

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205489Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 205489 Review #2

Drug Name/Dosage Form	Cotempla XR-ODT methylphenidate orally disintegrating tablets
Strength	8.7 mg, 17.3 mg, 25.9 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Neos Therapeutics Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
<i>N:0029</i>	<i>19-Dec-2016</i>	<i>All</i>
<i>N:0030</i>	<i>28 Apr-2017</i>	<i>All</i>
<i>N:0032</i>	<i>11-May-2017</i>	<i>All</i>
<i>N:0033</i>	<i>15-May-2017</i>	<i>Process</i>

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Andrei Ponta	Wendy Wilson-Lee
Drug Product	Andrei Ponta	Wendy Wilson-Lee
Process/ Microbiology	Bo Jiang	Akm Khaiuzzaman
Facility	Laura Fontan	Zhihao Peter Qui
Biopharmaceutics	Ge Bai	Kimberly Raines
Regulatory Business Process Manager	Grafton Adams	
Application Technical Lead	David Claffey	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	8 JUL 2016	
	Type III		Adequate	8 MAY 2007		
	Type III		Adequate	26 SEP 2014		
	Type III		Adequate information in NDA	N/A		

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Review #1	NDA 205489	
	NDA 21259	Metadata CD reference product
	IND 109108	Referenced IND

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

Recommend approval from a product quality perspective. The applicant adequately addressed the issues in the November 2015 CR letter. The clinical formulation has been successfully bridged to the commercial formulation. The modified (b) (4) process and controls were further developed, validated and found adequate. Data support a 15 month drug product expiry period.

II. Summary of Quality Assessments

A. Product Overview

Neos Therapeutics developed an extended-release orally disintegrating tablet (ER ODT) formulation of methylphenidate packaged in blisters, indicated for the treatment of ADHD. Marketing of three dosage strengths is proposed - 8.7 mg, 17.3 mg, 25.9 mg (equivalent to 10 mg, 20 mg, 30 mg HCl salt, respectively). Neos does not propose to market strengths equivalent to the Listed Drug's upper two strengths (40 mg and 60 mg) – instead the patient is directed to take two lower strength tablets. The 30 mg strength tablet size (660 mg) is larger than the 500 mg maximum size recommended in the Agency ODT guidance, however clinical studies have found no issues with the administration of these slightly larger than recommended tablets. In vitro data demonstrated that crushing or chewing did not impact the rate of drug dissolution.

There are several other approved methylphenidate extended release dosage forms, however this will be the first marketed methylphenidate ODT dosage form. This product's (b) (4) dosing schedule is intended to be the same as the Listed Drug, Metadate CD® (Methylphenidate HCl) extended-release capsules (NDA 21259). The ODT formulation is expected to be a more convenient dosage form for children.

The drug product formulation contains methylphenidate ionically-bound to a polystyrene sulfonate (b) (4) immediate release (IR) portion of the formulation consists of (b) (4) 25% (b) (4) methylphenidate (b) (4) IR resin and 75% (b) (4) ER/DR resin.

The tablet is designed to be administered once-daily in the morning. The IR portion allows drug plasma levels to relatively quickly reach levels to allow the patient to carry out morning tasks. The delayed release (b) (4) prevents release of the (b) (4) drug until the resin leaves the stomach. On reaching the higher postgastric pHs, the enteric DR (b) (4) dissolves and the drug is released throughout the day (u) (4). This biphasic release is reflected in the PK study results.

Of note is that the proposed product’s strengths are based on methylphenidate free base, whereas the other methylphenidate products’ strengths are based on the hydrochloride salt. This was found appropriate as the tablets do not contain the hydrochloride salt of methylphenidate.

Differences in the amounts of (b) (4) between the clinical batches and the commercial batches were the basis of the 2016 CR action. These issues were resolved in this review cycle.

Proposed Indication(s) including Intended Patient Population	<i>ADHD</i>
Duration of Treatment	<i>Chronic</i>
Maximum Daily Dose	<i>60 mg (based on HCl Salt)</i>
Alternative Methods of Administration	<i>N/A</i>

B. Quality Assessment Overview

DRUG SUBSTANCE: Methylphenidate is a central nervous system stimulant indicated for the treatment of attention deficit hyperactivity disorder (ADHD). It is present in the drug product ionically bound to sulfonate groups in polystyrene sulfonate (b) (4). It is derived from (b) (4).

(b) (4) Details of the manufacture of (b) (4) were referred to DMF (b) (4). This was found to be adequate to support this application. The manufacturing site (b) (4) was found acceptable by the facilities reviewer. A specification and CoAs were provided in the application. They met specification and conformed to the USP monograph (b) (4).

DRUG PRODUCT: Neos Therapeutics developed an extended-release orally disintegrating tablet (ER ODT) formulation of methylphenidate packaged in blisters, indicated for the treatment of ADHD. Marketing of three dosage strengths is proposed - 8.7 mg, 17.3 mg, 25.9 mg (equivalent to 10 mg, 20mg, 30 mg HCl salt, respectively). It is intended to be administered once daily.

Note that the proposed product strengths are based on methylphenidate free base whereas the other methylphenidate products’ strengths are based on the hydrochloride salt. This was found appropriate as the tablets do not contain the hydrochloride salt of methylphenidate.

Manufacturing process development: Drug product development focused on (b) (4)

(b) (4)

The revised manufacturing process was found to be scientifically sound and was successfully validated at the proposed commercial scale. (b) (4)

(b) (4) The in vivo bioequivalence study successfully bridged the clinical batch (2E116E) with the proposed commercial formulation.

Composition/Manufacturing process: (b) (4)

(b) (4)

(b) (4)

Drug product specification, batch analysis and stability: The drug product specification includes tests typical of an oral tablet and critical tests specific to the orally disintegrating dosage form. The disintegration test limit is in accordance with the 30-second guidance recommendation.

(b) (4)

(b) (4) The drug product specification was found acceptable in the previous review cycle. In this review cycle the biopharm review team found that the requested (b) (4) test and acceptance criteria for (b) (4) (b) (4) was acceptable and had discriminatory ability (b) (4).

Batch analysis data from seven new pilot scale registration batches using the modified drug product process met specification. Six months accelerated and nine months long-term storage results from new drug product batches were provided to support a proposed (b) (4) month expiry period; however a **15 months expiry period** was found more appropriate (b) (4)

The proposed dissolution method has discriminating ability in terms of *f*₂ comparison for (b) (4)

. The drug product shows in vitro alcohol dose dumping when 40% v/v ethanol is present in the dissolution medium. Data supported the extended release claim.

The manufacturing and testing sites were found to be acceptable by the OPF facilities review team.

C. Special Product Quality Labeling Recommendations

The drug product shows in vitro alcohol dose dumping when 40% v/v ethanol is present in the dissolution medium.

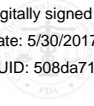
(b) (6)

(b) (4) OPQ recommends that the label indicate that the tablet should be administered immediately after removal from the package.



David
Claffey

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LABELING**R Regional Information****1.14 Labeling*****Labeling & Package Insert***

(b) (4)

Is the information accurate? Yes No

If "No," explain.

DOSAGE FORM AND STRENGTH**3. DOSAGE FORMS AND STRENGTHS**

^{(b) (4)} 8.6 mg Extended Release Orally Disintegrating Tablet: round, purple to light purple mottled (debossed "T1" on one side and plain on the other)

^{(b) (4)} 17.3 mg Extended Release Orally Disintegrating Tablet: round, purple to light purple mottled (debossed "T2" on one side and plain on the other)

^{(b) (4)} 25.9 mg Extended Release Orally Disintegrating Tablet: round, purple to light purple mottled (debossed "T3" on one side and plain on the other)

Is the information accurate? Yes No

If "No," explain.

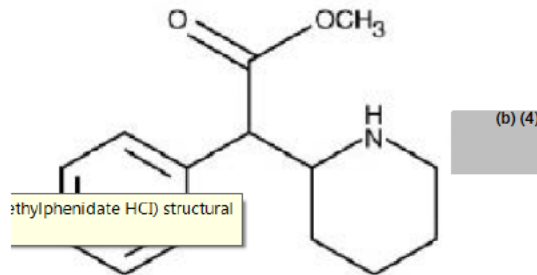
DESCRIPTION

11. DESCRIPTION

COTEMPLA XR-ODT is an extended-release orally disintegrating tablet (b) (4) intended for once daily administration. COTEMPLA XR-ODT contains approximately (b) (4)% immediate-release and (b) (4)% extended-release methylphenidate.

Methylphenidate (b) (4) a central nervous system (CNS) stimulant. The chemical name is methyl α -phenyl-2-piperidineacetate (b) (4) and its structural formula is shown in Figure 1.

Figure 1: Methylphenidate (b) (4) structure



$C_{14}H_{19}NO_2$ (b) (4) Mol. Wt. (b) (4)

COTEMPLA XR-ODT also contains the following inactive ingredients: Mannitol, Fructose, Microcrystalline Cellulose, Crospovidone, Methacrylic Acid, Polystyrene Sulfonate, Citric Acid, Colloidal Silicon Dioxide, Grape Flavor, Natural Masking Type Powder, Triethyl Citrate, Magnesium Stearate, Ethylcellulose, Sucralose, Lake Blend Purple, and Polyethylene Glycol.

Is the information accurate? Yes No

If "No," explain.

HOW SUPPLIED

16. HOW SUPPLIED/STORAGE AND HANDLING

COTEMPLA XR-ODT Extended Release Orally Disintegrating Tablets are available in three strengths: 8.6 mg tablets, round, purple to light purple, mottled, and debossed "T1" on one side of the tablet; 17.3 mg tablets, round, purple to light purple, mottled, and debossed "T2" on one side of the tablet; 25.9 mg tablets, round, purple to light purple, mottled, and debossed "T3" on one side of the tablet.

They are available as follows:

NDC 70165-100-30 8.6 mg tablets: carton of 30 tablets (5 blister cards (b) (4) (b) (4), 6 tablets (b) (4) with a reusable travel case.

NDC 70165-200-30 17.3 mg tablets: carton of 30 tablets (5 blister cards (b) (4) (b) (4), 6 tablets (b) (4) with a reusable travel case.

NDC 70165-300-30 25.9 mg tablets: carton of 30 tablets (5 blister cards (b) (4) (b) (4), 6 tablets (b) (4) with a reusable travel case.

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

i) Is the information accurate? Yes No

If "No," explain.

ii) Are the storage conditions acceptable? Yes No

If "No," explain.

Immediate Container Label



Reviewer's Assessment:

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

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

Conclusion:

The label is accurate and consistent with the information provided in the NDA. However, the Applicant does not include Rx only statement.

