Dose, Two-Period, Two-Treatment, Two-Way Crossover Bioequivalence Study of AMP XR OS, equivalent to 30 mg MAS/15 mL and Adderall Extended-Release 30 mg Capsules under Fasted Conditions

This was a single-dose study in which 42 healthy adult subjects received a single dose of the commercial scale formulation AMP XR OS (equivalent to 30 mg mixed amphetamine salts/15 mL) in one period and a single dose of Adderall XR 30 mg in another period, both under fasted conditions. No abuse related AEs were reported.

4.2 Safety Profile

A total of 193 subjects (164 adults and 29 children) were enrolled; of these, 185 subjects (156 adults and 29 children) received all scheduled doses of AMP XR-OS equivalent to 30 mg of MAS/15 mL. In the four adult Phase 1 clinical studies, AEs were monitored throughout the study duration including at check-in, Day 1, Day 2, Day 3, at the end of each treatment sequence , and at end of study or early termination. Subjects remained at the clinical site until completion of the 36 hour procedures and returned for outpatient visits at approximately 48 to 60 hours post-dose in each study period. In Study NT0201.1004, conducted in children with ADHD, AEs were monitored throughout the study including overnight plus at the 12-hour inpatient sampling period and 24-hour post-dose outpatient visit. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) by SOC and PT. The nature of the abuse-related AEs reported in the Phase 1 studies of AMP XR-OS is consistent with the mechanism of action of amphetamines as a central nervous system stimulant. Euphoric mood was reported in the test formulation and in the listed drug to a similar degree. Since agitation is also known to occur with amphetamine products, no excessive abuse-related AEs were reported.

4.3 Evidence of Abuse, Misuse, and Diversion in Clinical Trials

There was no evidence of abuse or drug accountability issues in the clinical trials conducted by the Sponsor. One subject was withdrawn for protocol non-compliance at Period 2 check-in (positive urine drug screen). Other drop outs were related to non-abuse-related events.

4.4 Tolerance and Physical Dependence Studies in Humans

No specific tolerance or physical dependence studies were conducted with AMP XR-OS. The tolerance and physical dependence profile is expected to be similar to other amphetamine products.

5. Regulatory Issues and Assessment

AMP XR-OS is expected to have similar abuse liability as other ER amphetamine products given its relative bioavailability when compared to the listed drug, Adderall XR and its similar pharmacokinetic profile.

Amphetamine is an established Schedule II (CII) compound that has been marketed in numerous immediate release (IR) and ER formulations since its initial US approval in 1960. The abuse potential of amphetamine has been well established. Existing amphetamine formulations have a CII classification, include a black box warning about abuse and dependence, and have related information throughout the label and the Medication Guide. Accordingly, the Sponsor has included a CII classification and abuse-related, amphetamine-specific information in the label and Medication Guide in line with other marketed amphetamine products. The Sponsor does not propose any schedule change to the CII classification of amphetamine in AMP XR-OS. The proposed label adequately addresses the abuse and dependence liability of AMP XR-OS including the black box warning.

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/s/

SHALINI M BANSIL
08/11/2017

MARTIN S RUSINOWITZ
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SILVIA N CALDERON
08/11/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: **August 11, 2017**

To: Brendan Muoio, Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Christine Bradshaw, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, Team Leader, OPDP

Subject: **NDA 204325 /O-1**
OPDP labeling comments for Adzenys ER (b) (4) (amphetamine) extended-release oral suspension, CII (Adzenys)

In response to DPP's consult request dated January 1, 2017, OPDP has reviewed the draft product labeling (PI), Medication Guide (MG) and carton/container labeling for Adzenys.

OPDP's comments on the draft PI for Adzenys are based on the version of the PI provided by Brendon Muoio via email on August 8, 2017. Combined OPDP and Division of Medical Policy Programs (DMPP) comments on the proposed Medication Guide were provided to DPP under separate cover.

Carton/Container Labeling

OPDP has reviewed the draft carton/container labeling for Adzenys submitted by the Sponsor on June 14, 2017, and downloaded from Global Submit on August 10, 2017.

OPDP notes that the carton/container labeling includes the following information, "1.25 mg/mL Amphetamine (equivalent to 2 mg/ml mixed salts of single-entity amphetamine product)" (emphasis added). We note that the PI does not include the underlined information. We defer to DPP.

If you have any questions, please feel free to contact me by phone at 301-796-6796 or by email at Christine.Bradshaw@fda.hhs.gov. OPDP appreciates the opportunity to provide comments on these materials. Thank you!

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/s/

CHRISTINE J BRADSHAW
08/11/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 09, 2017
To:	Mitchell Mathis, MD Director **Division of Psychiatry Products (DPP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)** **Mathilda Fienkeng, PharmD, RAC** Team Leader Office of Prescription Drug Promotion (OPDP)
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Christine Bradshaw, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	AMPHETAMINE XR-OS (amphetamine)
Dosage Form and Route:	extended-release oral suspension
Application Type/Number:	NDA 204325
Applicant:	Neos Therapeutics, Inc.

1 INTRODUCTION

On November 15, 2016, Neos Therapeutics, Inc. submitted for the Agency's review an original New Drug Application (NDA) 204325 for AMPHETAMINE XR-OS (amphetamine) extended-released oral suspension indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older. The application for AMPHETAMINE XR-OS is based on a bioequivalence bridge to the Listed Drug (LD), ADDERALL XR (NDA 021303), which was originally approved on October 11, 2001.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on January 10, 2017, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for AMPHETAMINE XR-OS (amphetamine) extended-released oral suspension.

