CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212038Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 212038
Review #1

Drug Name/Dosage Form	Adhansia XR (methylphenidate hydrochloride) Extended Release Capsules
Strength	25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Purdue Pharma (Canada)
US agent, if applicable	Cedric George

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0000	*4/27/2018*	*All*
0001	*6/20/2018*	*Drug Substance*
0004	*8/03/2018*	*Drug Product*
0006	*9/14/2018*	*Biopharm*
0007	*9/24/2018*	*Drug Product*
0009	*10/26/2018*	*Drug Substance, Drug Product, Process, Biopharm*
0012	*12/19/2018*	*Process*
0014	*2/04/2019*	*Process, Biopharm*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Sithamalli Chandramouli	Su Tran
Drug Product	Andrei Ponta	Wendy Wilson-Lee
Environmental	James Laurenson	Raanan Bloom
Facility	Cai Chunsheng	Rapti Madurawe
Biopharmaceutics	Parnali Chatterjee	Ta-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	
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)	acceptable	Aug 2017	
	Type II			acceptable	June 2018	
	Type II			acceptable	June 2018	Referenced by DMF (b) (4)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
	NDA 21121	Concerta listed drug
	NDA 10187	Ritalin listed drug

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

Recommend approval from a product quality perspective based on acceptable recommendations from OPQ drug substance, drug product, process, facilities and biopharmaceutics review teams.

II. Summary of Quality Assessments

A. Product Overview

This application seeks marketing approval for Adhansia XR (methylphenidate hydrochloride extended-release capsules) containing 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg of methylphenidate hydrochloride, for once-daily oral administration for the treatment of attention deficit hyperactivity disorder (ADHD). This is a 505(b)(2) relying on Concerta (NDA 21121) and Ritalin IR (NDA 10187). It is for patients six years or older. Patients are directed to take one dose daily (maximum 100 mg) with or without food in the morning. Data support the label claim that the capsules can be opened and sprinkled on food (apple sauce, yogurt (b) (4)) immediately before administration.

The proposed drug product is an extended-release methylphenidate hydrochloride (MPH) product (b) (4) .

Drug product consists of capsules filled with (b) (4) multilayer bead. The marketing of six strengths is proposed - 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg. Strengths are based on their methylphenidate hydrochloride salt content. The strengths are (b) (4) .

The beads consist of (b) (4) layers (b) (4) (b) (4) 80% of drug load is in (b) (4) layer (b) (4) (b) (4) immediate-release layer contains the remaining 20% drug-load. (b) (4)

Each capsule is a different color and has “MLR-02” and the drug product strength printed on them (b) (4) The drug product is packaged in HDPE containers with (b) (4)

(b) (4) 100 capsules and two 1 g desiccants. Data support a 24-month drug product expiry at controlled room temperature.

Proposed Indication(s) including Intended Patient Population	***ADHD in patients six and over***
Duration of Treatment	***Chronic***
Maximum Daily Dose	***100 mg***
Alternative Methods of Administration	***Capsule contents can be sprinkled on food immediately prior to administration.***

B. Quality Assessment Overview

Drug substance: Drug substance specification is based on the USP monograph for methylphenidate hydrochloride. Much of the drug substance information was referenced to DMFs held by (b) (4) and (b) (4). DMF (b) (4) (b) (4) was reviewed in Aug. 2017 (SD# 55) and found adequate. DMF (b) (4) ((b) (4)) was reviewed in June 2018 (SD# 11) and found adequate. DMF (b) (4) references DMF (b) (4) (SD# 9) as the source of (b) (4); it was also found adequate in June 2018.

DRUG PRODUCT: The proposed drug product is an extended-release methylphenidate hydrochloride (MPH) product (b) (4) It is for the treatment of attention-deficit/hyperactivity disorder (ADHD).

Drug product consists of capsules filled with a (b) (4) multilayer bead. The marketing of six strengths is proposed - 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg. Strengths are based on their methylphenidate hydrochloride salt content. The strengths are (b) (4) .
The beads consist of (b) (4) layers (b) (4) (b) (4) 80% of drug load is in (b) (4) layer (b) (4) (b) (4) immediate-release layer contains the remaining 20% drug-load.

The drug product is composed of methylphenidate HCl, and the following excipients: ammonio methacrylate copolymer dispersion (type B), anionic copolymer (consisting of methyl acrylate, methyl methacrylate and methacrylic acid), glyceryl monostearate, hypromellose, polyethylene glycol, polysorbate, silicon dioxide, sodium hydroxide, sodium lauryl sulfate, sorbic acid, sugar spheres, and triethyl citrate. Each capsule is a different color and has "MLR-02" and the drug product strength printed on them (b) (4) .

The drug product is packaged in 125 ml, 220 ml, or 325 ml HDPE bottles with (b) (4) caps with a foil inner seal. Each bottle will contain (b) (4) 100 capsules and two 1 g desiccants.

Stability data were found to support the proposed 24-month drug product expiry period when stored at controlled room temperature. Data support the label claim that the capsules can be opened and sprinkled on food (apple sauce, yogurt (b) (4)) immediately before administration.

The applicant claims a categorical exclusion from an EA citing 21 CFR§ 25.31(a) indicating that there will not be an increase the use of the active moiety. Additionally, the applicant confirms that to the best of their knowledge no extraordinary circumstances exist.

Process: The drug product manufacturing process was found to be adequately controlled. (b) (4)

Each of the drug substance and drug product manufacturing sites were found to be acceptable by OPF.

Biopharmaceutics: The two-stage dissolution method (six hours at pH (b) (4) then 10 hours at pH 7.4) and the dissolution acceptance criterion with four timepoints were found acceptable after discussions with the applicant. The In vitro dissolution data adequately bridged the formulation (capsule shell type) and manufacturing site (Canada vs US) changes. The biowaiver request for the non-bio-strengths, 25 mg, 35 mg, 45 mg, 55 mg, and 70 mg was granted. In an in vitro alcohol-induced dose dumping study found an appreciable increase in the release of methylphenidate at alcohol concentration of 40% v/v, but not at 5%-20% v/v alcohol concentrations. This information will be added to the labeling. The extended release claim was accepted.

C. Special Product Quality Labeling Recommendations (NDA only)

Alcohol dose dumping language needs to be added to labeling.

D. Final Risk Assessment (see Attachment)

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LABELING

I. Package Insert

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

ADHANSIA XR (methylphenidate hydrochloride) extended-release capsules, for oral use, CII
Initial U.S. Approval: 1955

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

----------INDICATIONS AND USAGE----------
(b) (4)

----------DOSAGE AND ADMINISTRATION----------
- Recommended starting dose for patients 6 years or older: 25 mg once daily (b) (4) in the morning. (b) (4) (b) (4)
- Capsules may be swallowed whole or opened and the entire contents sprinkled onto a tablespoon of applesauce (b) (4) or yogurt. (2.2)

----------DOSAGE FORMS AND STRENGTHS---------- (b) (4)
Extended-Release Capsules: 25 mg, 35 mg, 45 mg, 55 mg, 70 mg and 85 mg (b) (4)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to methylphenidate or product components. (4)
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days (4 (b) (4)

----------WARNINGS AND PRECAUTIONS----------
Serious Cardiovascular Events: Sudden death has been reported in association with CNS stimulants at recommended doses in (b) (4) with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease. (5.2)
- *Blood Pressure and Heart Rate Increases:* Monitor blood pressure and pulse. Consider the benefits and risks in patients for whom an increase in blood pressure or heart rate would be problematic. (5.3)
- *Psychiatric Adverse Reactions:* Use of CNS stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to ADHANSIA XR use. (5.4)
- *Priapism:* Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed. (5.5)
- *Peripheral Vasculopathy, including Raynaud's Phenomenon:* Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.6)
- *Long-Term Suppression of Growth:* Monitor height and weight at appropriate intervals in pediatric patients. (5.7)