Carton Labeling

(b) (4)

Reviewer's Assessment:

Item	Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The established name follows the proprietary name. The font size of the established name is at least half of the most prominent proprietary name font size.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR	The quantity of the active ingredient	Adequate

201.100(b)(4))	provided is accurate.	
Net contents (21 CFR 201.51(a))	The number of tablets is included on the label.	Adequate
Lot number per 21 CFR 201.18	There is a designated space for the lot number.	Adequate
Expiration date per 21 CFR 201.17	There is a designated space for the expiration date.	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	NA	NA
Sterility Information (if applicable)	NA	NA
“Rx only” statement per 21 CFR 201.100(b)(1)	The carton bears the “Rx only” statement.	Adequate
Storage Conditions	The label has the following storage conditions instructions: Controlled room temperature conditions [25°C (77°F); excursions 15 – 30°C (59 – 86°F)]	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	The NDC number is present on the top right section of the package.	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	The bar code appears on the label.	Adequate
Name of manufacturer/distributor	The manufacture is listed on the label.	Adequate
“See package insert for dosage information” (21 CFR 201.55)	A “See package insert for full prescribing information” statement is included on the side of the package.	Adequate

“Keep out of reach of children” (optional for Rx, required for OTC)	NA	NA
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	The drug product is for oral use.	Adequate

Conclusion:

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

List of Deficiencies:

1. *The blister packaging does not contain the RX only statement. Update the blister packaging accordingly.*

Conclusion :

The labeling is adequate pending the Sponsor updating the blister packaging.



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Wilson- Lee

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BIOPHARMACEUTICS

Product Background:

NDA 205489 for Methylphenidate Extended-Release Orally Disintegrating Tablets (Methylphenidate XR-ODT) was submitted on January 9, 2015. A Complete Response (CR) letter was issued on November 6, 2015 requesting the Applicant to optimize the (b) (4) operations and bridge the clinical and to-be-marketed formulations with an in vivo bioequivalence study (refer to CMC review for NDA 205489 dated 09/09/2015). An Amendment was submitted on December 19, 2016 in response to the CR letter, and this review covers the assessment of the response.

NDA: #205489

Drug Product Name / Strength: COTEMPLA XR ODT Methylphenidate Extended Release Orally Disintegrating Tablets / 8.7 mg, 17.3 mg, 25.9 mg (equivalent to 10 mg, 20mg, 30 mg HCl salt, respectively)

Route of Administration: Oral

Applicant Name: NEOS Therapeutics

Review Summary: To fulfill the request of biopharmaceutics review deficiencies listed in the CR letter dated December 19, 2016, the Applicant developed a ne (b) (4)

The Applicant also studied the in-Vitro alcohol dose dumping of the new commercial formulation of the drug product. The conclusion of biopharmaceutics assessment is **ADEQUATE**.

List Submissions being reviewed (table):

➤ Document(s) Reviewed (SD-#)	➤ Date Received
<i>Amendment – response to CR dated 11/06/2015</i>	<i>12/19/2016</i>

Highlight Key Outstanding Issues from Last Cycle:

The proposed to-be-marketed formulation has about (b) (4) % DR (b) (4) and about (b) (4) % ER (b) (4) than the in vivo clinical batch formulation. An in vivo bioequivalence study is required to establish the bridge between the two formulations. A CR was issued on 11/06/2015 including biopharmaceutics deficiencies (b) (4)

Concise Description Outstanding Issues Remaining: N/A

BCS Designation

Reviewer's Assessment: BCS Class II based on literature.

Solubility: Freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone.

Permeability: Not provided.

Dissolution: Drug product is formulated as Extended-Release Orally Disintegrating Tablets.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

For the finished drug product dissolution method and acceptance criteria please refer to CMC review for NDA 205489 dated 09/09/2015.

In the re-submission dated 12/19/2016, the Applicant addressed the biopharmaceutics related CR deficiencies. The biopharmaceutics related CR deficiencies were as follows:

1. The drug substance is (b) (4). Provide justification on the use of (b) (4)

Applicant's response on 12/19/2016: (b) (4) has been developed. Please see (b) (4) Report, Addendum II.

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

Reviewer’s Assessment:

Dissolution testing for the in vitro alcohol study was conducted using finished product test method TM-083 Dissolution of Methylphenidate Extended Release Orally Disintegrating Tablet (with modifications for the addition of ethanol to the media).

A dissolution study in ethanol was performed in order to evaluate the effects of ethanol on the release rate of the commercial formulation Methylphenidate XR-ODT. The in vitro ethanol dose dumping study evaluated the commercial formulation Methylphenidate XR-ODT using increasing concentrations of ethanol in the dissolution media (i.e. 0% to 40% v/v).

The dissolution results of the samples evaluated with ethanol were compared to the "control" dissolution results where ethanol was not used (0% ethanol). A dissolution f2 comparison was used to evaluate similarity of the results of the samples tested in ethanol with the results of the "control" (0% ethanol). This f2 comparison was used to evaluate the active pharmaceutical ingredient (API) release over the first two hours of the dissolution (in order to demonstrate the effect of alcohol specifically on the delayed release mechanism).

Figure 7 displays the dissolution results of the commercial scale formulation of Methylphenidate XR ODT in media with various concentrations of ethanol. Table 10 provides the results of the f2 comparison.

Figure 7. Dissolution Profiles for the Commercial Scale Formulation of Methylphenidate XR-ODT in Various Concentrations of Ethanol

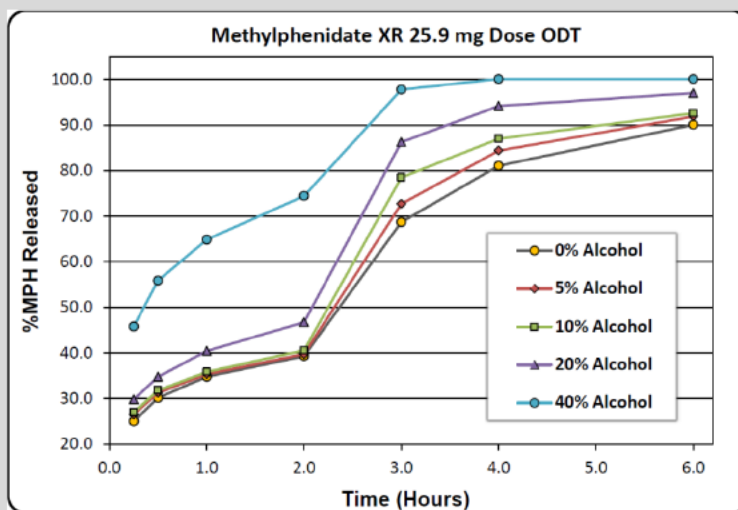


Table 10. f2 Comparison for Methylphenidate XR-ODT Dissolution in Various Concentrations of Ethanol

Time Points Used for Evaluation (Hours)	f2 Value in the Following Ethanol Concentration (v/v) Media when Compared to the Dissolution Results in the 0% “Control” Media			
	5% Ethanol	10% Ethanol	20% Ethanol	40% Ethanol
0.25, 0.50, 1.00, 2.00, 3.00, 4.00, 6.00	80.6	66.4	50.5	29.7

Based on the provided data by the Applicant, in-vitro alcohol dose dumping occurs when ethanol concentration is greater than 20%. The conclusion reached from this study by the Applicant “ (b) (4) Methylphenidate XR-ODT extended release (b) (4) was affected very little by ethanol concentrations up to 20% v/v” is reasonable. This effect is similar to the referenced product. Biopharmaceutics suggested language for Alcohol Effect in labeling are:” There are no in vivo study conducted for the effect of alcohol on drug exposure. An in vitro dissolution study showed alcohol-induced dose dumping potential in the presence of 40% alcohol. Does dumping was not observe in the presence of lower alcohol concentrations.”

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer’s Assessment:

Extended Release Claim was reviewed and found to be ADEQUATE based on the data provided by the Applicant from clinical studies with the clinical trial formulation: Lot #2E116 (page 104 of OPQ review and executive summary dated September 9, 2015). As requested, the applicant conducted a bioequivalence study (NT0102.1005) that compared the clinical trial formulation to the to-be-marketed formulation (Lot 6P081). The Applicant concluded the clinical trial formulation is bioequivalent to the to-be-marketed formulation under fasted conditions. From biopharmaceutics perspective, the to-be-marketed formulation of methylphenidate XR-ODT satisfy the extended release claim pending the review of clinical study data and conclusion drawn from bioequivalence study by Office of Clinical Pharmacology.

Biowaiver Request

Reviewer's Assessment:

The Applicant completed the required bridging study in the FDA CR letter, using the pilot scale clinical trial drug product (Lot 2E116) and the to-be-marketed commercial scale drug product (Lot 6P081). The bridging study was completed in the strength of 25.9 mg. The Applicant submitted Waiver for In Vivo Studies for the two lower strengths of 17.3 mg and 8.6 mg.

The justifications are:

1. All tablet strengths are in the same Orally Disintegrating Tablet (ODT) dosage form
2. (b) (4) the amount of active and inactive ingredients proportional for each strength
3. All strengths have the same drug release mechanism
4. The dissolution profile comparisons between the highest and lower strengths in three different media meet the f2 similarity requirements
5. The completed BA/BE study, NT0102.1001, utilized the 25.9 mg dosage form (administered as 2 x 25.9 mg ODTs for a total dose of 51.8 mg-equivalent to 60 mg methylphenidate HCl) compared to a 60 mg methylphenidate HCl capsule of the reference product. Bioequivalence was achieved for all endpoints with the exception of Cmax, which was approximately 25% higher than the RLD. Based on these findings, a clinical efficacy and safety study was performed. Statistically significant results were achieved in the efficacy and safety classroom study, NT0102.1004, which utilized all 3 strengths (8.6, 17.3, and 25.9 mg, which were given as one or two ODTs to achieve the target dose versus placebo). In addition, BA/BE study NT0102.1005 showed the dose of 2 x 25.9 methylphenidate XR-ODT of the to-be-marketed formulation bioequivalent for all endpoints compared to an equivalent dose of the initial clinical trial formulation.

Biopharmaceutics review is focused on dissolution profile comparisons. The Applicant provided dissolution profile comparisons between the highest and lower strengths in three different media. The conducted dissolution studies are listed in **Table 11**. The f2 results are listed in **Table 12**.