2 MATERIAL REVIEWED

- Draft AMPHETAMINE XR-OS (amphetamine) extended-release oral suspension MG received on November 15, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 2, 2017.
- Draft AMPHETAMINE XR-OS (amphetamine) extended-release oral suspension Prescribing Information (PI) received on November 15, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 2, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
08/09/2017

CHRISTINE J BRADSHAW
08/09/2017

BARBARA A FULLER
08/09/2017

LASHAWN M GRIFFITHS
08/09/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
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Division of Pediatric and Maternal Health
Silver Spring, MD 20993
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M E M O R A N D U M

From: Lily (Yeruk) Mulugeta, PharmD, Clinical Reviewer
Division of Pediatric and Maternal Health (DPMH)

Through: Hari Cheryl Sachs, MD, Team Leader (DPMH)

John Alexander, MD, MPH, Deputy Director (DPMH)

To: Division of Psychiatry Products (DPP)

Drug: Adzenys ER (amphetamine) extended-release oral suspension

Sponsor: **Neos Therapeutics, Inc.**

NDA: 204325

Proposed Indication:
Treatment of Attention-Deficit Hyperactivity Disorder (ADHD) 6 years and older

Dosage form and route of administration: Extended release oral suspension

Consult Request: DPP requested input from DPMH regarding product labeling

Background

Neos submitted a 505b2 application for Adzenys ER, an extended release oral suspension of amphetamine equivalent to 30 mg/15 mL mixed amphetamine salts (MAS) with a proposed indication of treatment of ADHD in adults and pediatric patients 6 years and older. The reference listed product is Adderall XR (NDA 021303). The sponsor has

already conducted a bioequivalence study in adult subjects that showed Adzenys ER to be bioequivalent to Adderall XR in the established metrics of Cmax, AUCinf, and specified pAUC parameters. The sponsor also conducted a pharmacokinetic study in children (6-12 years of age) with ADHD which showed comparable PK.

DPP has concluded that the product is bioequivalent to Adderall XR and that the submission supports approval in both adults and pediatric patients 6 years and older. The sponsor will need to address PREA requirements for patients 4 to 5 years of age. Because the reference product (Adderall XR) has ongoing pediatric studies related to PREA requirements for patients 4 to 5 years of age, the sponsor will likely not need to conduct new studies. The timelines of the PREA PMR studies have been adjusted to allow leveraging of data from completed PREA studies for the reference product.

Conclusions:
DPMH participated in labeling meetings and negotiations between 04/6/2017-08/2/2017. The proposed label mirrors that of Adderall XR with additional information specific to the administration formulation and juvenile toxicology class labeling. DPMH agrees with the Division's revisions to the sponsor's label and has no further edits to recommend. The reader is directed to final negotiated labeling which may reflect changes not discussed in this review.

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/s/

YERUK A MULUGETA
08/04/2017

HARI C SACHS
08/04/2017

JOHN J ALEXANDER
08/04/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 21, 2017
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 204325
Product Name and Strength:	Amphetamine Extended Release Oral Suspension 1.25 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Neos Therapeutics, Inc.
Submission Date:	November 15, 2016
OSE RCM #:	2016-2832
DMEPA Primary Reviewer:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container label and prescribing information for amphetamine extended release oral suspension, NDA 204325, submitted by Neos Therapeutics, Inc. on November 15, 2016. The Division of Psychiatry Products requested that we review the proposed container label and prescribing information for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed container label and prescribing information and identified the following areas of concern which may pose risk of medication error:

Container Label

1. The statement of strength lacks prominence due to the small font size which impairs its readability.

2. The equivalency statement is in two locations (principal display panel and side panel) and is, thus, duplicative and adds unnecessary clutter to the label.

3. The Medication Guide (MG) statement does not state how the MG is provided. This information needed by the healthcare professional dispensing the product.

4. The product will be provided in a round bottle with a horizontally positioned barcode which may hinder the readability of the barcode when scanned. This may lead to risk of product identification errors.

5. The expiration date format is not provided. The format of this important information should be provided for Agency review to determine whether it is potentially confusing.

6. The "Shake Well Before Use" statement is on the side panel where it may be overlooked. This statement is important to help ensure the product is well mixed prior to dispensing and administering the drug.

Prescribing Information

Section 16.2 *Storage and Handling* and Section 17 *Patient Counseling Information* uses inconsistent terms to describe the oral dosing device (b) (4) that the pharmacist should provide with this product. For consistency and to decrease risk of confusion, one term should be used throughout the labeling.

In Sections 4 (b) (4), we provide recommendations regarding the areas of needed improvement to help minimize the potential for medication errors to occur with the use of this product.

4 CONCLUSION & RECOMMENDATIONS

We identified areas on the proposed container label where important information should be revised, relocated or deleted to help ensure the safe use of the product. We provide recommendations in Sections 4 (b) (4) to address our concerns. We advise these recommendations are implemented prior to the approval of this application.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Full Prescribing Information

Section 16.2 *Storage and Handling* instructs the pharmacist to provide an oral dosing (b) (4) and Section 17 *Patient Counseling Information* states to use the product with an oral dosing device. The terms used are not consistent between the two sections (b) (4) and may lead to confusion. We recommend that one of these terms be used consistently throughout the labeling.