(b) (4)

- *FD&C Yellow No. 5:* ADHANSIA XR 45 mg capsules contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. (b) (4) (b) (4)

----------ADVERSE REACTIONS----------
(b) (4)

To report SUSPECTED ADVERSE REACTIONS, contact Purdue Pharma (b) (4) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: xx/xxxx

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	ADHANSIA XR (methylphenidate hydrochloride) extended-release capsules, for oral use
Dosage form, route of administration	Capsules, oral
Controlled drug substance symbol	CII
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Extended release capsules: 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg

Is the information accurate? ☒ Yes ☐ No

2. *Section 2 Dosage and Administration*

2.2. General Dosing Information

The recommended starting dose of ADHANSIA XR for patients 6 years or older is 25 mg once daily (b) (4) (b) (4) The dose should be titrated in intervals of no less than 5 days (b) (4) (b) (4) (b) (4) (b) (4)

ADHANSIA XR may be taken whole or the capsule may be opened and the entire contents sprinkled onto a tablespoon of applesauce, (b) (4) or yogurt. The entire mixture should be consumed immediately or within 10 minutes. If the mixture is not consumed within 10 minutes after mixing, it should be discarded and not stored. Patients should take the entire contents of the capsule sprinkled on the chosen food in its entirety, without chewing. The dose of a single capsule should not be divided. Patients should not take anything less than one capsule per day.

(b) (4) (b) (4) In the event of a missed dose, do not administer later in the day. Do not administer additional medication to make up for the missed dose [see *Adverse Reactions (6.1), Clinical Studies (14)*].

Pharmacological treatment of ADHD may be needed for extended periods. Periodically re-evaluate the long-term use of ADHANSIA XR, and adjust dosage as needed.

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	The drug product is an capsule that is to be taken orally in the morning. The capsule may be opened and its contents may be sprinkled onto a tablespoon of applesauce (b) (4) or yogurt and should be consumed immediately.

Is the information accurate? ☒ Yes ☐ No

3. *Section 3 Dosage Forms and Strengths*

3. DOSAGE FORMS AND STRENGTHS

- ***25 mg Extended-Release Capsules*** – blue capsule (imprinted with "MLR-02" on cap and "25 mg" on the body)
- ***35 mg Extended-Release Capsules*** – orange capsule (imprinted with "MLR-02" on cap and "35 mg" on the body)
- ***45 mg Extended-Release Capsules*** – yellow capsule (imprinted with "MRL-02" on cap and "45 mg" on the body)
- ***55 mg Extended-Release Capsules*** – light green capsule (imprinted with "MRL-02" on cap and "55 mg" on the body)
- ***70 mg Extended-Release Capsules*** – iron gray capsule (imprinted with "MLR-02" on cap and "70 mg" on the body)
- ***85 mg Extended-Release Capsules*** – white capsule (imprinted with "MRL-02" on cap and "85 mg" on the body)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Extended release capsules
Strengths: in metric system	25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg
Active moiety expression of strength with equivalence statement	Methylphenidate hydrochloride Reviewer's Note: Applicant will be asked to include the active in this section
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	• 25 mg Extended-Release Capsules – blue capsule (imprinted with "MLR-02" on cap and "25 mg" on the body) • 35 mg Extended-Release Capsules – orange capsule (imprinted with "MLR-02" on cap and "35 mg" on the body) • 45 mg Extended-Release Capsules – yellow capsule (imprinted with "MRL-02" on cap and "45 mg" on the body) • 55 mg Extended-Release Capsules – light green capsule (imprinted with "MRL-02" on cap and "55 mg" on the body) • 70 mg Extended-Release Capsules – iron gray capsule (imprinted with "MLR-02" on cap and "70 mg" on the body) • 85 mg Extended-Release Capsules – white capsule (imprinted with "MRL-02" on cap and "85 mg" on the body)

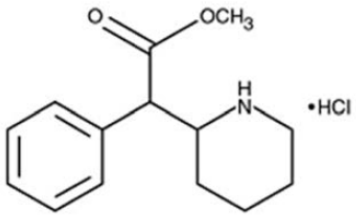
Is the information accurate? ☒ Yes ☐ No

Revisions identified and will be communicated to the Applicant as part of DPP labeling negotiations. This section is adequate assuming Applicant accepts edits.

4. *Section 11 Description*

11. DESCRIPTION

ADHANSIA XR™ (b) (4) capsules contain multilayered beads, composed of an immediate-release (IR) layer which contains approximately 20% of the methylphenidate dose, and a controlled release layer which contains approximately 80% of the methylphenidate dose, for (b) (4) oral administration. ADHANSIA XR is available in six capsule strengths. Each extended-release capsule (b) (4) contains 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, or 85 mg of methylphenidate hydrochloride (HCl) (b) (4) which is equivalent to 21.6 mg, 30.3 mg, 38.9, mg, 47.6 mg, 60.5 mg, and 73.5 mg of methylphenidate free base, respectively. Chemically, methylphenidate HCl is *d,l* (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride. Its molecular formula is $C_{14}H_{19}NO_2 \bullet HCl$. Its structural formula is:



Methylphenidate HCl USP is a white to off-white, odorless, fine crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.8 g/mol.

Inactive Ingredients: ammonio methacrylate copolymer dispersion (type B), anionic copolymer (consisting of methyl acrylate, methyl methacrylate and methacrylic acid), glyceryl monostearate,

hypromellose, poylethylene glycol, polysorbate, silicon dioxide, sodium hydroxide, sodium laurylsulfate, sorbic acid, sugar spheres, triethyl citrate.

Each strength capsule also contains colorant ingredients in the capsule shell as follows:

- 25 mg FD&C Blue No. 1
- 35 mg FD&C Yellow No. 6, Titanium Dioxide
- 45 mg FD&C Yellow No. 5, Titanium Dioxide
- 55 mg FD&C Blue No. 1, Yellow Iron Oxide, Titanium Dioxide
- 70 mg Black Iron Oxide, Titanium Dioxide
- 85 mg Titanium Dioxide

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	ADHANSIA XR (methylphenidate hydrochloride) extended-release capsules, for oral use
Dosage form and route of administration	Extended release capsules: 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg
Active moiety expression of strength with equivalence statement (if applicable)	Methylphenidate: 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, or 85 mg of methylphenidate hydrochloride (HCl) (b) (4) which is equivalent to 21.6 mg, 30.3 mg, 38.9, mg, 47.6 mg, 60.5 mg, and 73.5 mg of methylphenidate free base, respectively
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Ammonio methacrylate copolymer dispersion (type B), anionic copolymer (consisting of methyl acrylate, methyl methacrylate and methacrylic acid), glyceryl monostearate, hypromellose, polyethylene glycol, polysorbate, silicon dioxide, sodium hydroxide, sodium laurylsulfate, sorbic acid, sugar spheres, and triethyl citrate. Each strength capsule also contains a different colorant to easily distinguish between

	strengths: • 25 mg – FD&C Blue No. 1 • 35 mg –FD&C Yellow No. 6, Titanium Dioxide • 45 mg – FD&C Yellow No. 5, Titanium Dioxide • 55 mg – FD&C Blue No. 1, Yellow Iron Oxide, Titanium Dioxide • 70 mg –Black Iron Oxide, Titanium Dioxide • 85 mg – Titanium Dioxide
tatement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	A central nervous system stimulant
Chemical name, structural formula, molecular weight	$C_{14}H_{19}NO_2 \bullet HCl$ – 269.77 g/mol
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone

Is the information accurate? ☒ Yes ☐ No

5. ***Section 16 How Supplied/Storage and Handling***

16. HOW SUPPLIED/STORAGE AND HANDLING

ADHANSIA XR™ (methylphenidate hydrochloride extended-release) capsules are available as follows:

- ***25 mg Capsules*** – blue, (imprinted with "<MLR-02>" and "25 mg")
  Bottles of 100 .....NDC (b) (4)
- ***35 mg Capsules*** – orange, (imprinted with "<MLR-02>" and "35 mg")
  Bottles of 100 .....NDC
- ***45 mg Capsules*** – yellow, (imprinted with "<MLR-02>" and "45 mg")
  Bottles of 100 .....NDC
- ***55 mg Capsules*** – light green, (imprinted with "<MLR-02>" and "55 mg")
  Bottles of 100 .....NDC
- ***70 mg Capsules*** – iron gray, (imprinted with "<MLR-02>" and "70 mg")
  Bottles of 100 .....NDC
- ***85 mg Capsules*** – white, (imprinted with "<MLR-02>" and "85 mg")
  Bottles of 100 .....NDC

Storage and Handling

(b) (4) stored between 20° C to 25° C (68° F to 77° F); excursions permitted from 15° C to 30° C (59° F to 86° F) [see USP Controlled Room Temperature]. Protect from light and moisture.