Table 11. Methylphenidate XR-ODT- Comparative Dissolution at Three pH Levels

Commercial Scale Lot Number	Strength	Dissolution Media for each Strength ODT	Number of Vessels	Sampling Times (hours)
6P087	8.6 mg base (10 mg salt)	1) (b) (4) 2) (b) (4) 3) (b) (4) 4) pH 1.2 (0 to 2 hours) & pH 6.8 (2.0 – (b) (4) hours)	12	0.17, 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, & 8.0.
6P083	17.3 mg base (20 mg salt)			
6P081	25.9 mg base (30 mg salt)			

Table 12. f2 Results of Comparative Dissolution Studies

Dissolution Media	(b) (4)									Current Method (Dual pH) TM-083		
Batches Compared	6P087 (8.6mg) vs 6P081 (25.9mg)	6P083 (17.3mg) vs 6P081 (25.9mg)	6P081 (25.9mg) vs 2E116 (25.9mg)	6P087 (8.6mg) vs 6P081 (25.9mg)	6P083 (17.3mg) vs 6P081 (25.9mg)	6P081 (25.9mg) vs 2E116 (25.9mg)	6P087 (8.6mg) vs 6P081 (25.9mg)	6P083 (17.3mg) vs 6P081 (25.9mg)	6P081 (25.9mg) vs 2E116 (25.9mg)	6P087 (8.6mg) vs 6P081 (25.9mg)	6P083 (17.3mg) vs 6P081 (25.9mg)	6P081 (25.9mg) vs 2E116 (25.9mg)
Graphed in Figure	1			2			3			4		5
f ₂ Results	77.5	93.5	85.7	85.3	98.3	60.6	84.8	88.8	78.0	86.3	85.8	81.8

f2 results obtained in different pH dissolution media demonstrate the similarity of release between the higher and lower strengths of commercial scale manufactured Methylphenidate Extended Release ODT. The requested Waiver for In Vivo Studies for the lower strengths can be granted from the perspective of biopharmaceutics.

List of Deficiencies: N/A

Primary Biopharmaceutics Reviewer Name and Date: Ge Bai, Ph.D., 4/10/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Kimberly Raines, Ph.D. 4/12/2017



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Bai

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, Stability	Drug substance appears relatively stable.	L	Release and stability testing	Acceptable	
Physical stability of Tablet Hardness, Friability	Will require evaluation. (b) (4)	H	Release and stability testing. Use of (b) (4)	Acceptable	It is noted that the manufacturer of the (b) (4)
Content Uniformity	Tested at release. Will require evaluation as the (b) (4)	M	Release and stability testing. (b) (4)	Acceptable	
Physical stability (solid state)	(b) (4)	L	Release and stability testing	Acceptable	

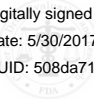
	(b) (4)				
Palatability	(b) (4)	M	Flavorings and other excipients. No palatability issues seen in the clinic. The (b) (4)	Acceptable	
Microbial Limits		L	Release and stability testing	Acceptable	
Disintegration	(b) (4)	M	Release and stability testing. All results passed.	Acceptable	
Dissolution		L	Release and stability testing	Acceptable	
Alcohol dose dumping		H	Labeling statement.	Acceptable	

APPEARS THIS WAY ON ORIGINAL



David
Claffey

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David
Claffey

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Comments: Great. Thanks!



QUALITY ASSESSMENT



Recommendation: Complete Response

NDA 205489

COTEMPLA XR ODT

Methylphenidate Extended Release Orally Disintegrating Tablets

Review #1

Review Date: 9 SEP 2015

Drug Name/Dosage Form	Methylphenidate Extended Release Orally Disintegrating Tablets
Strength	8.7 mg, 17.3 mg, 25.9 mg (equivalent to 10 mg, 20mg, 30 mg HCl salt, respectively)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	NEOS Therapeutics

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Initial	9 JAN 2015
N-008	6 MAR 2015
N-009	17 MAR 2015
N-010	19 MAR 2015
N-012	10 APR 2015
N-014	21 APR 2015
N-017	16 JUL 2015
N-018	20 JUL 2015
N-020	7 AUG 2015
N-021	20 AUG 2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Application Technical Lead	David Claffey	
Regulatory Business Process Manager	Dahlia Woody	
Drug Substance	Gene Holbert	DND API/Branch I
Drug Product	Andrei Ponta	DNDP
Drug Process/ Microbiology	Akm Khairuzzaman	OPF
Facility	Linda Ng	OPF
Biopharmaceutics	Ge Bai	
ORA Lead	Jose Martinez	



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Quality Review Data Sheet

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

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	07/14/2015	No further comments letter 07/14/2015

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	NDA 21259	Listed Drug (Metadate CD)
IND	IND 109108	

3. CONSULTS: N/A



Executive Summary

I. Recommendations: Complete Response

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues

The commercial drug product will have $\frac{(b)(4)}{(4)}\%$ (w/w) delayed release and $\frac{(b)(4)}{(4)}\%$ (w/w) $\frac{(b)(4)}{(4)}$ extended release $\frac{(b)(4)}{(4)}$ than the clinical drug product. These differences were supported by in vitro data. However the OPQ review team determined that changes of this extent, especially to the extended release $\frac{(b)(4)}{(4)}$, would require bioequivalence studies. Refer to page 7 of this document for a summary of the approvability issues.

2. Action letter language, related to critical issues:

Deficiencies:

1. Bridge the clinical and commercial drug product formulations with a bioequivalence study. The commercial drug product will have $\frac{(b)(4)}{(4)}\%$ $\frac{(b)(4)}{(4)}$ (w/w) delayed release and $\frac{(b)(4)}{(4)}\%$ $\frac{(b)(4)}{(4)}$ extended release $\frac{(b)(4)}{(4)}$. This difference was supported by in vitro data. However changes of this extent, especially to the extended release $\frac{(b)(4)}{(4)}$ require bioequivalence studies.
2. Establish, validate and fully justify an unequivocal commercial $\frac{(b)(4)}{(4)}$ $\frac{(b)(4)}{(4)}$ operation and control. You state in 3.2.P.2.3 that the commercial scale process will use $\frac{(b)(4)}{(4)}$ but state in the 20 AUG 2015 amendment $\frac{(b)(4)}{(4)}$

Other Deficiencies and comments for action letter: refer to page 127.

3. Benefit/Risk Considerations

Several other dosage forms of methylphenidate are currently marketed. The proposed product would benefit the public with a dosage form that can be administered more conveniently. However the proposed product will contain $\frac{(b)(4)}{(4)}$ the amount of



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extended release (b) (4) than the product studied in clinical studies. The risk to the patients of faster release, higher C_{max} with possible shorter duration of effect are unknown. Bioequivalence studies will be need to assess this risk.

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

II. Summary of Quality Assessments

DRUG PRODUCT: Neos Therapeutics developed an extended-release orally disintegrating tablet (ER ODT) formulation of methylphenidate packaged in blisters, indicated for the treatment of ADHD. Marketing of three dosage strengths is proposed - 8.7 mg, 17.3 mg, 25.9 mg (equivalent to 10 mg, 20mg, 30 mg HCl salt, respectively). It is intended to be administered once daily. This will be the first marketed methylphenidate ODT dosage form.

There are several other approved methylphenidate extended release dosage forms. Metadate ER (methylphenidate HCl extended-release tablets) are taken every eight hours. Metadate CD (methylphenidate extended release capsules) is taken once daily. This product's dose and dosing schedule is intended to be the same as the Listed Drug, Metadate CD® (Methylphenidate HCl) extended-release capsules (NDA 21259).

Tablet strength and size: The marketed Metadate CD capsules have dosage strengths of 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg. However, Neos proposes to market only the three smaller strengths - 10 mg, 20 mg, and 30 mg (salt equivalent). (b) (4)

(b) (4) DMEPA requested that all tablets be packaged in single blisters (b) (4)

(b) (4). The 30 mg strength tablet size (660 mg) is larger than the 500 mg maximum size recommended in the Agency ODT guidance, however clinical studies have found no issues with the administration of these slightly larger than recommended tablets. (b) (4)

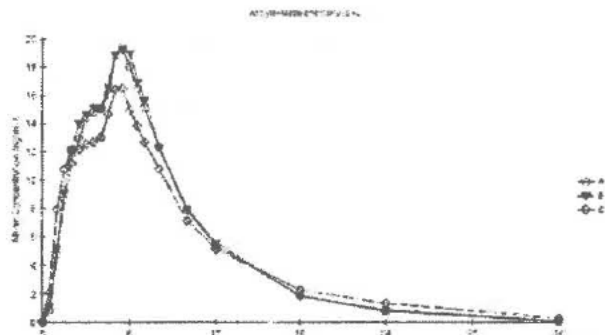
(b) (4). In vitro data demonstrated that crushing or chewing did not impact the rate of drug dissolution.

(b) (4), the labeling will be revised to express the proposed strength in terms of methylphenidate base. This is in accordance with the USP <1121> salt policy and Agency salt naming guidance.

Extended release mechanism: The drug product formulation contains methylphenidate ionically bonded to a polystyrene sulfonate (b) (4)

(b) (4) 25% (b) (4) methylphenidate (b) (4) IR resin and 75% (b) (4) ER/DR resin. The tablet is designed to be administered in the morning. The IR portion allows drug plasma levels to relatively quickly reach levels to allow the patient to carry out morning tasks. The delayed release (b) (4) prevents release of the (b) (4) drug until the resin leaves the stomach. On reaching the higher postgastric pHs, the enteric DR (b) (4) dissolves and the drug is

released throughout the day (b) (4) This biphasic release can be seen in the PK study results:



Note: Treatment A is the formulation from this study that was selected for development and Treatment C is the RLD, Metadate CD

Manufacturing process development: Drug product development focused on (b) (4)
(b) (4)

Composition/Manufacturing process: (b) (4)
(b) (4)

The drug product is manufactured at Neos Therapeutics. The facilities reviewer attended the PAI and found the site acceptable.

Drug product specification, batch analysis and stability: The drug product specification includes tests typical of an oral tablet and critical tests specific to the orally disintegrating dosage form. The



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disintegration test limit is in accordance with the 30-second guidance recommendation. (b) (4)

(b) (4)

(b) (4) The drug product specification was found acceptable. Batch analysis data from seven pilot scale registration batches met specification. Stability data on these seven batches, through six months accelerated conditions and 12 months long term storage conditions supported the proposed (b) (4) drug product expiry period. It is noted that the stability samples were stored for (b) (4) in the stability studies. It was determined that this should not impact the evaluation of the expiry period. (b) (6)

(b) (6)

(b) (4) OPQ recommends that the label indicate that the tablet should be administered immediately after removal from the package.

The proposed dissolution method has discriminating ability in terms of *f*₂ comparison (b) (4)

(b) (4) The drug product shows in vitro alcohol dose dumping when 40% v/v ethanol is present in the dissolution medium. Data supported the extended release claim.

Drug Substance: Methylphenidate is a central nervous system stimulant indicated for the treatment of attention deficit hyperactivity disorder (ADHD). It is present in the drug product ionically bound to sulfonate groups in polystyrene sulfonate (b) (4)

(b) (4). Details of the manufacture of (b) (4) were referred to DMF (b) (4). This was found to be adequate to support this application. The manufacturing site (b) (4) was found acceptable by the facilities reviewer. A specification and CoAs were provided in the application. They met specification and conformed with the USP monograph (b) (4).

Summary of main issue preventing an approval recommendation

The main approvability issue centers around (b) (4) differences between the clinical and the proposed commercial drug product formulations – (b) (4). These changes are discussed in detail in the drug product, process and biopharm sections of this review. Information on this issue evolved through the review cycle as the data were provided piecemeal and were often contradictory. It took considerable teamwork to piece together the current status of this issue. The following is a brief summary of the main CR issues:

Delayed Release (DR) (b) (4) change: The w/w level of delayed release (b) (4) between the clinical and commercial batches was (b) (4) by (b) (4)%. This was not apparent in the initial application. After the 13 AUG 2015 telecon the applicant provided a written justification (20 AUG



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2015) for this difference at Agency request.