4.2 RECOMMENDATIONS FOR NEOS THERAPEUTICS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Label

1. The statement of strength lacks prominence due to the small font size. To improve the readability of the statement, increase the font size and delete the adjacent word (b) (4) Additionally, place an asterisk next to the statement of strength (on the right side) to refer the reader to the equivalency statement that is on the side panel (see A.2, below).

2. The equivalency statement is in two locations [principal display panel (PDP) and side panel] and is, thus, duplicative. We recommend you delete the equivalency statement that is located on the PDP. Additionally, place an asterisk in front of the equivalency statement that is located on the side panel (see Comment A.1, above).

3. A Medication Guide (MG) should be dispensed with your product. Each container or package shall therefore instruct the authorized dispenser to provide a MG to each patient and shall state how that MG is provided. Add a statement, similar to one of the statements below, to the principal display panel of the container label in accordance with 21 CFR 208.24(d):

    a. (b) (4) or
    b. "Attention Pharmacist: Dispense the accompanying Medication Guide to each patient."

4. Your product will be provided in a round bottle, however, the barcode is positioned horizontally. Due to the bottle curvature, the barcode may not be scannable which may lead to product identification errors. To improve the scannability of the barcode, reorient the horizontal barcode to a vertical position.

5. The expiration date format is not provided. Please indicate the format that you intend to use (for example, MMMYYYY or MMMDDYYYY). Clearly presented formatting may help to decrease the risk of dispensing or using deteriorated drug product.

6. The "Shake Well Before Use" statement is on the side panel where it may be overlooked. This statement of instruction is important to help ensure that the product is well mixed prior to dispensing and administering the drug. Therefore, we recommend that this statement be moved to a position on the lower 1/3 portion of the PDP.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for amphetamine extended release oral suspension that Neos Therapeutics, Inc. submitted on November 15, 2016.

Table 2. Relevant Product Information for Amphetamine Extended Release Oral Suspension	
Initial Approval Date	N/A
Active Ingredient	amphetamine
Indication	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older
Route of Administration	Oral
Dosage Form	Extended Release Oral Suspension
Strength	1.25 mg/mL
Dose and Frequency	Pediatric Patients: The recommended starting dose is 6.3 mg (5 mL) once daily in the morning. Increase in increments of 3.1 mg (2.5 mL) or 6.3 mg (5 mL) at weekly intervals. The maximum dose is 18.8 mg (15 mL) daily for patients 6 to 12 years, and 12.5 mg (10 mL) daily for patients 13 to 17 years. Adult Patients: The recommended dose is 12.5 mg (10 mL) daily.
How Supplied	Bottles of 450 mL
Storage	Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F)
Container Closure	Child-resistant closure

APPENDIX G. LABEL AND LABELING

G.1 List of Label and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Amphetamine Extended Release Oral Suspension label and labeling submitted by Neos Therapeutics, Inc. on November 15, 2016.

- Container Label
- Prescribing Information (Image not shown)

G.2 Container Label Image

(b) (4)

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LORETTA HOLMES
07/21/2017

LOLITA G WHITE
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and
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PLLR Labeling Memorandum

Date: June 26, 2017 **Date consulted:** December 29, 2016

From: Jane Liedtka, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Brendan Muoio, PharmD, RAC, Regulatory Project Manager (RPM)
Division of Psychiatry Products (DPP)

Drug: Adzenys ER (amphetamine extended-release oral suspension)

NDA: 204325

Applicant: Neos Therapeutics, Inc.

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Indication: Adzenys ER is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.

Materials Reviewed:

- DPMH consult request dated December 29, 2016, DARRTS Reference ID 4035114.
- Sponsor's submitted background package for NDA 204325, submitted on November 15, 2016.

- DPMH consult review of Dyanavel XR (amphetamine extended-release oral suspension), NDA 208147. Miriam Dinatale, D.O. October 19, 2015, DARRTS Reference ID 3833180.
- DPMH consult review of Concerta (methylphenidate HCl) Extended-Release Tablets CI, NDA 21121. Jane Liedtka, M.D. January 4, 2017, DARRTS Reference ID 4035893.
- DPMH consult review of Vyvanse (lisdexamfetamine dimesylate) Capsules, NDA 021977/S-041. Christos Mastroyannis, M.D. August 28, 2016, DARRTS Reference ID 3995016.

Consult Question:

Review of the FPI for Pregnancy and Lactation Labeling Rule compliance.

INTRODUCTION

On December 29, 2016, DPP consulted DPMH to provide input for appropriate labeling of the pregnancy and lactation sections of Adzenys ER to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

BACKGROUND

On November 15, 2016, Neos Therapeutics, Inc., submitted a New Drug Application (NDA) via the 505(b) (2) regulatory pathway, for NDA 204325, Adzenys ER. Adzenys ER is a CNS stimulant indicated for the treatment of ADHD in patients (b) (4) (b) (4) The reference listed drug (RLD) for this application is Adderall XR, which was ed in the US on October 11, 2001. The original submission contained an adequate review of the literature to support PLLR labeling.