Dispense in tight container (USP). (b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	ADHANSIA XR (methylphenidate hydrochloride) extended-release capsules, for oral use: 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg
Available units (e.g., bottles of 100 tablets)	Bottles of 100 capsules
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	• 25 mg Extended-Release Capsules – blue capsule (imprinted with "MLR-02" on cap and "25 mg" on the body) • 35 mg Extended-Release Capsules – orange capsule (imprinted with "MLR-02" on cap and "35 mg" on the body) • 45 mg Extended-Release Capsules – yellow capsule (imprinted with "MRL-02" on cap and "45 mg" on the body) • 55 mg Extended-Release Capsules – light green capsule (imprinted with "MRL-02" on cap and "55 mg" on the body) • 70 mg Extended-Release Capsules – iron gray capsule (imprinted with "MLR-02" on cap and "70 mg" on the body) • 85 mg Extended-Release Capsules – white capsule (imprinted with "MRL-02" on cap and "85 mg" on the body)
Special handling (e.g., protect from light)	Protect from light and moisture
Storage conditions	USP controlled room temperature
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Purdue Pharmaceuticals L.P.

Reviewer's Assessment of Package Insert: ***Adequate***

Prescribing Information complies with all regulatory requirements from a CMC perspective.

II. Labels:

1. ***Container and Carton Labels***

(b) (4)

Item	Information provided in the container label
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	ADHANSIA XR (methylphenidate hydrochloride) extended-release capsules, (b) (4)
Dosage strength	Complies
Net contents	Complies
"Rx only" displayed prominently on the main panel	Complies
NDC number (21 CFR 207.35(b)(3)(i))	Complies
Lot number and expiration date (21 CFR 201.17)	Does not comply Reviewer's Note: Applicant will be asked to include the lot number and expiration date on the container label
Storage conditions	Complies
Bar code (21CFR 201.25)	Complies
Name of manufacturer/distributor	Purdue Pharmaceuticals L.P.
And others, if space is available	Not Applicable

Reviewer's Assessment of Labels: *Adequate*

The carton/container label complies with regulatory requirements from a CMC perspective, with the exception of the proprietary name. It bears the "Rx only" statement, the NDC number, name of manufacturer, net contents, bar code, strength, and the name (proprietary and established).

Revisions identified and will be communicated to the Applicant as part of DPP labeling negotiations. The carton/container labeling is adequate assuming Applicant accepts edits.

List of Suggested Edits Communicated to Applicant:

1. *The strength of the drug product is based on the salt form of the drug substance. Update the strength of the drug product to be reported as the active (e.g. xx mg of methylphenidate) in the phyician's insert, carton/container labeling, and the med guide per the FDA guidance, "Naming of Drug Products Containing Salt Drug Substances"*
2. *The dosage forms and strengths do not contain information regarding the active moiety of the drug substance. Include "methylphenidate" after the strength of the product (e.g. 25 mg methylphnidate).*
3. *Include the lot number and expiration date on the container labels.*

Overall Assessment and Recommendation: Adequate

Primary Labeling Reviewer Name and Date: Andrei Ponta, Ph.D. 13-Oct-2018

Andrei Ponta

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Wendy Wilson- Lee

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BIOPHARMACEUTICS

NDA: 212038
Drug Product Name / Strength: Adhansia XR™ (Methylphenidate Hydrochloride Extended-Release Capsules), 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg
Route of Administration: Oral
Applicant Name: Purdue Pharma (Canada)
Primary Reviewer: Parnali Chatterjee, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.

Background:

The Applicant is seeking approval for the proposed Adhansia XR™ (PRC-063; methylphenidate hydrochloride extended-release capsules) of 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg strengths to be administered orally, once daily, for the treatment of attention deficit hyperactivity disorder (ADHD) *via* the 505(b)(2) regulatory pathway.

This application is, in part, relying on the FDA's findings on safety and efficacy for the previously approved Listed Drugs (LD), Concerta® (NDA 021121 approved on 08/01/2000) and Ritalin® IR (NDA 010187 approved on 12/05/1955). Several single- and repeat-dose (with 45 and 55 mg strengths) comparative bioavailability/bioequivalence (BA/BE) studies (Studies 063-004, 063-006, 063-007, and 063-016) were conducted to characterize pharmacokinetic (PK) properties of PRC-063 in adults and adolescents, and provide comparison with/bridge to the Listed Drugs. In addition, the Applicant conducted five clinical efficacy and safety studies in pediatrics and adults. The Applicant requested a biowaiver for the lower strengths, 25 mg, 35 mg, 45 mg, 55 mg, and 70 mg, of the drug product. Additionally, a bioequivalence (BE) study (063-018) was conducted with the 85 mg strength TBM drug product to establish the 'bridge' between the drug product manufactured at Purdue Pharmaceuticals, Canadian site and drug product manufactured at Purdue Pharmaceuticals, L.P., US site.

REVIEW SUMMARY:

This Biopharmaceutics Review evaluated **1)** the proposed dissolution method, **2)** the proposed dissolution acceptance criteria, **3)** bridging of the formulations, manufacturing sites, and manufacturing processes between the Canadian and US sites throughout the product development stage, and **4**) the biowaiver request for the non-biostrengths, 25 mg, 35 mg, 45 mg, 55 mg, and 70 mg of the proposed Adhansia XR™.

Based on the review of the provided information/data, Biopharmaceutics has the following comments and recommendations:

- ***Dissolution Method:***
  The proposed and the final FDA-approved dissolution methods are summarized below:

Parameters	Proposed Method	FDA Recommended Method
Apparatus/Speed Sinkers	USP Apparatus 2 (paddle)/ (b) (4) Triprong sinkers	USP Apparatus 2 (paddle)/ **75 rpm** Triprong sinkers
Media/Volume		
0-6 hours	Simulated Gastric Fluid without enzyme, pH 1.2/*900 mL*	Simulated Gastric Fluid without enzyme, pH 1.2/*900 mL*
7-16 hours	Phosphate buffer, pH 7.4/*900 mL*	Phosphate buffer, pH 7.4/*900 mL*
Bath temperature	37.0±0.5 C	37.0±0.5 C

- ***Dissolution Acceptance Criteria***:

The Applicant proposed dissolution acceptance criteria for batch release and for stability testing of Adhansia XR™ is permissive and not acceptable. In order to have a tighter control on the (b) (4), an additional 6-hour time-point was recommended and was agreed upon during the review cycle. The FDA-approved acceptance criteria for the drug product is as follows:

Final Agreed Upon Dissolution Acceptance Criteria	Time (hours)	Percent (%) Released
	1	(b) (4)%
	6	NMT (b) (4)%
	8	(b) (4)%
	16	NLT (b) (4)%

- ***Bridging of the Formulations:***
  - *Bridging of formulations due to change in capsule shell:*

The initial drug product was developed as a (b) (4) product. (b) (4) the (b) (4) shell was replaced with (b) (4) capsule shell in the commercial TBM drug product. The bridge between the (b) (4) drug product and (b) (4) drug product is established based on the similar dissolution profile data (similarity factor '*f2*' values >50) for the 25 mg, 45 mg, 55 mg, and 100 mg (not proposed) strength drug product batches manufactured at Purdue Pharma Canada.