(b) (4)

(b) (4)

biopharm review team determined that such (b) (4) change (b) (4) cannot be supported by in vitro data only – and that bioequivalence studies would be required.

(b) (4) The

(b) (4) cannot be

Extended Release (ER) (b) (4) **change:** The amount of ER (b) (4), was (b) (4) (b) (4)% on a w/w basis between the clinical and the proposed commercial formulation.

The cause of this change is a result of the continued development of the drug product formulation after the clinical studies, likely as a result of (b) (4) operations.

Contradictory information was provided – for example, in the initial application the applicant clearly states that the (b) (4) (3.2.P.2.3):

(b) (4)



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(b) (4)



The bottom line is that the applicant will need to bridge the clinical and commercial formulations with a bioequivalence study. This will need to be accompanied by a final commercial process with a narrative explaining the differences in a clear, comprehensive and non-contradictory manner.

A. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Cotempla XR ODT
Non Proprietary Name of the Drug Product	Methylphenidate extended release orally disintegrating tablets
Non Proprietary Name of the Drug Substance	Methylphenidate
Proposed Indication(s) including Intended Patient Population	ADHD
Duration of Treatment	Chronic
Maximum Daily Dose	60 mg (based on HCl salt)
Alternative Methods of Administration	N/A

B. Biopharmaceutics Considerations

1. BCS Classification:
 - Drug Substance:
 - Drug Product:

2. Biowaivers/Biostudies
 - Biowaiver Requests
 - PK studies



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- IVIVC

C. Novel Approaches N/A

D. Any Special Product Quality Labeling Recommendations. Use tablets immediately after removal from blister, alcohol dose dumping warning.

E. Process/Facility Quality Summary (see Attachment A)

F. Life Cycle Knowledge Information N/A. Will be completed when approval action is recommended.

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Supervisor Comments and Concurrence:

Mahesh R. Ramanadham -S

Digitally signed by Mahesh R. Ramanadham -S
DN: cn=S, o=US Government, ou=FDA, ou=People, o=FDA, ou=People, c=US
c=Mahesh R. Ramanadham -S
Date: 2015.09.02 15:28:55 -0400

Concur, Mahesh Ramanadham 8-21-15

Note: additional reviewers can be added, as appropriate

ASSESSMENT OF THE BIOPHARMACEUTICS

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

Methylphenidate (b) (4) is a central nervous system stimulant. The proposed product is an extended release ODT tablet intended for once daily administration and for the treatment of attention-deficit hyperactivity disorder (ADHD). The methylphenidate (b) (4) drug substance is freely soluble in water (solubility is ~ 150 mg/mL). Methylphenidate (b) (4) is unstable at low and high pH. (b) (4)

1. The drug product, Methylphenidate Extended Release ODT is available in three strengths: 10 mg, 20 mg and 30 mg. (b) (4)

The formulation (b) (4) contains IR portion (25% of label claimed methylphenidate) and ER/DR portion (75% of label claimed methylphenidate). (b) (4)

. The to-be-marketed formulation is different from that of the drug product used in the clinical studies.

Table 1. Drug Substance Solubility

(b) (4)

(b) (4)

DISSOLUTION METHOD



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The dissolution method and acceptance criteria are summarized in Tables 2 and 3. The Applicant agreed to adopt the recommended dissolution method and acceptance criteria in the response to IR comments dated 07/14/2015.

Table 2. Proposed Dissolution Method

Apparatus	USP Type II, Paddle
Cannula	Metal
Stirring Speed	75 rpm
Acid Stage Medium (0-2 hours)	0.1 N HCl
Buffer Stage Medium (2-8 hours)	pH 6.8 Phosphate buffer
Medium Volume	900 mL, acid stage 1000 mL, buffer stage
Sampling Times	0.5, 2.0, 3.0, 4.0 and 6.0hours

Table 3. Recommended Dissolution Acceptance Criteria

Dissolution Time Points	Acceptance Criteria
0.5 hours (pending)	(b) (4)
2 hours	
3 hours	
4 hours	
6 hours	

Dissolution Method Development

The dissolution method was evaluated to determine the effect that varying dissolution parameters would have on the *in vitro* drug release (for more detail refer to Drug Product at \\CDSESUB1\evsprod\NDA205489\0000\m3\32-body-data\32p-drug-prod\active\32p2-pharm-dev)). The following method parameters were evaluated:

- **Selection of dissolution apparatus**
Both USP and the FDA recommend USP Apparatus II for dissolution testing of extended release drug product. Thus, USP Apparatus II was chose.
- **Selection of paddle speed**



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(b) (4)

paddle speed of 75 rpm was chosen.



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(b) (4)



- **Determination of the dissolution media**
The Applicant followed the USP general chapter <711> to choose the dissolution media for this extended/delayed release drug product: an acid stage medium (specified as 0.1 N HCl) for the first two hours followed by a buffer stage medium (specified as a pH 6.8 phosphate buffer). With both media, the drug substance has high solubility.
- **Determination of the volume of dissolution media**
The Applicant followed the USP general chapter <1092> to determine the volume of the dissolution media for the acid stage and the buffer stage. A 900 mL volume was chosen for acid stage (most common) and 1000 mL for buffer stage (adding buffer to the vessel to reach target pH of 6.8).
- **Selection of dissolution sample time points**

(b) (4)





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(b) (4)

(b) (4) Thus, the first time point was chosen at 0.5 hours. Two hours time point is the typical time to evaluate the effectiveness of a delayed-release (b) (4) prior to the pH change. The three hours time point was selected to ensure that the release was as rapid as intended but to also ensure that the pH change did not result in the dose dumping of the remaining MPH. The four hours time point is selected to ensure the steady release of the MPH from the extended release (b) (4) over the next hour so that about (b) (4)% of the MPH had released at this time. The six hours time point (agreed by the Applicant in the response to IR comments dated 07/14/2015) is selected to ensure that the steady release of the MPH from the finished drug product would continue until a minimum of (b) (4)% of the MPH label claim had released.

Table 4. Release of drug substance during the first 30 minutes of dissolution testing

ODT Lot & Strength	(b) (4)
10 mg Lot 2E110E2	(b) (4)
10 mg Lot 2E111E2	
10 mg Lot 2E112E2	
20 mg Lot 2E117E2	
30 mg Lot 2E116E3	
30 mg Lot 1E101E2	
30 mg Lot 2E108E3	

(b) (4)



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(b) (4)



Reviewer's Assessment:

The Applicant conducted studies to determine the solubility of the drug substance, the type of dissolution apparatus, pH and volume of the dissolution medium, paddle speed, sampling time points and whether deaeration is needed. The proposed dissolution method is based on the optimal parameters of the results of these studies.

DISSOLUTION METHOD DISCRIMINATING ABILITY

(b) (4)



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(b) (4)

Reviewer's Assessment:

The Applicant conducted studies to evaluate the discriminating ability of the proposed dissolution method. The proposed dissolution method has discriminating ability in terms of *f2* comparison (b) (4) but not for level of (b) (4) and change of (b) (4) tested.

DISSOLUTION METHOD ACCEPTANCE CRITERIA

In the original submission, the Applicant proposed the dissolution acceptance criteria as shown in Table 10. The justification was based on the dissolution data from the clinical and stability batches listed in Table 11. The average release rates of these batches for each strength ODT are shown in Table 12 and Figure 10.

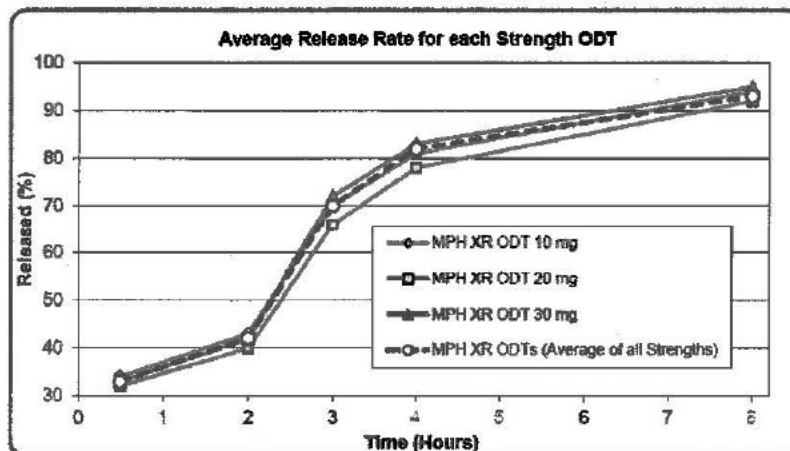
Table 10. Initially proposed dissolution testing acceptance criteria

Dissolution Time Points	Acceptance Criteria
0.5 hour	(b) (4)
2 hours	
3 hours	
4 hours	
(b) (4)	

Table 11. Clinical and stability batches used to set dissolution acceptance criteria

ODT Strength	Batch	Use
10 mg	2E110E	Stability
	2E111E	Stability
	2E112E	Stability
20 mg	2E117E	Clinical Efficacy Study / Stability
30 mg	1E101E	Clinical Pharmacokinetic Study / Stability
	2E108E	Stability
	2E116E	Clinical Efficacy Study / Stability

Figure 10. Average dissolution profiles from clinical and stability batches





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Table 12. Average dissolution data from clinical and stability batches

MPH XR ODTs 10 mg – Stability Summary (Batches 2E110, 2E111, & 2E112)

Time Point	Specifications	Average Release (All 3 Batches)	Lowest Average Release	Highest Average Release	Lowest Individual Tablet	Highest Individual Tablet
0.5 hours						(b) (4)
2.0 hours						
3.0 hours						
4.0 hours						
						(b) (4)

MPH XR ODTs 20 mg – Stability Summary (Batches 2E117)

Time Point	Specifications	Average Release	Lowest Average Release	Highest Average Release	Lowest Individual Tablet	Highest Individual Tablet
0.5 hours						(b) (4)
2.0 hours						
3.0 hours						
4.0 hours						
						(b) (4)

MPH XR ODTs 30 mg – Stability Summary (Batches 1E101, 2E106, & 2E116)

Time Point	Specifications	Average Release (All 3 Batches)	Lowest Average Release	Highest Average Release	Lowest Individual Tablet	Highest Individual Tablet
0.5 hours						(b) (4)
2.0 hours						
3.0 hours						
4.0 hours						
						(b) (4)

The Applicant was asked to provide data to justify the first time point at 0.5 hours. The provided data are discussed in previous sections (Table 4). The Applicant was also asked to change the last time point (b) (4) to 6 hours, which is better supported by the provided dissolution data. The Applicant agreed to change the last time point (b) (4) to 6 hours in the response to IR comments dated 07/14/2015.