Pregnancy and Lactation Labeling Rule

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*," also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. [1] The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

[1] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

DATA REVIEW

Pregnancy

DPMH has completed a review of another amphetamine extended release oral suspension, Dyanavel XR[2] (NDA 208147) and of a lisdexamfetamine dimesylate product, Vynase Capsules[3] (NDA 021977). See these reviews for background on ADHD and Pregnancy, amphetamine drug characteristics, nonclinical information (the current applicant did not perform any additional nonclinical studies beyond what was performed for the RLD) and details regarding the published studies describing the use of amphetamine during pregnancy.

Applicant Review of Published Literature Regarding Amphetamine Use during Pregnancy

The Applicant conducted a search of the published literature regarding use of amphetamine AND pregnancy in PubMed, Embase platform and LILACS database. They cited the National Toxicology Program (NTP)'s Center for the Evaluation of Risks to Human Reproduction (CERHR) comprehensive report on the developmental and reproductive effects of amphetamines from 2005[4]. This document (and the referenced articles within it) will be discussed further under the section of this review entitled "DPMH's Review of the Literature". A total of seven articles were identified by the Applicant beyond those discussed in the NTP document; one of these seven was a meta-analysis of ten studies. These will also be discussed below under the section of this review entitled "DPMH's Review of the Literature".

Overall, the Applicant did not state any conclusions regarding the risk of major malformations following pregnancy exposure to amphetamine beyond those made by the authors of the NTP report.

Applicant Review of Pharmacovigilance Database

Pregnancy and lactation were exclusion criteria in the Neos sponsored studies, NT0201.1005, NT0201.1006, NT0201.1007, and NT0201.1008. The Applicant did not report any pregnancies.

DPMH Review of Literature Regarding Amphetamine Use during Pregnancy

A limited literature search was performed by DPMH to capture any new information published since the search conducted for the Dyanavel XR[2] DPMH consult noted above. DPMH conducted a search of published literature in PubMed using the search terms

[2]DPMH consult review of Dyanavel XR (amphetamine extended-release oral suspension), NDA 208147. Miriam Dinatale, D.O. October 19, 2015, DARRTS Reference ID 3833180.
[3] DPMH consult review of Vyvanse (lisdexamfetamine dimesylate) Capsules, NDA 021977/S-041. Christos Mastroyannis, M.D. August 28, 2016, DARRTS Reference ID 3995016.
[4] NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Amphetamines, March 2005.

"amphetamine and pregnancy" "amphetamine and pregnant women," "amphetamine and pregnancy and birth defects," "amphetamine and pregnancy and congenital malformations," "amphetamine and pregnancy and stillbirth," "amphetamine and spontaneous abortion" and "amphetamine and pregnancy and miscarriage" covering January of 2014 through the June of 2017. Besides what DPMH had previously reviewed and what the Applicant reviewed in their review of literature, there were no new publications regarding the use of amphetamine during pregnancy. Several publications reporting on the effects of methamphetamine use during pregnancy were identified but no new information (not already discussed in previous DPMH reviews) was noted.

The NTP report (based on a literature review by a 13 member expert panel on the use of amphetamines and methamphetamines during pregnancy published prior to December 31, 2004) made the following conclusions:

- Human data are insufficient for an evaluation of the developmental toxicity of amphetamine following prenatal exposure.
- There are sufficient data to conclude that intraperitoneal injection of amphetamine in pregnant mice at doses of 50 mg/kg body weight/day given between gestational days 9 and 11 increases the incidence of malformations (microphthalmia, amelia, excencephaly, cleft lip) in the offspring.
- Several rat and mouse studies reported effects on fetal or neonatal viability, but the evidence is not sufficient to permit conclusions due to limitations of the studies.
- Based on the experimental animal data, the expert panel was concerned that neurobehavioral alterations due to prenatal amphetamine exposure could be seen in humans in both therapeutic and non-therapeutic settings.
- There is no interpretable human data on methamphetamine use during pregnancy and developmental toxicity.
- There is sufficient data from experimental animal studies to conclude that methamphetamine induces reduced pup weights, reduced litter sizes, and neurobehavioral alterations (abnormal neurobehavioral test results) in rats exposed to methamphetamine in utero.
- Based on the animal data, the expert panel had concerns about potential adverse perinatal outcomes and neurobehavioral alterations due to prenatal methamphetamine exposure in humans in both therapeutic and non-therapeutic settings.
- Published literature regarding amphetamine exposure during pregnancy and the risk of congenital abnormalities and infant withdrawal symptoms is inconsistent.[5,6,7,8,9]
- The expert panel concluded that the available data are limited due to inadequate study design, outdated methods and insufficient numbers of patients treated only with

[5] Nora, *et al*. Dexamphetamine: a possible environmental trigger in cardiovascular malformations. Lancet 1970; 1: 1290-1.
[6] Milkovich L and Van den Berg BJ: Effects of antenatal exposure to anorectic drugs. Am J Obstet Gynecol 129:637-42, 1977.
[7] Heinonen, OP.; Slone, D.; Shapiro, S. Birth defects and drugs in pregnancy. Littleton, Mass: Publishing Sciences Group; 1977.
[8] Levin JN: Amphetamine ingestion with biliary atresia. J Pediatr 1971; 79:130.
[9] Felix RJ, Chambers CD, Dick LM, Johnson KA, Jones KL. Prospective pregnancy outcome in women exposed to amphetamines. Teratology 2000; 61: 441. Abstract.

amphetamines. Many of the studies reviewed involve confounding factors (illicit use of amphetamines and concurrent use of other illicit drugs, alcohol, and tobacco) and that long term neurodevelopment effects of amphetamine exposure during pregnancy are unknown.