  - *Bridging of formulations due to a change in manufacturing process and manufacturing site:*

Two Supply Chains (1 and 2) in different countries and locations are identified for the manufacture of the proposed PRC-063 drug product. Adequate in vitro dissolution profile data for the 25 mg, 55 mg, and 85 mg strength drug product (PRC-063 ER capsules) manufactured at Purdue Pharma Canada and Purdue Pharma, LP (US) were provided that demonstrated similar dissolution profile data ('*f2*' values >50) for the two drug products. Results support the bridge for the TBM drug products (PRC-063 ER capsules) from Supply

Chain 2 to that of Supply Chain 1 (i.e., 'bridge' the formulation and manufacturing site changes).

- ***Biowaiver of the Non-Bio-Strengths***:
  A 'waiver' of the in vivo studies was requested and granted for the non-biostrengths, 25 mg, 35 mg, 45 mg, 55 mg, and 70 mg strengths of the drug product based on (**i**) compositional proportionality between active and inactive ingredients with respect to active and inactive ingredients between the drug product manufactured at Supply Chain 1 and Supply Chain 2 for all proposed strengths of the drug product, (**ii**) comparative in vitro dissolution data for all strengths of the proposed drug product manufactured at Supply Chain 1 and Supply Chain 2, and 85 mg strength bio-batch using the proposed dissolution method (**iii**) pharmacokinetic (PK) linearity over the 35 mg-85 mg dose range in pediatric subjects, and (**iv**) adequate BA/BE data for the 85 mg strength drug product.

- ***Alcohol Dose-Dumping Potential***:
  In vitro dissolution profile data for the 70 mg (b) (4) drug product in presence of varying amounts of alcohol (0-40% v/v ethanol) in 0.1 N HCl for 2 hours show that alcohol concentrations at >35% v/v have the potential to significantly increase the drug release from the proposed ER drug product. The pertinent labeling recommendation is as follows:

  Alcohol Effect
  In an invitro alcohol-induced dose dumping study, a significant increase (approximately 75%) in the release of methylphenidate was observed at alcohol concentration of 40% v/v, but not at 5%-20% v/v alcohol concentrations.

- ***Extended-Release Claim***:
  The Extended-Release claim is granted based on the following data/information: (1) in vitro dissolution data for all strengths of the drug product showing complete release of methylphenidate from each strength of the drug product at the end of 16 hours following (b) (4) once the dissolution medium is switched at 6 hours from acidic pH 1.2 to basic pH 7.4, (2) results of a relative BA study (Study 063-004) in healthy subjects with a single daily dose of the 45 mg and 55 mg (b) (4) drug product showing a prolonged Tmax for *d,l*-methylphenidate from the proposed drug product as compared to the LD, Ritalin® IR, and (3) results of a BE study (Study 063-018) demonstrating comparable PK profiles of the TBM (b) (4) formulations manufactured at the two Supply Chains.

- ***Biopharmaceutics Risk Assessment:***
  From a Biopharmaceutics perspective, the proposed drug product is a modified-release product, thus the risk of dissolution failure during batch release and stability testing is considered high. To mitigate dissolution failures, a tighter acceptance criterion is recommended at 6-hour sampling time-point to ascertain that the (b) (4) is not compromised. Furthermore, labeling recommendation is provided as a mitigation strategy for the effect of alcohol on co-admininstration with the drug product in view of the significant increases in drug release in vitro at higher alcohol concentrations.

- ***OVERALL REVIEW RECOMMENDATION:***
  From the Biopharmaceutics perspective, NDA 212038 for Adhansia XR™ (PRC-063; methylphenidate hydrochloride extended-release capsules) 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

➢ LIST OF SUBMISSIONS REVIEWED:

Submissions Reviewed	Reference ID
Original NDA Submission 212038	Dated 04/27/2018, SDN 1 (\\cdsesub1\evsprod\nda212038\0000\m2\23-qos\23p-purdue-pharma-lp\drug-product-pplp.pdf)
Response to Information Request Comment #1	Dated 09/06/2018, SDN 7 (\\cdsesub1\evsprod\nda212038\0006\m1\us\cover-0006.pdf)
Response to Information Request Comment #2	Dated 10/26/2018, SDN 10 (\\cdsesub1\evsprod\nda212038\0009\m1\us\cover-0009.pdf)
Response to Information Request Comment #3 and 4	Dated 02/04/2019, SDN 15 (\\cdsesub1\evsprod\nda212038\0014\m1\us\response-to-info-request-04dec2018-22jan2019.pdf)

➢ *DRUG PRODUCT:*

The proposed drug product (PRC-063) is composed of (b) (4) with 80% of the methylphenidate dose (see **Figure 1,** (b) (4) an immediate-release methylphenidate layer (b) (4) approximately 20% of the methylphenidate dose (b) (4)

(b) (4)

Figure 1. Schematic of the proposed PRC-063 drug product

(b) (4)

The qualitative and quantitative composition of the 85 mg proposed PRC-063 TBM drug product is provided in **Table 1**.

- ***MANUFACTURING SITES FOR THE PROPOSED DRUG PRODUCT:***

The Applicant identified two Supply Chains in the current submission for the manufacture of the proposed PRC-063 drug product. Supply Chain 1 includes (b) (4)

On the other hand, under Supply Chain 2, (b) (4) for the manufacture of the to-be-marketed (TBM) drug product, PRC-063 ER capsules.

To bridge the TBM drug product (PRC-063 ER capsules) from Supply Chain 1 and Supply Chain 2, the Applicant provided in vitro dissolution profile data for the 25 mg, 55 mg, and 85 mg strength drug product (PRC-063 ER capsules) and conducted a bioequivalence (BE) study, 063-018, with the 85 mg strength TBM PRC-063 ER capsules.

Table 1. Composition of Adhansia XR™ (Methylphenidate Hydrochloride Extended- Release (b) (4) Capsules), 85 mg, from Canadian and US Supply Chains

Component and Quality Standard (% w/w)	BE Study 063-018		Stability Studies		Commercial
	Canada	USA	Canada	USA	USA
(b) (4)					

Component and Quality Standard (% w/w)	BE Study 063-018		Stability Studies		Commercial
	Canada	USA	Canada	USA	USA
[redacted]					(b) (4)
Total Finished Product	100.00	100.00	25 mg: 100.0 35 mg: 100.0 45 mg: 100.0 55 mg: 100.0 70 mg: 100.0 85 mg: 100.0	25 mg: 100.0 35 mg: 100.0 45 mg: 100.0 55 mg: 100.0 70 mg: 100.0 85 mg: 100.0	25 mg: 100.0 35 mg: 100.0 45 mg: 100.0 55 mg: 100.0 70 mg: 100.0 85 mg: 100.0

- ***BCS DESIGNATION***

An official BCS designation for the proposed drug product was not requested in the current submission.

- ***Solubility:***

The active ingredient in the proposed drug product is methylphenidate hydrochloride, which is a white to off-white crystalline drug substance. It has 2 chiral centers and therefore, there are four potential isomers, erythro and threo isomers. The pka of methylphenidate hydrochloride is 8.71 at 21.5 C. The current submission does not contain any equilibrium solubility data for methylphenidate hydrochloride in buffer solutions across the physiological pH range 1.2-6.8.