(b) (4)



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(b) (4)



Reviewer's Assessment: The proposed dissolution acceptance criteria for finished drug product are supported by dissolution data from clinical and stability batches and captures well the expected release of the drug substance from both the IR portion and the ER portion of the drug product. The Applicant provided data to support the selection of the first sampling point at 0.5 hours. The proposed acceptance criteria for finished drug product are acceptable.

(b) (4)



IN VITRO ALCOHOL DOSE DUMPING

The Applicant conducted an in vitro dissolution study to evaluate the effect of ethanol (0% to 40% v/v in dissolution medium) on the release rate of the Methylphenidate XR-ODT. The

results indicate that the effect of alcohol on the integrity of (b) (4) Methylphenidate XR-ODT extended release (b) (4) was minimal for ethanol concentrations up to 20% v/v (Figure 11). When using 40% v/v ethanol concentration, the release of the drug substance is more than 50% at 0.5 hr and more than 70% at 2.0 hr, indicating in vitro alcohol dose dumping. The Methylphenidate XR-ODT and the RLD (dose dumping effect in Figure 12) showed similar in vitro results with the methylphenidate releasing faster as the ethanol concentration increases.

Figure 11. Alcohol dose dumping for the drug product

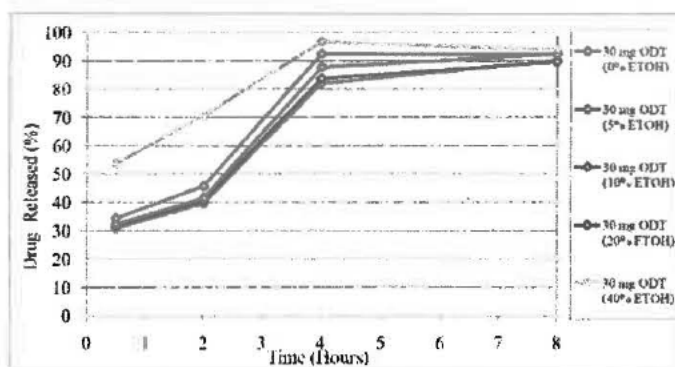
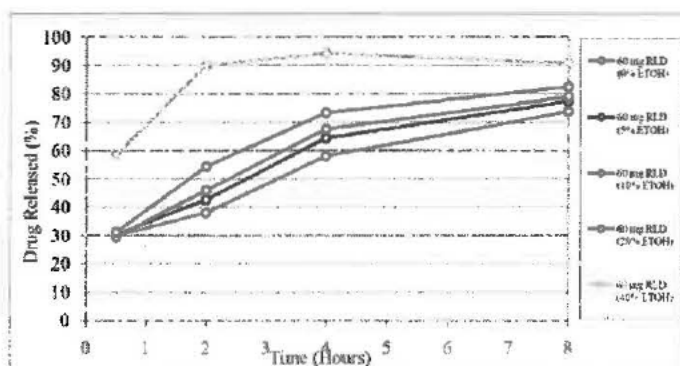


Figure 12. Alcohol dose dumping for the reference product, Metadate CD



Reviewer's Assessment: The drug product shows in vitro alcohol dose dumping when 40% v/v ethanol is present in the dissolution medium. This effect is similar to that observed for the reference drug product. The Applicant was requested to include the findings of the in vitro alcohol dose dumping in in the product label.



EVALUATION OF IMPACT OF CHEWING ON DISSOLUTION

(b) (4). During the review cycle, the Applicant was asked to provide data showing that chewing has no impact on dissolution of the drug product under review. In response to IR comments, the Applicant provided the requested data on a submission dated 07/14/2015. The Applicant altered the ODT product mechanically using crushing/grinding procedures as follows:

- Eighteen (18) ODTs were weighed and transferred into a glass mortar.
- The crushed ODTs were crushed by repeatedly striking the ODTs with the pestle for 1 minute.
- The ground ODTs were ground in a circular motion to achieve the maximum grinding action on the individual ER/DR (b) (4) particles with the following description of forces applied:
 - Severe = significant force for 5 minutes (significantly more force applied than required in typical tablet grinding procedures)
 - Intense = strong force for 2 minutes (more force applied than required in typical tablet grinding procedures)
 - Normal = typical force used to grind tablets, 1 minute
- The entire crushed/ground sample was transferred into a plastic bag, sealed and labeled.
- The chewed ODTs were prepared by placing an ODT in a plastic bag and then sliding a lab glove finger over the ODT to prevent tearing the bag. The ODTs were chewed using an aggressive chewing action consisting of 8 bites with the first and second molars. Each bite was a complete bite where the teeth were completely closed.
- Simulated chewing studies using ODT placebos were performed with the following observations: – Biting or chewing the ODT significantly accelerates this already fast disintegration.

According to the Applicant, when taken orally it would be difficult to utilize the level of chewing performed in the study since the ODTs disintegrate so rapidly. The ODTs tend to completely break apart into small particles when the ODT is bitten the first time. Three (3) bites was the typical requirement to completely disintegrate the ODT.

The camera pictures, microscope pictures and particle size distribution of the ODT (b) (4) and the mechanically altered ODTs are shown in Table 14. Results indicate that only when the ODTs are intensively and severely ground, the particle size distribution of the formulation (b) (4) changes dramatically, especially for D50 and D90. The dissolution profiles of the intact ODT and the mechanically altered ODT are shown in Figure 13. The comparison shows that only intensively and severely ground ODT possibly have different dissolution profiles when compared to the intact ODT. This is consistent with the data provided by the

Applicant when studying the mechanically altered drug- (b) (4) as discussed previously. Chewing has no impact on the dissolution of the ODT.

Table 14. Comparison of camera pictures, microscope pictures and particle size of ODTs altered with different mechanical forces

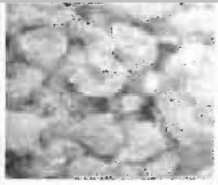
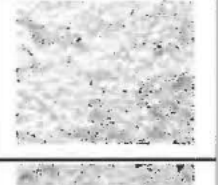
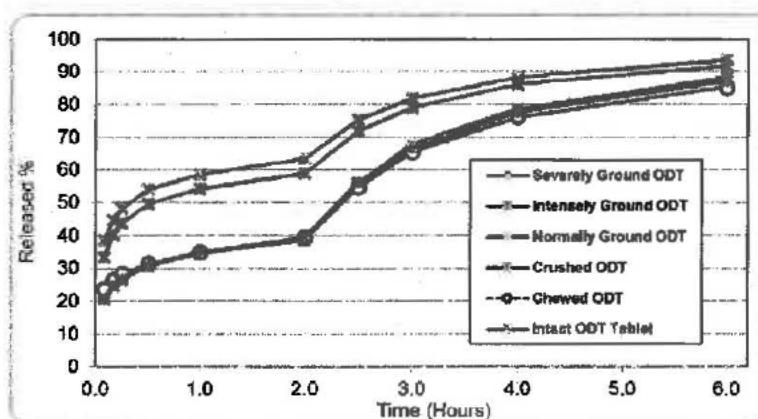
Sample Description	Camera Picture	Microscope Picture	Particle Size Distribution
(b) (4)			
Crushed ODT Tablet by Mortar and Pestle			(b) (4)
Normally Ground ODT Tablet by Mortar and Pestle			
Intensely Ground ODT Tablet by Mortar and Pestle			
Severely Ground ODT Tablet by Mortar and Pestle			
Chewed ODT Tablet in Plastic Bag			

Figure 13. Comparison of dissolution profiles of ODTs altered with different mechanical forces



Reviewer's Assessment: As requested by the FDA during the review cycle, the Applicant evaluated the effect of chewing on the in vitro performance of the drug product. Data provided indicate that impact of chewing on the ODT is similar to the impact of crushing on particle size. In both cases, the dissolution profile of the ODT did not change significantly. (b) (4)

(b) (4)

EXTENDED RELEASE DESIGNATION CLAIM

The Applicant provided sufficient information to support the extended release designation claim for methylphenidate XR-ODT. The data from three clinical trials (NT0102.1001, NT0102.1002, and NT0102.1003) showed no evidence of dose dumping (Table 15 shows administration with a meal will not introduce dose dumping). Data from the same set of clinical studies showed methylphenidate XR-ODT has similar pharmacokinetic profile to the reference drug, Metadate CD (Figure 14). As shown in Figure 15, Metadate CD, the reference drug has comparable steady-state performance to the immediate release methylphenidate HCl (Refer to OCP review for NDA 021259, Metadate CD located in Drugs@FDA). Thus, methylphenidate XR-ODT has comparable steady-state performance to the immediate release methylphenidate HCl too.

Table 15. NT0102.1002 Pharmacokinetic parameters for d-MPH, N=23

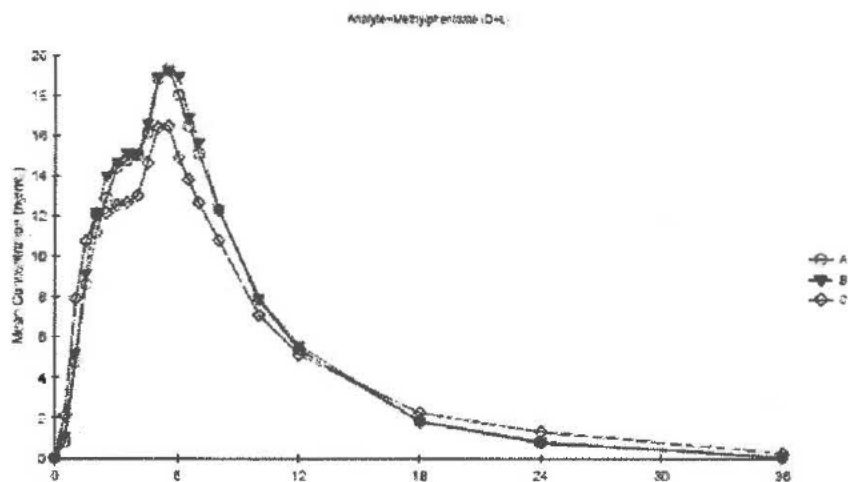
Parameter	Treatment A			Treatment B		
	MPH XR-ODT Fasted (Reference)			MPH XR-ODT Fed (Test)		
	Mean	SD	CV%	Mean	SD	CV%
T_{max} (hr)	5.02	0.90	17.91	4.90	0.98	19.92
C_{max} (ng/mL)	26.8	8.69	32.42	23.4	8.05	34.39
$AUC_{0-\infty}$ (hr*ng/mL)	212.8	67.46	31.70	234.7	64.75	27.59
AUC_{inf} (hr*ng/mL)	218.2	69.04	31.65	242.9	65.75	27.06
λ_z (hr ⁻¹)	0.1801	0.0268	14.86	0.1629	0.0244	15.00
$T_{1/2}$ (hr)	3.93	0.60	15.14	4.37	0.81	18.48
$T_{1/2\beta}$ (hr)	24.00	0.01	0.03	25.57	4.13	16.16