See Appendix B, C, and D from the DPMH Review Dyanavel XR[2] for the NTP expert panel review of strengths and weaknesses of the studies reviewed.

The previous DPMH review on Dyanavel XR[2] came to the following conclusions;

1. There are insufficient data to make a clear statement about the safety of amphetamine. This was based on the review of the NTP report and additional publications identified from 2005 through 2015.
2. Published literature about amphetamine abuse during pregnancy notes that amphetamine can cause prematurity and low birth weight.[10,11,12, 13,14]
3. Amphetamine prevents the transport of serotonin and norepinephrine (both are vasoconstrictors) into the syncytiotrophoblast[15]. Accumulation of norepinephrine and serotonin in the inter-villous space leads to increased sympathetic activity and results in the following:
    - Cardiac stimulation and hypertension in the mother
    - Vasoconstriction of blood vessels and decreased blood flow to the placenta increasing the risk for intrauterine growth restriction
    - Stimulation of uterine contractions increasing the risk of premature delivery.
4. Once amphetamine crosses the placenta, it is believed that it reaches the developing fetus, causes cardiac stimulation and vasoconstriction of blood vessels in the fetus, similar to what is seen in the mother, resulting in hypertension in the fetus and affecting fetal growth and development. [16, 17,18,19]

[10] Eriksson, M. *et al.* The Influence of Amphetamine Addiction on Pregnancy and the Newborn Infant. Acta Paediatr Scand. 1978; 67: 95-99.
[11] Larsson, G. *et al*. Amphetamine addiction and pregnancy. Psychosocial and medical aspects. Acta Psychiatr Scand. 1979; 60: 334-46.
[12] Eriksson, M. *et al.* Amphetamine addiction and pregnancy. II. Pregnancy, delivery and the neonatal period. Socio-medical aspects. Acta Obstet Gynecol Scand. 1981; 60: 253-9.
[13] Furara, *et al.* The outcome of pregnancy associated with amphetamine use. Journal Obstet Gynaecol. 1999. 19(4): 377-80.
[14] Little BB *et al.* Methamphetamine abuse during pregnancy: outcome and fetal effects. Obstet Gynecol 72 (4):541- 4, 1988.
[15] Syncytiotrophoblast: is the outer layer of the trophoblast that actively invades the uterine wall forming the outermost fetal component of the placenta.
[16] Ganapathy, Vadivel. Drugs of abuse and human placenta. Life Sciences. 2011; 88 (21-22): 926-930.
[17] Salisbury, *et al.* Fetal Effects of Psychoactive Drugs. Clinics in Perinatology. 2009. 36 (3): 595-619.
[18] Ross, et al. Developmental Consequences of Fetal Exposure to Drugs: What We Know and What We Still Must Learn. Neuropsychopharmacology Reviews. 2015; 40: 61-87.
[19] Ramamoorthy, *et al.* Human placental monoamine transporters as targets for amphetamines. American Journal of Obstet Gynecol. 1995; 173: 1782-7.

Based on this information, DPMH proposes the following for the "Risk Summary" labeling in Section 8.1:

> The limited available data from published literature and postmarketing reports on use of amphetamine in pregnant women are not sufficient to inform a drug-associated risk for (b) (4). Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines (*see Clinical Considerations*). In an embryofetal development study, amphetamine had no effects on embryofetal morphological development (b) (4) rats and rabbits (b) (4) organogenesis (b) (4) doses (b) (4) times the maximum recommended human dose (MRHD) of (b) (4) mg/day given to adolescents, on a mg/m^2 (b) (4) basis. However, in a pre- and post-natal development study, amphetamine (d- to l- ratio of 3:1) administered orally to pregnant rats during gestation and lactation caused a decrease in pup survival and a decrease in pup body weight that correlated with a delay in developmental landmarks at clinically relevant doses of amphetamine. In addition, adverse effects on reproductive performance were observed in pups whose mothers were treated with amphetamine. Long-term neurochemical and behavioral effects have also been reported in animal developmental studies using clinically relevant doses of amphetamine (*see Data*).

This will be followed by the standard "estimated background risk" statement.

DPMH proposes the following for the "Clinical Considerations" labeling in Section 8.1:

> Amphetamines, such as Adzenys ER, may cause vasoconstriction, (b) (4) In addition, amphetamines can stimulate uterine contractions increasing the risk of premature delivery. (b) (4)
>
> Monitor infants born to mothers taking amphetamines for symptoms of withdrawal, such as feeding difficulties, irritability, agitation, and excessive drowsiness.

There is a pregnancy registry through Massachusetts General Hospital called the National Pregnancy Registry for Pyschostimulants. DPMH recommends including information in the labeling for Adzenys ER regarding this registry, in order to encourage participation. Since the registry is new, there is, at present, no data available to include in the current labelling.