However, it should be noted that the Applicant stated methylphenidate hydrochloride to be highly soluble in water. In addition, methylphenidate hydrochloride is not stable at pH>7.0. It undergoes degradation to methylphenidate related substance or compound A ([redacted] (b) (4)) and the erythro isomer of methylphenidate.

Reviewer's Assessment of Drug Substance Solubility:

The equilibrium solubility data for the drug substance cannot be assessed due to the lack of pertinent information in the current submission.

- ***Permeability/Absorption:***

The Applicant relied on the clinical pharmacology information referenced in the US Prescribing Information for Ritalin® LA and Ritalin® IR tablets. In the current submission, the Applicant conducted a bioavailability (BA) study in pediatric patients (Study 063-017) with 35 mg, 55 mg, and 85 mg proposed drug product (PRC-063) manufactured at Purdue Pharma, Canada. The

median T_{max} was found to be between 9.00-9.97 hours across the three dose groups. The C_{max} and AUC was found to increase with increasing dose, indicating dose-linearity over 35 mg to 85 mg of the proposed drug product (PRC-063).

Reviewer's Comment:
Based on literature reports, methylphenidate exhibits moderate-high gastro-intestinal permeability.

Particle Size Distribution:
According to the Applicant, the particle size distribution (PSD) of methyphenidate hydrochloride would not have an impact on the in vivo performance of the drug product as the drug substance is (b) (4) for the manufacture of PRC-063 ER capsules.

- ***DISSOLUTION INFORMATION:***

Dissolution testing was identified as a critical quality attribute (CQA) for the proposed drug product and is utilized as a quality control tool during the product development process, for the batches used in the pivotal BA and clinical PK studies, and for batches on stability. The dissolution method was also utilized to select the final drug product formulation, the final manufacturing process, to bridge the formulations from Supply Chain 1 and Supply Chain 2, and for the 'waiver' of in vivo bioequivalance studies for the 25 mg, 35 mg, 45 mg, 55 mg, 70 mg strengths of the drug product.

- ***PROPOSED DISSOLUTION METHOD:***

The proposed dissolution method (MPX-FP-DS-05 at Purdue Pharma, Canada, is same as TM-0282 at Purdue Pharma, L.P., US) and dissolution acceptance criteria proposed for the dissolution testing of the proposed drug product are shown in **Table 2.**

Table 2. Proposed Dissolution Method (MPX-FP-DS-05 at Purdue Pharma, Canada and TM-0282 at Purdue Pharma, L.P., US) and Dissolution Acceptance Criteria for Adhansia XR™ (Methylphenidate Hydrochloride Extended-Release Capsules), 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg Strength

Parameters	Method	
Apparatus/Speed *Sinkers* *Media/Volume* 0-6 hours 7-16 hours *Bath temperature*	USP Apparatus 2 (paddle)/(b) (4) rpm Triprong sinkers Simulated Gastric Fluid without enzyme, pH 1.2/*900 mL* Phosphate buffer, pH 7.4/*900 mL* 37.0±0.5 C	
Dissolution Acceptance Criteria	Time (hours)	Percent (%) Released
	(b) (4)	(b) (4) %
		(b) (4) %
		NLT (b) (4) %

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(b) (4)

[redacted]

Discriminating Ability of the Proposed Dissolution Method:

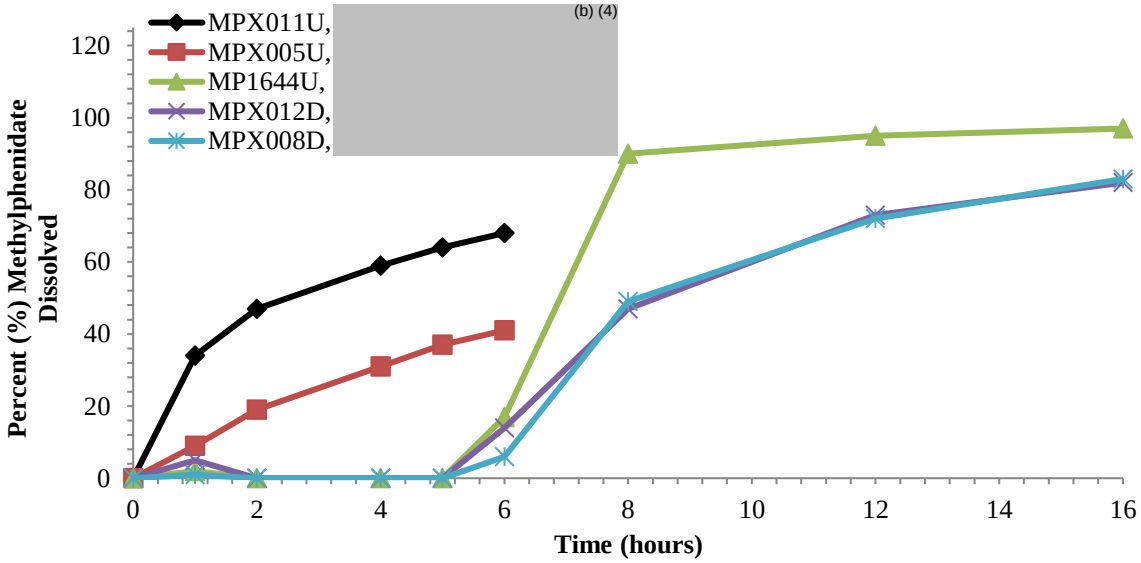
To support the proposed dissolution method, five formulations of the Methylphenidate (b) (4) beads were manufactured with varying amounts of the (b) (4) (b) (4) (see **Table 3**). The dissolution profile data (**Figure 5**) was

obtained using the earlier version of the proposed dissolution method, MPX-FP-DS-04. It should be noted that the dissolution methods MPX-FP-DS-04 and MPX-FP-DS-05 (final proposed dissolution method) are very similar, except (b) (4). The final proposed dissolution method MPX-FP-DS-05 includes 1 hour, 6 hour, 8 hour and 16 hours sampling time-points, whereas the earlier version, MPX-FP-DS-04 (b) (4)

Table 3. Formulations containing varying amounts of (b) (4) and (b) (4) to support the discriminating ability of the proposed dissolution method

Ingredients	Formula A MEP (b) (4) beads MPX011U	Formula B MEP (b) (4) beads MPX005U	Formula C MEP (b) (4) beads MP1644U	Formula D MEP (b) (4) beads MPX012D	Formula E MEP (b) (4) beads MPX008D
Methylphenidate IR (b) (4)	(b) (4)				

Figure 5. Mean dissolution profile data for the aberrant formulations of the drug product to support the discriminating power of the proposed dissolution method (MPX-FP-DS-04)



From **Figure 5**, the formulations MPX011U and MPX005U containing (b) (4), released methylphenidate immediately within 30 minutes. On the other hand, formulations containing (b) (4) started releasing methylphenidate after 6 hours. Based on the dissolution profile data for the aberrant formulations, the proposed dissolution method is capable of rejecting batches with differences in the amount of the (b) (4) tested.

- ***PROPOSED DISSOLUTION ACCEPTANCE CRITERIA:***

The Applicant proposed [redacted] (b) (4) as the dissolution acceptance criteria for batch release and stability testing of each strength of the proposed drug product.

Dissolution Data at Batch Release:

The dissolution profile data for Adhansia XR™, 25 mg, 55 mg, and 85 mg drug product manufactured at Purdue Pharma Canada and Purdue Pharma, LP (US) are shown in **Tables 4a-4c** and in **Table 5**. Lots MPGC1645-25A, 55A, and 85A (**Table 4a**), and Lots MPGC1646-25A, 55A, and 85A (**Table 4b**) were manufactured at Purdue Pharma Canada. On the other hand, Lot CW6DG0 (25 mg), XW6DM0 (55 mg), and CW6HB0 (85 mg) were manufactured at Purdue Pharma, LP (US).