Abbreviations: CV=coefficient of variation; hr=hour; SD=standard deviation

Note: Full precision data used in pharmacokinetic analysis

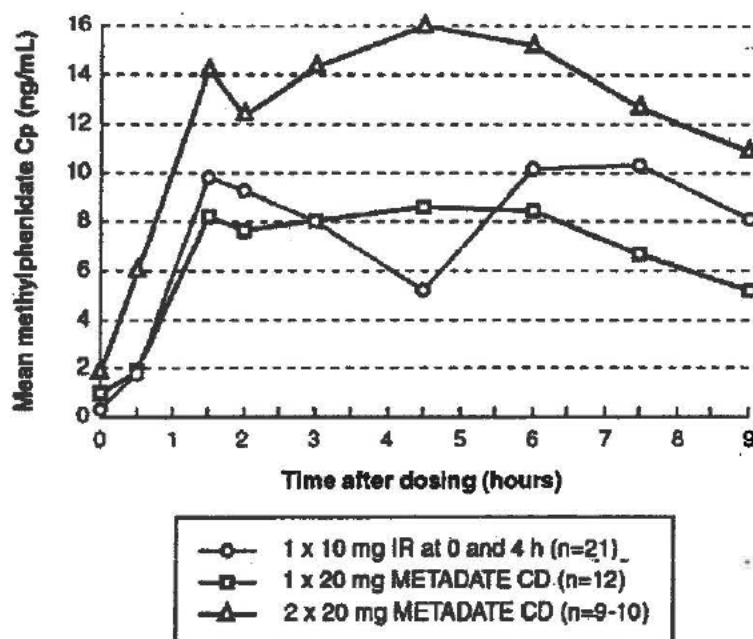
Source: NT0102.1002 Tables 14.2.9 and 14.2.10

Figure 14. NT0102.1001 Mean Total MPH (*d + l*) Concentration-Time Profiles after Administration of Test Formulation 1 (Treatment A), Test Formulation 2 (Treatment B), and Reference Product (Treatment C)



Note: Treatment A is the formulation from this study that was selected for development and Treatment C is the RLD, Metadate CD

Figure 15. Comparison of immediate release (IR) and Metadate CD formulations after repeated doses of methylphenidate HCl



Clinical data from clinical studies NT0102.1001, NT0102.1002, & NT0102.1003 showed that the drug product formulation for methylphenidate XR-ODT provides consistent pharmacokinetic performance between individual dosage units. In addition methylphenidate XR-ODT has less dose frequency (once daily) compared to the approved immediate release methylphenidate products (e.g. RITALIN® hydrochloride, methylphenidate hydrochloride USP tablets, 2-3 times daily).

Reviewer's Assessment:

Data provided by the Applicant from clinical studies support the extended release designation claim for methylphenidate XR-ODT. Specifically, the product under review meets the requirements delineated under CFR 320.25f, as follows:

- The BA profile established for the drug product rules out the occurrence of any dose dumping
- The drug product's steady-state performance is comparable (e.g. degree of fluctuation is similar or lower) to a currently marketed noncontrolled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.
- The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units;
- The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.

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

Based on Applicant's CMC IR response dated 07/20/2015, there will be a change in the concentration of formulation components for the to-be marketed drug product as shown in Table 16. The change (b) (4) falls in to Level 3 change based on SUPAC-MR guidance. A single-dose bioequivalence study is required to support this type of formulation change. However, the Applicant did not conduct bioequivalence study to bridge the clinical formulation to the to-be marketed formulation of methylphenidate XR-ODT.

Table 16. Formulation change from clinical batches to to-be-marketed batches

Ingredient	Clinical Lot 1E101A (30 mg)		Clinical Lot 2E110E (30 mg)		Clinical Lot 2E117E (20 mg)		To-be-marketed (30 mg)		To-be-marketed (20 mg)	
	% w/w	mg/tab	%w/w	mg/tab	%w/w	mg/tab	%w/w	mg/tab	%w/w	mg/tab
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Croscopolidone, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sucralose	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Citric Acid (b) (4) USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4) scrape (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Natural Masking Type Powder (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Lake Blend Purple (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Magnesium Stearate, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total Tablet Weight	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

The Applicant implemented a (b) (4) for the commercial formulation. The Applicant provided some dissolution data in response to IR comments dated 08/20/2015 to justify that the change in formulation will not impact the in vivo performance of the drug product (Tables 17 and 18 and Figures 17 to 19). However, further analysis of these data suggest that the formulation change needs to be supported by bioequivalence study. Specifically, Figure 17 shows that, the dissolution of the ER (b) (4) (b) (4) dissolution testing acceptance criteria (Table 14), indicating the proposed ER (b) (4) (b) (4) However, the dissolution of the ODTs (b) (4) meet the recommended dissolution testing acceptance criteria as shown in (b) (4)

Figure 18, indicating that the dissolution method, as expected for major formulation changes, does not discriminate for batches with inadequate (b) (4) levels of drug- (b) (4) Dissolution testing, as stated in guidance for industry, is not the appropriate approach to evaluate the clinical impact of major formulation changes; therefore, an in vivo BE study is needed to support the proposed changes.

Table 17. Material produced to facilitate selection of the ER (b) (4)



(b) (4)

Figure 16. ER (b) (4) release profiles at various (b) (4)



Figure 17. Methylphenidate XR-ODT release profiles at various (b) (4)



Table 18. Pilot and commercial scale ER (b) (4) dissolution results

Batch Description	Lot Number	Dissolution Time Points (b) (4)
Pivotal Clinical	2E116	
Pivotal Clinical	2E117	
Bioequivalence Clinical	1E101	
Bioequivalence Clinical	1E102	
R&D Commercial Scale	215	
Validation Commercial Scale	5P032	
Validation Commercial Scale	5P033	
Validation Commercial Scale	5P034	

Figure 18. Comparison of the pilot and commercial scale ER dissolution





Dissolution characterization at three pH levels for different strengths

Dissolution testing was conducted at three pH levels on all strengths of drug product. The dissolution profiles comparison is shown in Figure 19. Dissolution profiles of different strengths are similar (based on *f2* testing shown in Table 5) at the three tested pH levels and with the proposed dissolution method. The comparisons of both the 20 mg and 30 mg ODTs to the 10 mg ODT using the proposed dissolution test method resulted in *f2* values of 60.4 and 62.8 while the comparison of the 20 mg ODT to the 30 mg ODT resulted in a *f2* value of 92.7. The above data support the approval of the lower strengths of the drug product.

Figure 19. Comparison of dissolution profiles among ODTs tested in dissolution media with different pH levels



Table 19. *f2* comparison of dissolution profiles among ODTs tested in dissolution media with different pH levels

Dissolution Media	(b) (4)								
Batches Compared	2E110 (10mg) vs 2E117 (20 mg)	2E110 (10mg) vs 2E116 (30 mg)	2E117 (20mg) vs 2E116 (30 mg)	2E110 (10mg) vs 2E117 (20 mg)	2E110 (10mg) vs 2E116 (30 mg)	2E117 (20mg) vs 2E116 (30 mg)	2E110 (10mg) vs 2E117 (20 mg)	2E110 (10mg) vs 2E116 (30 mg)	2E117 (20mg) vs 2E116 (30 mg)
<i>f2</i> Results	72.5	69.8	96.5	54.0	57.6	87.9	68.9	63.2	89.4



QUALITY ASSESSMENT
NDA # 205489



Reviewer's Assessment: The formulation changes implemented to the clinical trial formulation are considered major (b) (4) (b) (4) requiring in vivo BE data. The Applicant did not provide bioequivalence data to bridge the formulation change on the release controlling (b) (4) The provided dissolution data (b) (4) and finished drug product are not sufficient and cannot be used to bridge the change of the formulation. The Applicant will be requested to conduct bioequivalence study demonstrating that the change in formulation from clinical batches to the to-be-marketed batches does not impact the in vivo performance of the drug product.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

PRODUCT PROPERTY/ IMPACT OF CHANGE/ CQAS	Initial Risk Assessment	Comments	Updated Risk Ranking after Review Cycle	Comments on mitigation strategy
Dissolution	Moderate	Medium risk. Risk Assessment based on the data/document submitted by the applicant and reviewer's previous experience, it appears that the formulation of the drug product and its manufacturing process are very robust with respect to dissolution CQA. The possibility that there will be large batch to batch variability in dissolution that can potentially impact safety and efficacy is low and will be a review issue. However, because this is a modified release drug product, considering the possibility of dose dumping, the overall risk is medium.	Low	An adequate, discriminating dissolution method was developed. The NDA's dissolution method and acceptance criteria for the drug product were found acceptable.
Alcohol dose-dumping	High	The clinical relevance of about 30% higher release in the presence of 40% alcohol will be a review issue.	Low	Ethanol concentration of 40% in dissolution medium triggers alcohol dose-dumping (about 90% and 70% release of methylphenidate within two hours from the 60 mg and 30 mg strengths, respectively). Warning is included in the labeling in regards to the consumption of alcohol and its potential impact on the safety of the drug product



Reviewer's Assessment and Signature:

The Applicant conducted a comprehensive dissolution method development to identify the appropriate dissolution apparatus, dissolution medium and volume, paddle rotation speed, etc. The Applicant adopted the recommended dissolution acceptance criteria which are supported by the dissolution data of clinical and stability batches and provided data to demonstrate the rationale of choosing the first time point at 0.5 hr.

(b) (4)

(b) (4)

the drug substance is (b) (4) given that (b) (4), the Applicant will be requested to justify the use of two-stage dissolution testing with the use of HCL on the first stage.

The proposed dissolution method has discriminating ability for (b) (4) but it does not have discriminating ability for (b) (4) within the ranges tested. As requested during the review cycle, the Applicant provided data demonstrating that chewing alters the drug product in a similar way to crushing and does not impact the in vitro release of the drug product.

(b) (4) Data provided demonstrated that alcohol dose-dumping occurs in vitro setting in the presence of 40% v/v Ethanol in the dissolution medium. This effect is similar to that observed for the reference product, Metabate CD. The Applicant was requested to include the findings of the in vitro alcohol dose dumping in the drug product label. Clinical data supports the extended release designation claims of the drug product.

A formulation change for the to-be marketed drug product from the drug product used in clinical studies is being proposed. The formulation change is mainly in the (b) (4) and the change is considered a major change (e.g., it falls in Level 3 category based on SUPAC-MR guidance) requiring in vivo BE data. However, no bioequivalence data were provided to bridge this change in formulation. The in vitro dissolution data of (b) (4) and ODT drug product provided are not sufficient (as per guidance) to demonstrate that the change in formulation would not impact the in vivo performance of the ODT drug product.

From the Biopharmaceutics perspective the provided information/data are not sufficient and therefore a Complete Response action is recommended for NDA 205489.