Lactation

Applicant's Review of the Literature Amphetamine Use during Lactation

The Applicant conducted a search of the published literature in PubMed, Embase platform and LILACS database regarding the use of amphetamine during lactation. The references identified for amphetamine were the same as were previously reviewed by DPMH for prior amphetamine reviews. Several additional references for methamphetamine were also identified. See below section of this review entitled "DPMH Review of Literature Regarding Amphetamine Use during Lactation" for discussion of the relevant publications.

DPMH Review of Literature Regarding Amphetamine Use during Lactation

The reader is referred to the previous DPMH review on Dyanavel XR[2] by Miriam Dinatale, D.O. for further details regarding the published literature describing the use of amphetamine during lactation. A limited literature search was performed by DPMH to capture any new information published since the search conducted for the Dyanavel XR[2] consult noted above. DPMH conducted a search of published literature in PubMed using the search terms "amphetamine and lactation" covering January of 2014 through June of 2017. Besides what DPMH had previously reviewed, there was no additional information regarding the use of amphetamine during lactation.

Below is a Summary of the conclusions from the previous DPMH review:

- The characteristics of amphetamine (low molecular weight, low protein-binding, high pH) suggest that amphetamine is present in breast milk.
- The NTP-expert panel concluded that amphetamine does pass into breast milk in humans and would expose the infant to the drug.[4]
- LactMed discourages breastfeeding in mothers who are abusing amphetamines.[20]
- The American Academy of Pediatrics (AAP) Committee on Drugs 2013[21] reports that amphetamine exposure via illicit use in the breastfeeding infant has resulted in cases of infant hypertension, tachycardia and seizures. In animal studies of postnatal exposure, long-term behavioral effects (learning and memory deficits), as well as altered locomotor activity, have been observed. Because current published data are insufficient to determine the long-term effects on infants exposed to stimulants through breast milk, the AAP recommends that amphetamines not be used by breastfeeding women.

[20] Lactmed. Amphetamines. http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~RlRu5g:1. Accessed 9/9/2015.
[21] American Academy of Pediatrics: Committee on Drugs. The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on Selected Topics. Pediatrics. 2013; 132 (3): e796-809.

- In Hale's *Medication and Mother's Milk*,[22] Dr. Thomas Hale, a breastfeeding expert, classifies breastfeeding as "probably safe" with clinical doses of amphetamine taken by a breastfeeding woman but "hazardous" if amphetamine was abused.
- Studies reviewed identify a range of concentrations of amphetamine in breast milk between 3.9% and 13.8% of the maternal concentration.[23,24]
- An additional case report regarding a 36 year old lactating women taking 20 mg of amphetamine throughout pregnancy and lactation reported milk: plasma ratios ranging from 2.8 (on day 10) to 7.5 (on day 42).[25]
- Given the lack data on long-term neurodevelopmental effects and the potential risks on a breastfed infant exposed to amphetamine, labeling for Adzenys ER will remain consistent with labeling for other amphetamines and will recommend that the drug should not be used by a breastfeeding mother.

Based on this information, DPMH proposes the following for the "Risk Summary" labeling in Section 8.2:

> Risk Summary
> Based on limited case reports in published literature, amphetamine (d-or d, l-) is present in human milk, at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.9 and 7.5. There are no reports of adverse effects on the breastfed infant. Long-term neurodevelopmental effects on infants from (b) (4) exposure are unknown. It is possible that large dosages of amphetamine might interfere with milk production, especially in women whose lactation is not well established. Because of the potential for serious adverse reactions in nursing infants, advise patients that breastfeeding is not recommended during treatment with Adzenys ER.

DPMH proposes the following for the (b) (4) labeling in Section 8.2:

(b) (4)

[22]Hale, Thomas. Medications and Mother's Milk: A Manual of Lactational Pharmacology, 15th edition. HalePublishing, L.P. 2012
[23] Ohman, et al. Narcolepsy Treated with Racemic Amphetamine during Pregnancy and Breastfeeding. Journal of Human Lactation. 2015. 31; 374-376.
[24] Ilett, *et al.* Transfer of dexamphetamine into breastmilk during treatment for attention deficit hyperactivity disorder. British Journal of Clinical Pharmacology. 2007. 63 (3): 371-5.
[25] Steiner, et al. Amphetamine Secretion in Breast Milk. Eur J Clin Pharmacol. 1984; 27 (1): 123-124.

(b) (4)

Applicant Review of the Literature

The Applicant completed a search of the published literature in PubMed, Embase platform and LILACS database involving the use of amphetamine and effects on fertility. No relevant publications were identified.

DPMH Review of Data

DPMH reviewed amphetamine and effects on fertility in a recent review for another amphetamine product, and the reader is referred to the DPMH review on Dyanavel XR[2] by Miriam Dinatale, D.O.

A limited literature search was, therefore, performed by DPMH to capture any new information published since the search conducted for the Dyanavel XR[2] consult noted above. DPMH conducted a search of published literature in PubMed and Embase using the search terms “amphetamine and fertility” covering January of 2014 through November 15, 2016. Besides what DPMH had previously reviewed, there was no additional information regarding the use of amphetamine and fertility.

In animal studies, amphetamine did not adversely affect fertility or early embryonic development in rats at doses up to 7.7 times the maximum recommended human dose of methylphenidate (20mg/day).

The reader is referred to the full Pharmacology/Toxicology review by Ikram Elayan, Ph.D. for further details.