Table 4a. Mean dissolution profile data for the drug product batches (Lots MPGC1645-25A, 55A, and 85A) manufactured at Purdue Pharma Canada

Sample Information		1 hour	6 hour	8 hour	16 hour	f_2
MPGC1645-85A[1]	Mean (n=12)	20	26	45	96	NA
	Minimum	[redacted] (b) (4)				
	Maximum					
	%RSD	2.6	1.5	3.6	1.4	
MPGC1645-55A[2]	Mean (n=12)	20	26	45	96	100
	Minimum	[redacted] (b) (4)				
	Maximum					
	%RSD	1.0	4.3	5.9	2.1	
MPGC1645-25A[3]	Mean (n=12)	20	26	45	96	100
	Minimum	[redacted] (b) (4)				
	Maximum					
	%RSD	2.8	4.3	5.7	1.9	
Specification		[redacted] (b) (4)				

f_2= Calculated Similarity Factor with Respect to 85 mg Strength (Lot No. MPGC1645-85A).

Table 4b. Mean dissolution profile data for the drug product batches (Lots MPGC1646-25A, 55A, and 85A) manufactured at Purdue Pharma Canada

Sample Information		1 hour	6 hour	8 hour	16 hour	f_2
MPGC1646-85A[1]	Mean (n=12)	20	25	42	94	84
	Minimum	[redacted] (b) (4)				
	Maximum					
	%RSD	1.8	2.5	2.8	2.0	
MPGC1646-55A[2]	Mean (n=12)	20	25	41	94	80
	Minimum	[redacted] (b) (4)				
	Maximum					
	%RSD	2.3	2.7	2.7	1.9	
MPGC1646-25A[3]	Mean (n=12)	21	26	43	96	91
	Minimum	[redacted] (b) (4)				
	Maximum					
	%RSD	2.9	3.1	3.0	1.6	
Specification		[redacted] (b) (4)				

f_2= Calculated Similarity Factor with Respect to 85 mg Strength (Lot No. MPGC1645-85A).

Table 4c. Mean dissolution profile data for the drug product batches (Lot CW6DG0 (25 mg), XW6DM0 (55 mg), and CW6HB0 (85 mg) manufactured at Purdue Pharma, LP (US)

Sample Information		1 hour	6 hour	8 hour	16 hour	f_2
CW6HB0	Mean (n=12)	20	26	44	93	86
	Minimum	(b) (4)				
	Maximum					
	%RSD	2.0	4.1	3.9	2.7	
XW6DM0	Mean (n=12)	20	27	47	96	91
	Minimum	(b) (4)				
	Maximum					
	%RSD	4.3	3.5	2.2	1.8	
CW6DG0	Mean	20	27	46	94	90
	Minimum	(b) (4)				
	Maximum					
	%RSD	4.6	4.8	3.6	1.8	
Specification		(b) (4)				NLT 50

f_2= Calculated Similarity Factor with Respect to 85 mg Strength (Lot No. MPGC1645-85A).

From **Tables 4a-4c,** mean dissolution profile data for drug product batches manufactured at Purdue Pharma Canada and Purdue Pharma, LP (US) are similar, with the similarity factor '*f2*' values >50 for batches manufactured at the Canadian and the US sites. The dissolution profile data for 25 mg, 55 mg, and 85 mg strength drug product support the proposed dissolution acceptance criteria of "(b) (4)*% in 1 hour and* (b) (4)*% in 8 hours".*

Table 5. Mean dissolution profile data for 25 mg, 45 mg, 55 mg, and 100 mg strengths of the proposed drug product batches manufactured at Purdue Pharma Canada

Table 2.3.P 9 In-vitro Dissolution Results Comparing Hard Gelatin and HPMC VCaps® Plus Capsules

Time (hr)	25 mg (b) (4)	25 mg	45 mg	45 mg	55 mg	55 mg	100 mg	100 mg (b) (4)
1	21	20	19	19	21	22	21	21
	(b) (4)							
	RSD 3.8%	RSD 6.0%	RSD 2.0%	RSD 2.4%	RSD 2.5%	RSD 2.0%	RSD 2.4%	RSD 2.7%
6	25	24	24	24	25	25	25	25
	(b) (4)							
	RSD 3.3%	RSD 2.7%	RSD 1.7%	RSD 2.7%	RSD 3.5%	RSD 1.9%	RSD 1.9%	RSD 1.8%
8	46	43	42	45	47	46	45	45
	(b) (4)							
	RSD 4.3%	RSD 3.9%	RSD 2.3%	RSD 2.9%	RSD 3.7%	RSD 3.3%	RSD 3.8%	RSD 5.7%
12	95	89	83	86	92	91	89	89
	(b) (4)							
	RSD 3.0%	RSD 3.6%	RSD 3.0%	RSD 1.4%	RSD 2.3%	RSD 1.8%	RSD 3.1%	RSD 1.7%
16	102	96	97	98	100	98	97	98
	(b) (4)							
	RSD 2.6%	RSD 3.20%	RSD 1.7%	RSD 1.2%	RSD 2.3%	RSD 2.2%	RSD 2.6%	RSD 1.9%
f_2	69		81		90		98	

a. Bulk bead Lot MP1530 was used for the 45 mg strength capsule, all other strengths were encapsulated with Bulk bead Lot 0150/2016

Dissolution Data at Long-Term and Accelerated Stability Testing:

The dissolution profile data for the 25 mg, 35 mg, 45 mg, 55 mg, and 70 mg strengths of the drug product manufactured at Purdue Pharma, Canada, and Purdue Pharma, LP (US) exhibit no significant trend in the dissolution data at long-term (25 C/60% RH) conditions for 36 months and on accelerated (40 C/75% RH) stability conditions for 9 months (refer to \\cdsesub1\evsprod\nda212038\0000\m3\32-body-data\32p-purdue-pharma-canada\32p8-stab\stability-data.pdf for drug product batches manufactured at Purdue Pharma, Canada and

\\cdsesub1\evsprod\nda212038\0000\m3\32-body-data\32p-purdue-pharma-lp\32p8-stab\stability-data.pdf for drug product batches manufactured at Purdue Pharma, LP (US)).

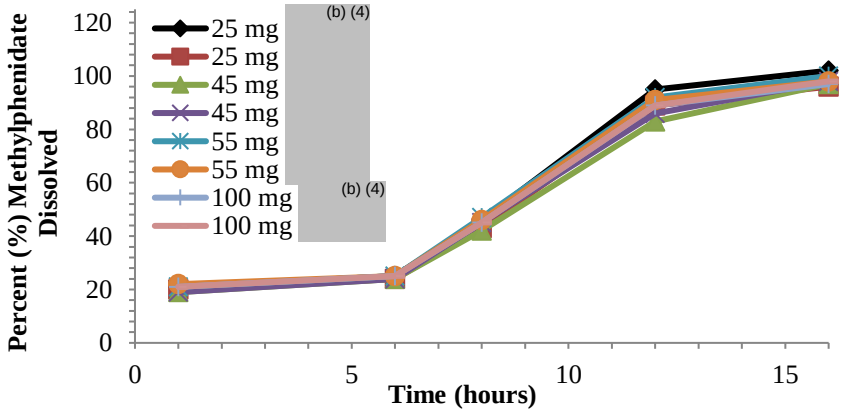
However, because (b) (4), a 6-hour time-point was recommended in order to have a tighter control on the (b) (4). The Applicant proposed NMT (b) (4)% at 6 hours, which was found to be acceptable.

Reviewer's Assessment:
Based on the totality of the dissolution data, from a Biopharmaceutics perspective, the proposed dissolution method is adequate for batch release and stability testing of the propopsed Adhansia XR™. The analytical method (HPLC/UV) associated with the proposed dissolution method will be evaluated by the CMC Reviewer.