QUALITY ASSESSMENT
NDA # 205489



The following deficiencies should be conveyed to the Applicant as appropriate:

1. The drug substance is use of (b) (4) . Provide justification on the (b) (4)

2. (b) (4)

3. The formulation changes implemented to the clinical trial formulation are considered major (e.g. (b) (4)
(b) (4) . The provided dissolution data (b) (4) and
finished drug product are not sufficient and cannot be used to bridge the proposed change in the formulation. Specifically, (b) (4)

Therefore, you are requested to conduct a bioequivalence study demonstrating that the change in formulation from clinical batches to the to-be-marketed batches does not impact the in vivo performance of the drug product.

Ge Bai
Biopharmaceutics Reviewer
Office of New Drug Product
Division of Biopharmaceutics

**Ge
Bai -S**

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Supervisor Comments and Concurrence:

Sandra Suarez
Biopharmaceutics Lead (acting)
Office of New Drug Product
Division of Biopharmaceutics

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Note: additional reviewers can be added, as appropriate



ASSESSMENT OF MICROBIOLOGY

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

Points to consider

- What are the microbiological specifications for the drug product and how were they justified (for transdermal or wound treatment products, what was the scientific basis for determining whether the product was to be sterile or non-sterile)?
- If the drug product (whether preserved or inherently antimicrobial) is intended for multi-dose administration, how was the antimicrobial effectiveness demonstrated for the drug product?
- What are the relevant microbiological tests, test methods, and acceptance criteria necessary for release of the finished drug product, and what were the corresponding results for the exhibit batches?
- If the drug product release specification includes a test for bacterial endotoxins, how was the acceptance criterion established and calculated?
- For sterility and pyrogen (or endotoxin) release testing for the finished drug product, how was the analytical method validated?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment:

2.3.P.6 Reference Standards or Materials

22. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Point to consider

- How was the container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment:



A APPENDICES

A.2 Adventitious Agents Safety Evaluation

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

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment:

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

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment:

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

Supervisor Comments and Concurrence:



Note: additional reviewers can be added, as appropriate

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

1. Is the applicant's claim for categorical exclusion acceptable?
2. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

Pursuant to 21 CFR 25.31, Neos Therapeutics, Inc. claims a categorical exclusion from the requirement of an Environmental Assessment for Methylphenidate XR-ODT, which is a new dosage form that is directly substitutable for an already approved product (Metadate CD®), based upon paragraph (a) of the regulation: there would be no increase in the use of the active moiety.

Reviewer's Assessment: Inadequate

The applicant's claim for categorical exclusion does not include the extraordinary circumstances clause.

Information to be Requested

- Revise your request for categorical exclusion to include the statement that you do not have any knowledge of extraordinary circumstances that might cause this action to have a significant impact on the quality of human environment per CFR 25.15(d).

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

The environmental assessment is inadequate. The following deficiency should be conveyed to the applicant:

- Revise your request for categorical exclusion to include the statement that you do not have any knowledge of extraordinary circumstances that might cause this action to have a significant impact on the quality of human environment per CFR 25.15(d).

Andrei Ponta, Ph.D.

1- Sep-2015

Secondary Review Comments and Concurrence:

- I. **Review of Common Technical Document-Quality (Ctd-Q) Module 1 Labeling & Package Insert**
 1. **Package Insert**



QUALITY ASSESSMENT
NDA # 205489



(b) (4)

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: TRADENAME XR-ODT Established Name: Methylphenidate	The proposed proprietary name is pending.
Dosage form, route of administration	<u>Form:</u> Extended release oral disintegrating tablets <u>Route:</u> Oral (10 mg , 20 mg, and 30 mg)	The label and information provided in NDA are in agreement.
Controlled drug substance symbol (if applicable)	TRADENAME XR-ODT contains methylphenidate, a Schedule II controlled substance.	The controlled substance symbol designating the schedule in which the controlled substance is listed is included.
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Extended release orally disintegrating tablet: 10 mg , 20 mg, and 30 mg equivalent strengths	The label and information provided in NDA are in agreement; however, the applicant will be asked to provide the amount of methylphenidate base in each tablet.

Conclusion:

The drug product formulation does not contain HCl, (b) (4)
 (b) (4). Therefore, the applicant defines the dosage strength of Methylphenidate XR-ODT in terms of the equivalent quantity of methylphenidate hydrochloride. This means that 8.648 mg of the free base is equivalent to 10 mg of Methylphenidate HCl. For example, the "30 mg Methylphenidate XR-ODT" contains a 26 mg dose of methylphenidate base, which is equivalent to 30 mg of methylphenidate hydrochloride. The applicant will be asked to include information regarding the amount of methylphenidate base in each tablet.



**QUALITY ASSESSMENT
NDA # 205489**



(b) "Full Prescribing Information" Section

3 DOSAGE FORMS AND STRENGTHS

(b) (4) mg Extended Release Orally Disintegrating Tablet: round, purple to light purple mottled (debossed "T1" on one side and plain on the other)

(b) (4) mg Extended Release Orally Disintegrating Tablet: round, purple to light purple mottled (debossed "T2" on one side and plain on the other)

(b) (4) mg Extended Release Orally Disintegrating Tablet: round, purple to light purple mottled (debossed "T3" on one side and plain on the other)

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablet	The label and information provided in NDA are in agreement.
Strengths: in metric system	10 mg , 20 mg, and 30 mg	The label and information provided in NDA are in agreement.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	10 mg ODT: Round, purple to light purple mottled tablet, debossed "T1" on one side and plain on the other side 20 mg ODT: Round, purple to light purple mottled tablet, debossed "T2" on one side and plain on the other. 30 mg ODT: Round, purple to light purple mottled tablet, debossed "T3" on one side and plain on the other side.	The label and information provided in NDA are in agreement.

Conclusion:

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

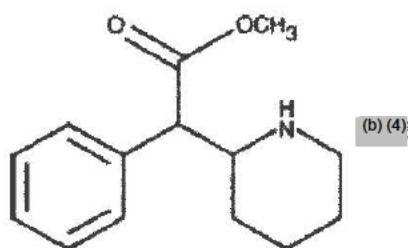
#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION

TRADENAME XR-ODT is an extended-release orally disintegrating tablet (b) (4) intended for once daily administration. TRADENAME XR-ODT contains approximately (b) (4)% immediate-release and (b) (4)% extended-release methylphenidate.

Methylphenidate (b) (4) is a central nervous system (CNS) stimulant. The chemical name is methyl α -phenyl-2-piperidineacetate (b) (4), and its structural formula is shown in Figure 1.

Figure 1: Methylphenidate (b) (4) structure



$C_{14}H_{19}NO_2$ (b) (4) Mol. Wt. (b) (4)

TRADENAME XR-ODT also contains the following inactive ingredients: (b) (4) Polystyrene (b) (4), Polyethylene Glycol, Ethylcellulose, Triethyl Citrate, (b) (4), Crospovidone, Sucralose, Citric Acid (b) (4), (b) (4) Grape (b) (4) Natural Masking Type (b) (4), Lake Blend Purple, Magnesium Stearate.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary: TRADENAME XR-ODT Established Name: Methylphenidate	The label and information provided in NDA are in agreement.
Dosage form and route of administration	<u>Form:</u> Extended release oral disintegrating tablets <u>Route:</u> Oral (10 mg, 20 mg, and 30 mg)	The label and information provided in NDA are in agreement.
Active moiety expression of strength with equivalence statement for salt (if applicable)	TRADENAME XR-ODT uses the same dosage nomenclature as all other approved methylphenidate products including the RLD, where the dosage strength is defined in terms of the equivalent quantity of methylphenidate hydrochloride.	The label is missing this information.
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Polystyrene Sulfonate, (b) (4), Ethylcellulose, Methacrylic Acid (b) (4), Triethyl Citrate, (b) (4), Crospovidone, Sucralose, Citric Acid (b) (4) Grape (b) (4) Natural Masking Type Powder (b) (4), Lake Blend Purple (b) (4), and Magnesium Stearate	The label and information provided in NDA are in agreement. However, the label lists Methacrylic Acid (b) (4)
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ therapeutic class	A central nervous system stimulant	The label and information provided in NDA are in agreement.
Chemical name, structural formula, molecular weight	The chemical name is methyl α -phenyl-2-piperidineacetate (b) (4). Its molecular formula is $C_{14}H_{19}NO_2$ (b) (4) and its molecular weight	The label and information provided in NDA are in agreement.



QUALITY ASSESSMENT
NDA # 205489



	is (b) (4)	
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa, solubility, or pH)	(b) (4)	The label is missing this information.

Conclusion:

The label is accurate; however, it does not include information regarding the active moiety expression of strength and the important chemical or physical properties.

Information to be Requested:

1. Information regarding the active moiety expression of strength and the important chemical or physical properties of the drug substance is absent in the package insert description section (#11). Include this information in the label per CFR 201.57(c)(12).

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

16 HOW SUPPLIED/STORAGE AND HANDLING

TRADENAME Extended Release Orally Disintegrating Tablets are available in three strengths:
 10 mg tablets, round, purple to light purple, mottled, and debossed "T1" on one side of the tablet;
 20 mg tablets, round, purple to light purple, mottled, and debossed "T2" on one side of the tablet;
 30 mg tablets, round, purple to light purple, mottled, and debossed "T3" on one side of the tablet.

They are available as follows:

- NDC (b) (4) 10 mg tablets: carton of 30 tablets (5 blister cards (b) (4) (b) (4) 6 tablets (b) (4) with a reusable travel case.
- NDC (b) (4) 20 mg tablets: carton of 30 tablets (5 blister cards (b) (4) (b) (4) 6 tablets (b) (4) with a reusable travel case.
- NDC (b) (4) 30 mg tablets: carton of 30 tablets (5 blister cards (b) (4) (b) (4) 6 tablets (b) (4) with a reusable travel case.

(b) (4)

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



QUALITY ASSESSMENT
NDA # 205489



Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Form: Extended release oral disintegrating tablets Strength: Oral (10 mg, 20 mg, and 30 mg)	The label and information provided in NDA are in agreement.
Available units (e.g., bottles of 100 tablets)	Tablets (10 mg, 20 mg, and 30 mg) are to be supplied in blister packaging, with each blister pack containing six tablets. (b) (4) (b) (4)	The label and information provided in NDA are in agreement.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	10 mg ODT: Round, purple to light purple mottled tablet, debossed "T1" on one side and plain on the other side 20 mg ODT: Round, purple to light purple mottled tablet, debossed "T2" on one side and plain on the other. 30 mg ODT: Round, purple to light purple mottled tablet, debossed "T3" on one side and plain on the other side.	The label and information provided in NDA are in agreement.
Special handling (e.g., protect from light, do not freeze)	The drug product is stable to short term excursions between 15°C and 30°C.	The label and information provided in NDA are in agreement.
Storage conditions	Store at 25° C (77° F) [see USP controlled room temperature].	The label and information provided in NDA are in agreement.