(b) (4)

RECOMMENDATIONS

DPMH revised the HPI and sections 8.1, 8.2 and 17 in Adzenys ER labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed ADZENYS ER (amphetamine) Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: (b) (4)
Lactation: Breastfeeding not recommended (8.2)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADZENYS ER during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388.

Risk Summary
The limited available data from published literature and postmarketing reports on use of prescription amphetamine in pregnant women are not sufficient to inform a drug-associated risk for major congenital malformations or miscarriage. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines (*see Clinical Considerations*). (b) (4) (b) (4) no effects on (b) (4) morphological development (b) (4) rats and rabbits (b) (4) organogenesis (b) (4) doses (b) (4) times the maximum recommended human dose (MRHD) of (b) (4) mg/day given to adolescents, on a mg/m2 (b) (4) basis. However, in a pre- and post-natal development study, amphetamine (d- to l- ratio of 3:1) administered orally to pregnant rats during gestation and lactation caused a decrease in pup survival and a decrease in pup body weight that correlated with a delay in developmental landmarks at clinically relevant doses of amphetamine. In addition, adverse effects on reproductive performance were observed in pups whose mothers were treated with amphetamine. Long-term neurochemical and behavioral effects have also been reported in animal developmental studies using clinically relevant doses of amphetamine (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations
Fetal/Neonatal adverse reactions

Amphetamines, such as ADZENYS ER, cause vasoconstriction and thereby may decrease placental perfusion. In addition, amphetamines can stimulate uterine contractions increasing the risk of premature delivery. Infants born to amphetamine dependent mothers have an increased risk of premature delivery and low birth weight.

Monitor infants born to mothers taking amphetamines for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness.

Data

Animal Data

Amphetamine, (b) (4) had no apparent effects on embryofetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately (b) (4) times, respectively, the maximum recommended human dose (MRHD) of (b) (4) mg/day given to adolescents, on a mg/m2 (b) (4) basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately (b) (4) times the MRHD given to adolescents on a mg/m^2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A (b) (4) study was conducted (b) (4) amphetamine (d- to l-enantiomer ratio of 3:1) in which pregnant rats received daily oral doses of 2, 6, and 10 mg/kg from gestation day 6 to lactation day 20. These doses are approximately (b) (4) times the MRHD of (b) (4) mg/day (b) (4) (b) (4) given to adolescents, on a mg/m^2 basis. All doses caused hyperactivity and decreased weight gain in the dams. A decrease in pup survival was seen at all doses. A decrease in pup body weight was seen at 6 and 10 mg/kg which correlated with delays in developmental landmarks, such as preputial separation and vaginal opening. Increased pup locomotor activity was seen at 10 mg/kg on day 22 postpartum but not at 5 weeks post-weaning. When pups were tested for reproductive performance at maturation, gestational weight gain, number of implantations, and number of delivered pups were decreased in the group whose mothers had been given 10 mg/kg.

A number of studies (b) (4) in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d, l-) at doses similar to those used clinically can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

8.2 Lactation

Risk Summary

Based on limited case reports in published literature, amphetamine (d-or d, l-) is present in human milk, at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.9 and 7.5. There are no reports of adverse effects on the breastfed infant. Long-term neurodevelopmental effects on infants

from (b) (4) exposure are unknown. It is possible that large dosages of amphetamine might interfere with milk production, especially in women whose lactation is not well established. Because of the potential for serious adverse reactions in nursing infants, advise patients that breastfeeding is not recommended during treatment with ADZENYS ER.

(b) (4)

17 Patient Counseling Information

(b) (4)

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with ADZENYS ER. Advise patients of the potential fetal effects from the use of ADZENYS ER during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

(b) (4) not to breastfeed if they are taking ADZENYS ER *[see Use in Specific Populations (8.2)]*.

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

/s/

JANE E LIEDTKA
06/26/2017

MIRIAM C DINATALE
06/26/2017

LYNNE P YAO
06/27/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 204325 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Adzenys ER (b) (4) Established/Proper Name: Amphetamine extended-release Dosage Form: Suspension Strengths: 1.25 mg/ml Route(s) of Administration: Oral		
Applicant: Neos Therapeutics, Inc. Agent for Applicant (if applicable):		
Date of Application: 11/15/2016 Date of Receipt: 11/15/2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: 9/15/2017	Action Goal Date (if different):	
Filing Date: 1/14/2017	Date of Filing Meeting: 1/3/2017	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.		
Type of Original NDA: AND (if applicable)		☐ 505(b)(1) ☒ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2) NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***		☐ 351(a) ☐ 351(k)

Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 110281	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.***	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☐ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☒	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		

• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If no,** include template language in the 74-day letter. ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*	☒	☐		

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	
Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included.* ***Forms** include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☒	☐	☐	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* : 11/28/2016	☒	☐	☐	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[3]***	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labeling ☐ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	Review of data under referenced NDA, 204326.
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☐	☒	☐	PI and patient labeling does not contain REMS.
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 5/2/2013	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 6/19/2014	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1/3/2017