- ***Bridging of the Formulations:***
- *Bridging of formulations due to change in capsule shell:*

The initial drug product was developed as a (b) (4) product. Bulk beads of the drug product were encapsulated in (b) (4) shells to manufacture various strengths of the drug product and used for early product development activities, including stability testing and clinical trials. However, forced degradation studies and accelerated stability studies on the (b) (4) drug product demonstrated (b) (4). Therefore, in order to (b) (4) the (b) (4) shell was replaced with (b) (4) capsule shell in the commercial TBM drug product. To bridge the (b) (4) drug product and (b) (4) drug product, comparative dissolution testing was conducted for 25 mg, 45 mg, 55 mg, and 100 mg strengths of the proposed drug product batches manufactured at Purdue Pharma Canada (see **Figure 6**).

Figure 6. Mean dissolution profile data for the 25 mg, 45 mg, 55 mg, and 100 mg drug product batches manufactured with (b) (4) shell and (b) (4) capsule shell using the proposed dissolution method



The mean dissolution profile data for 25 mg, 45 mg, 55 mg, and 100 mg drug product batches manufactured at Purdue Pharma Canada with (b) (4) shell and (b) (4) capsule shell (RD-R-MPX-15-24 and RD-

R-MPX-16-04) using the proposed dissolution method are similar, with similarity factor '*f2*' values >50.

Additionally, the (b) (4) drug product were used in the clinical studies 063-004, 063-005, 063-006, 063-007, and 063-016 to determine the pharmacokinetic profile and in the placebo-controlled phase 3 studies, 063-009, 063-008, 063-010, 063-012, and 063-013 for safety and efficacy evaluation.

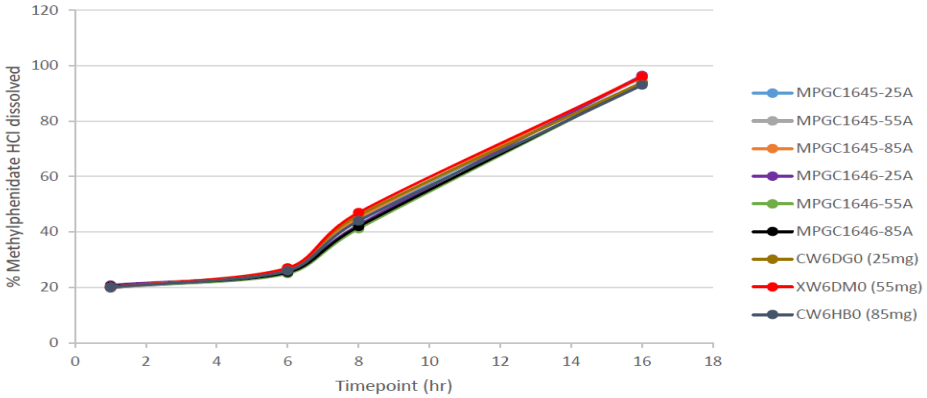
The (b) (4) drug product manufactured in Purdue Pharma, Canada were used in the clinical studies 063-017 and 063-018 to determine the pharmacokinetic profile and in the placebo-controlled phase 3 studies, 063-015 for safety and efficacy evaluation.

➢ *Bridging of formulations due to a change in manufacturing process and manufacturing site:*
Two Supply Chains are identified in the current submission for the manufacture of the proposed PRC-063 drug product. Supply Chain 1 includes (b) (4) .

On the other hand, Supply Chain 2 includes (b) (4) for the manufacture of the to-be-marketed (TBM) drug product, PRC-063 ER capsules.

To 'bridge' the TBM drug product (PRC-063 ER capsules) from Supply Chain 2 to that of Supply Chain 1, the Applicant provided in vitro dissolution profile data (see **Figure 7** and **Tables 4a-4c)** for the 25 mg, 55 mg, and 85 mg drug product manufactured at Purdue Pharma Canada and Purdue Pharma, LP (US). Lots MPGC1645-25A, 55A, and 85A, and Lots MPGC1646-25A, 55A, and 85A were manufactured at Purdue Pharma Canada. On the other hand, Lot CW6DG0 (25 mg), XW6DM0 (55 mg), and CW6HB0 (85 mg) were manufactured at Purdue Pharma, LP (US).

Figure 7. Mean dissolution profile data for the drug product batches manufactured at Purdue Pharma, Canada and Purdue Pharma, LP (US)



From **Figure 7**, mean dissolution profile data for drug product batches manufactured at Purdue Pharma Canada and Purdue Pharma, LP (US) are similar, with the similarity factor '*f2*' values >50 for batches manufactured at the Canadian and the US site.

Additionally, the Applicant conducted a bioequivalence (BE) study, 063-018, with the 85 mg strength TBM PRC-063 ER capsules to bridge the two Supply Chains, Purdue Pharma Canada and Purdue Pharma, LP (US). The 90% confidence interval for the mean ratios for Cmax and $AUC_{0-\infty}$ for the drug products between the two sites are between 80-125% indicating that the products from the two Supply Chains are bioequivalent. Refer to Office of Clinical Pharmacology (OCP) review for details.

Based on the totality of the in vitro dissolution data and in vivo bioavailability studies, adequate 'bridging data' is provided to bridge the changes in formulation and manufacturing site for the commercial TBM drug product to the formulations used in early product development and clinical studies.

- ***Alcohol Dose-Dumping Potential:***

Dissolution testing was conducted for the 70 mg (b) (4) drug product in presence of varying amounts of alcohol (0-40% ethanol) to investigate the alcohol-induced dose-dumping potential for the proposed ER drug product. The alchohol dose-dumping study was conducted for up to 2 hours using the originally proposed dissolution testing condition, as shown in **Table 8**. Note that the Division of Biopharmaceutics typicaly recommends that such study be conducted to obtain the full profile, with particular attention paid to the first 2 hours.

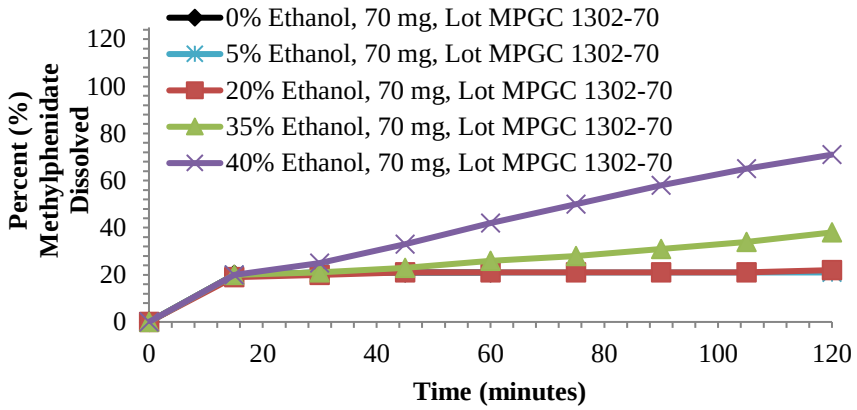
Table 8. Dissolution parameters for alcohol-dose dumping study of Adhansia XR™ (Methylphenidate Hydrochloride Extended-Release Capsules), 70 mg strength (b) (4)

Parameters	Method
Apparatus/Speed	USP Apparatus 2 (paddle)/100 rpm
Media/Volume	
0-2 hours	0.1 N HCl/*900 mL* With 0%, 10%, 20%, 35%, and 40% v/v ethanol
Bath temperature	37.0±0.5 C
Sampling Time-Points	15, 30, 45, 60, 75, 90, 105, and 120 minutes

The in vitro dissolution profile data (N=12 units) for 70 mg strength (b) (4) drug product (Lot no. MPGC 1302-70) manufactured at Purdue Pharma, Canada, in presence of 0%, 10%, 20%, 35%, and 40% ethanol is provided in **Figure 8** and in **Appendix I (Table 3)**.