Conclusion:

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

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

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

For more information call 1-(888)-319-1789

(b) (4)

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

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Item # XXXXX

Rev. XX YYYY

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

Conclusion:

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

2. Container and Carton Labeling

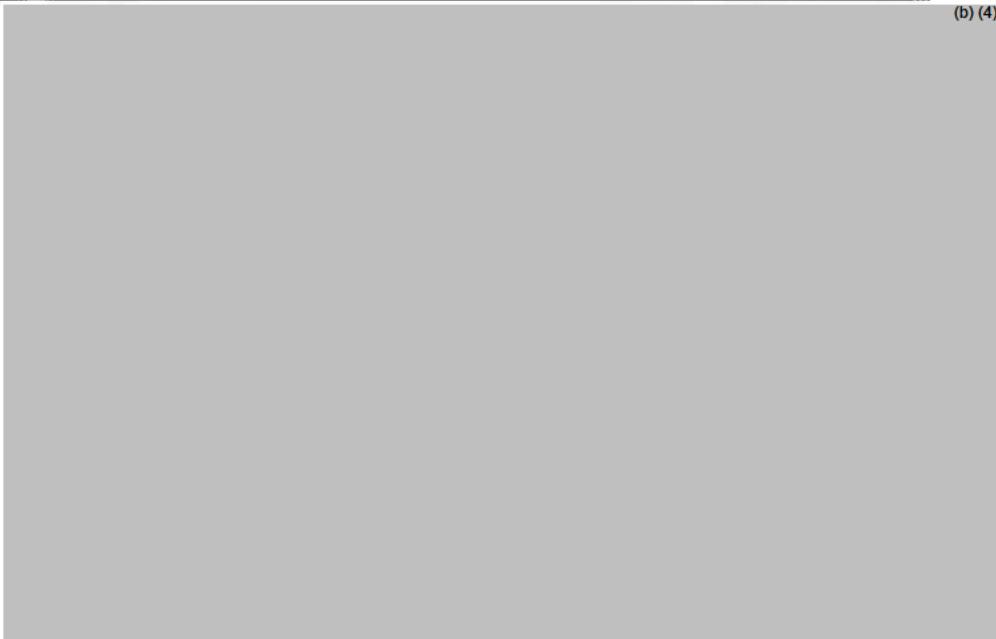
1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



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(b) (4)



Reviewer's Assessment:

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

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

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:



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The label is accurate; however, it does not include net contents information, a Rx only statement, or an NDC number.

Information to be Requested:

2. The Rx only statement and the NDC number is absent in the immediate container label (blister packaging). Include this information in the label per 21 CFR 201.51(a), CFR 201.100(b)(1), and 21 CFR 201.2, respectively.

(b) (4)

2) **Cartons**

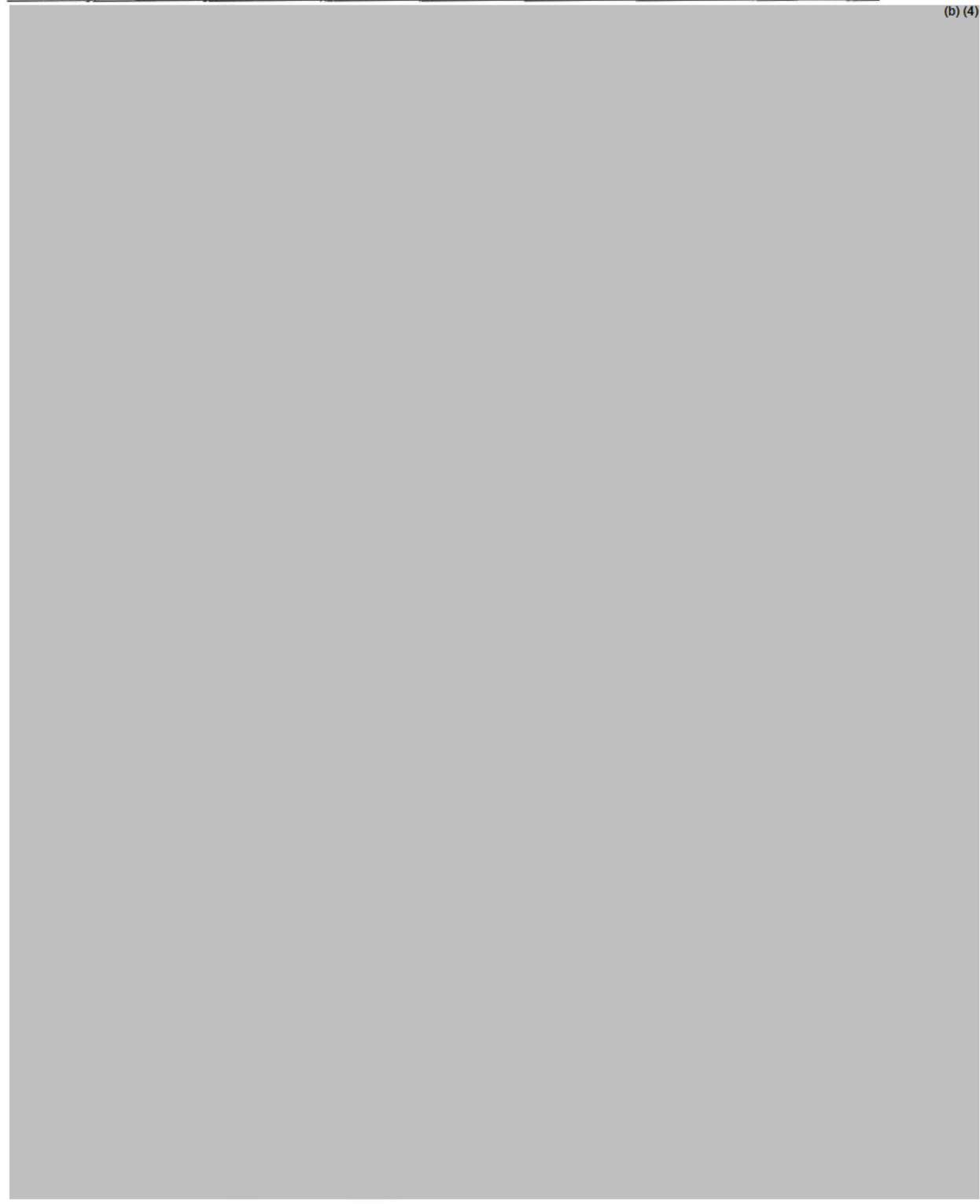
1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



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(b) (4)



Item	Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i),	The established name follows the proprietary name. The font size of the established name is at least half	Adequate



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FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	of the most prominent proprietary name font size.	
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The quantity of the active ingredient provided is accurate.	Adequate
Net contents (21 CFR 201.51(a))	The number of tablets is included on the label.	Adequate
Lot number per 21 CFR 201.18	There is a designated space for the lot number.	Adequate
Expiration date per 21 CFR 201.17	There is a designated space for the expiration date.	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	NA	NA
Sterility Information (if applicable)	NA	NA
*"Rx only" statement per 21 CFR 201.100(b)(1)	The carton bears the "Rx only" statement.	Adequate
Storage Conditions	The label has the following storage conditions instructions: Controlled room temperature conditions [25°C (77°F); excursions 15 – 30°C (59 – 86°F)]	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	The NDC number is present on the top right section of the package.	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	The bar code appears on the label.	Adequate
Name of manufacturer/distributor	The manufacture is listed on the label.	Adequate
*"See package insert for dosage information" (21 CFR 201.55)	A "See package insert for full prescribing information" statement is included on the side of the package.	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	NA	NA
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	The drug product is for oral use.	Adequate

Conclusion:

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

II. Review



iii. Attachments

A. Lifecycle Knowledge Management: N/A due to CR recommendation.

a) Drug Substance

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Initial Risk Ranking*	Justification	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments**
	H, M, or L			N/A	N/A due to CR recommendatio n

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
		H, M, or L		N/A	N/A due to CR recommendation

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.



List of Deficiencies for Action Letter

1. Bridge the clinical and commercial drug product formulations with a bioequivalence study. The commercial drug product will have (b) (4)% (b) (4) (w/w) delayed release and (b) (4)% (b) (4) extended release (b) (4). This difference was supported by in vitro data. However changes of this extent, especially to the extended release (b) (4) require bioequivalence studies.

2. Establish, validate and fully justify an unequivocal commercial (b) (4) operation and control. You state in 3.2.P.2.3 that the commercial scale process will use (b) (4) (b) (4), but state in the 20 AUG 2015 amendment (b) (4)

(b) (4)

Other Deficiencies:

3. Change the dosage strengths so that they reflect methylphenidate base content. This will be in accordance with the USP <1121> salt policy and Agency salt naming guidance. The proposed dosage strength is based on methylphenidate hydrochloride. However the drug product does not contain methylphenidate hydrochloride.

4. The drug substance is (b) (4). Provide justification on (b) (4)

5. (b) (4)

6.

a. (b) (4)

b. (b) (4)



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c.

(b) (4)

7. The amount of extended and delayed release (b) (4) in the final drug product formulation will vary. Provide the acceptable extended and delayed release (b) (4) range for the final drug product formulation. Provide justification demonstrating that the permitted range does not impact drug product quality and efficacy.
8. Provide a table indicating the composition of the to-be marketed drug product formulation. Ensure the table has the following information:
- The targeted drug product composition (mg and w/w%)
 - The minimum acceptable amount of each excipient (b) (4), sucralose, triethyl (b) (4), ethylcellulose, methacrylic acid (b) (4) for a drug product composition (mg and w/w%)
 - The maximum acceptable amount of each excipient (b) (4), sucralose, triethyl (b) (4), ethylcellulose, methacrylic acid (b) (4) for a drug product composition (mg and w/w%)
9. Provide a table with the drug product composition of each drug product batch manufactured including previous and newly prepared batches. Indicate which batches were used in clinical trials. Ensure the information is accurate and consistent as there were multiple discrepancies in previously provided data.
10. Provide release and three months' accelerated and long-term stability data from three batches manufactured using the commercial manufacturing process. Ensure the newly manufactured batches have the same drug product formulation as the batches used in the BE study.
11. You indicate that the polystyrene sulfonate specification contains a (b) (4) specification matching the manufacturer's requirements. Provide justification for choosing this (b) (4) (b) (4) acceptance criterion.

OPQ comments:

- We note that the application included inconsistent information on critical issues, including those used to support the differences in the clinical and commercial formulations - including differences in (b) (4) level for the clinical batches. The application also contained contradictory statements such as on whether (b) (4). These inconsistencies make definitive formulation comparisons between the clinical and commercial batches impossible.
- Be advised that (b) (4). This is because of the significant difference between the formulations and the fact that it comprises (b) (4)% of tablet weight.



IV. Administrative

A. Application Technical Lead (ATL) Signature

**David J. Claffey -
S**

Digitally signed by David J. Claffey -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People,
0,9,2342.19200300.100.1.1=1300225565,
cn=David J. Claffey -S
Date: 2015.09.09 09:20:32 -04'00'

Concur with CR recommendation