BACKGROUND: NDA 204325 Adzenys ER (b) (4) (amphetamine extended-release oral suspension) for the treatment of ADHD was submitted on November 15, 2016 via the 505(b)(2) regulatory pathway. Data in support of the application comes, in part, from literature reviews conducted for referenced NDA, 204326 (amphetamine extended-release orally disintegrating tablets; Neos Therapeutics, Inc.) as well as five Phase 1 studies (submitted with NDA 204325) to establish a bioequivalence bridge to the reference listed drug, Adderall XR. The Applicant will also rely on safety and efficacy data used to form the basis for approval of the reference listed drug.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Brendan Muoio	Y
	CPMS/TL:	Steven Hardeman Keith Kiedrow	N
Cross-Discipline Team Leader (CDTL)	Hao Zhu		Y
Division Director/Deputy	Mitchell Mathis Tiffany Farchione		Y
Office Director/Deputy	Ellis Unger Robert Temple		N
Clinical	Reviewer:	Bernard Fischer	Y
	TL:	Jasmine Gatti	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Pharmacology	Reviewer:	Kofi Kumi	N
	TL:	Hao Zhu	Y
• Genomics	Reviewer:	N/A	N/A
• Pharmacometrics	Reviewer:	N/A	N/A
Biostatistics	Reviewer:	N/A	N/A

	TL:	N/A	N/A

APPEARS THIS WAY ON ORIGINAL

Nonclinical Pharmacology/Toxicology)	Reviewer:	Deepa Rao	Y
	TL:	Ikram Elayan	Y
Statistics (carcinogenicity)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC) Review Team:	ATL:	David Claffey	N
	RBPM:	Grafton Adams	N
• Drug Substance	Reviewer:	Andrei Ponta Wendy Wilson-Lee	N
• Drug Product	Reviewer:	Andrei Ponta Wendy Wilson-Lee	N
• Process	Reviewer:	Chunsheng Cai Akm Khairuzzaman	N
• Microbiology	Reviewer:	Elizabeth Bearr Erika Pfeiler	N
• Facility	Reviewer:	Rose Xu Derek Smith	N
• Biopharmaceutics	Reviewer:	Mei Ou Ta-Chen Wu	Y
• Immunogenicity	Reviewer:	N/A	N/A
• Labeling (BLAs only)	Reviewer:	N/A	N/A
• Other (e.g., Branch Chiefs, EA Reviewer)	N/A		N/A
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	TBD	N/A
	TL:	TBD	N/A
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Christine Bradshaw	N
	TL:		N/A
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Loretta Holmes	N
	TL:	Lolita White	N
OSE/DRISK (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Bioresearch Monitoring (OSI)	Reviewer:	TBD	N/A
	TL:	TBD	N/A
Controlled Substance Staff (CSS)	Reviewer:	Shalini Bansil	Y
	TL:	Martin Rusinowitz Michael Klein	N
Other reviewers/disciplines			
• Discipline	Reviewer:		
	TL:		
Other attendees	Colleen Locicero (ODEI ADRA)		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO BA/BE studies
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: No clinical studies were performed for the 505(b)(2) application. Site audits for BA/BE studies have been requested.	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: 505(b)(2) ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☒ Not Applicable ☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Mitchell Mathis, MD (Division Director) **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): N/A **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): Filing Meeting: 1/3/2017 Mid-Cycle Meeting: 4/6/2017 Wrap-up Meeting: 8/9/2017 **Comments**: None	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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

/s/

BRENDAN MUOIO
01/13/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 204325

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Adzenys ER (b) (4) (amphetamine extended-release) oral suspension

Applicant: Neos Therapeutics, Inc.

Receipt Date: November 15, 2016

Goal Date: September 15, 2017

1. Regulatory History and Applicant's Main Proposals

Neos Therapeutics, Inc. submitted NDA 204325 (amphetamine extended-release oral suspension) for the treatment of attention deficit hyperactivity disorder (ADHD) on November 15, 2016 via the 505(b)(2) regulatory pathway. Data in support of the application comes, in part, from literature reviews conducted for referenced NDA, 204326 (amphetamine extended-release orally disintegrating tablets; Neos Therapeutics, Inc.), as well as five Phase 1 studies (submitted with NDA 204325) to establish a bioequivalence bridge to the reference listed drug, Adderall XR. The Applicant will also rely on safety and efficacy data used to form the basis for approval of the reference listed drug.

A request to consider Adzenys ER (b) (4) for the proprietary name is currently under review.

The proposed indication is for the treatment of ADHD in patients 6 years and older.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by February 17, 2017. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *The length of the HL exceeds one-half page. No waiver request of this requirement was submitted.*

NO 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment: *Horizontal line separating HL from TOC is missing.*

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment: *No white space present before the Contraindications and Use In Specific Populations headings.*

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *Font size of numerical identifiers for referenced sections in HL - Warnings and Precautions is not consistent.*

YES 7. Headings in HL must be presented in the following order:

Selected Requirements of Prescribing Information

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment: *Font size is not consistent within sections of the HL.*

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES

13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES

20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 35. All text in the BW should be **bolded**.

Comment:

YES 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *Postmarketing adverse reaction data statement is not verbatim. The modified statement will be subject to review:*

"The following adverse reactions are from clinical trials and spontaneous postmarketing reports of other amphetamine products in pediatric patients and adults with ADHD. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure."

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Subsection Title
2.2 Subsection Title
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Subsection Title
5.2 Subsection Title
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
6.2 or 6.3 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Subsection Title
7.2 Subsection Title
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Subpopulation X
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Subsection Title
14.2 Subsection Title
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

BRENDAN MUOIO
01/13/2017