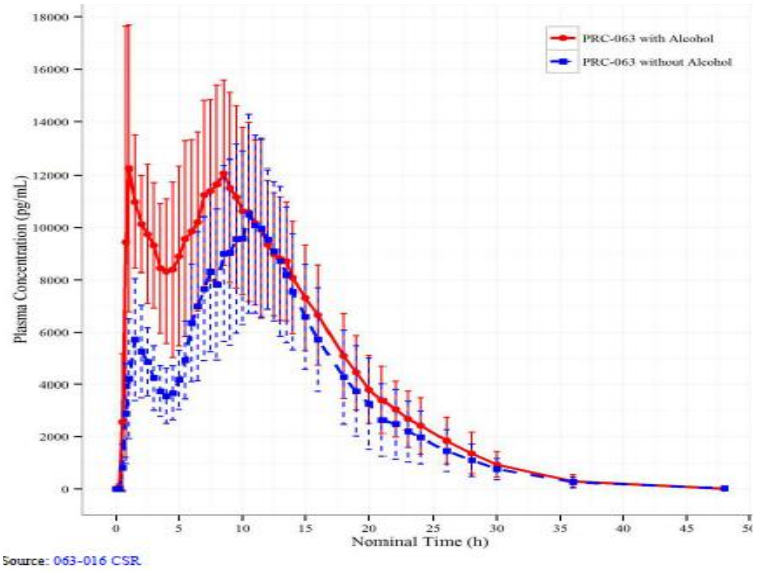
Figure 8 shows that ethanol concentration at >35% v/v increases the release of methylphenidate from the 70 mg strength drug product (*f2*<50). At 40% v/v ethanol, >75% release of methylphenidate is observed from the drug product in 2 hours.

Figure 8. Effect of alcohol on mean dissolution profile data for the 70 mg strength drug product (Lot No. MPGC 1302-70) manufactured at Purdue Pharma, Canada



A bioavailability (BA) study 063-016 was conducted with a single dose of 70 mg (b) (4) drug product manufactured at Purdue Pharma, Canada, with 250 mL 40% alcohol (see **Figure 9** for the concentration-time profiles). More rapid release of *d,l*-methylphenidate with shortened T_{max} (~1 hour), as well as increased Cmax and $AUC_{0-\infty}$, were observed. Refer to OCP review for details.

Figure 9. Mean pharmacokinetic profile for *d,l*-methylphenidate following co-administration of 70 mg (b) (4) drug product and 250 mL 40% alcohol from the bioavailability Study 063-016



The Applicant's proposed labeling for the alcohol-induced dose-dumping potential of the proposed drug product is as follows:

Based on the observed results, the recommended labelling will be – " (b) (4)

(b) (4)

Based primarily on the the in vitro dissolution data,this Reviewer recommends the following labeling language for the proposed drug product:

Alcohol Effect
In an in vitro alcohol-induced dose dumping study, an appreciable increase in the release of methylphenidate was observed at alcohol concentration of 40% v/v, but not at 5%-20% v/v alcohol concentrations.

- ***Biowaiver:***

The current submission contains a request for waiver of in vivo bioavailability/bioequivalance studies for the lower 25 mg, 35 mg, 45 mg, 55 mg, and 70 mg strengths based on 21 CFR 320.22(d)(2)(i)-(iii).

The information/data are provided to support the biowaiver request include (**i**) in vivo BA/BE data (Study 063-018) for the 85 mg strength drug product to bridge the Supply Chain 1 to Supply Chain 2, (**ii**) PK linearity over the 35-85 mg dosing range in pediatric subjects (Study 063-017), (**iii**) compositional proportionality with respect to active and inactive ingredients between the drug product manufactured at Supply Chain 1 and Supply Chain 2 for all proposed strengths, and (**iv**) comparative in vitro dissolution profiles for all strengths of the proposed drug product manufactured at Supply Chain 1 and Supply Chain 2, and 85 mg strength bio-batch using the proposed dissolution method.

Based on the totality of the information, the biowaiver request for the 25 mg, 35 mg, 45 mg, 55 mg, and 70 mg strengths is GRANTED.

- ***Extended-Release Claim:***

To support the Extended-Release (ER) claim of the proposed Adhansia XR™ (PRC-063; methylphenidate hydrochloride extended-release capsules), the following information/data are assessed to support the claim, based on 21 CFR§320.25(f)(1)i-iv:

1. Not more than 35% release of methylphenidate is observed in acidic pH 1.2 medium up to 6 hours (b) (4). Attainment of near complete release of the methylphenidate is achieved in 16 hours in the in vitro dissolution studies following change of the acidic dissolution medium from SGF, pH 1.2 to basic phosphate buffer, pH 7.4 at 6 hours (refer to **Figure 6**).

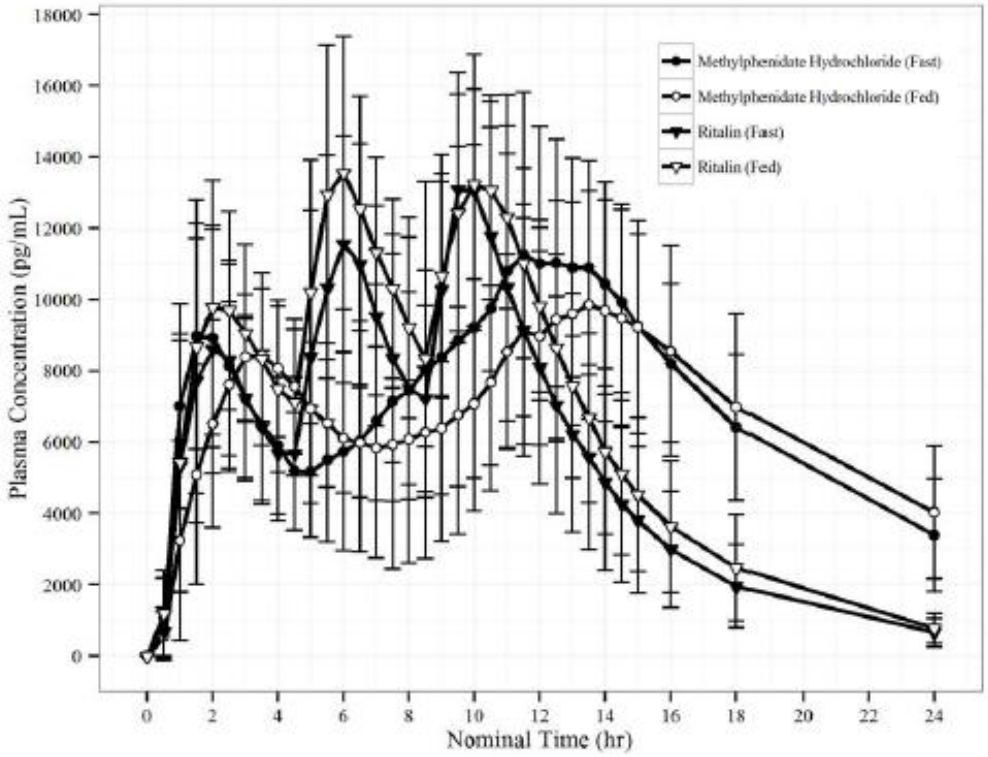
2. Following administration of single oral doses of 45 mg and 55 mg (b) (4) drug product in healthy subjects (Study 063-004, see **Figure 10**), the median Tmax for *d,l-*

methylphenidate was approximately 11.5~12.5 hours as compared to (i) approximately 9.50~6.04 hours following administration of 20 mg Ritalin® IR tablet three times a day, and (ii) approximately 6.8 hours for 18 mg strength Concerta®. The prolonged Tmax and rise of concentration-time curves of the proposed drug product, as well as comparable drug exposure, as compared to the LD, Concerta®, and Ritalin® IRprovide support for the extended-release claim for the proposed drug product.

3. The PK profiles of the TBM (b) (4) formulations manufactured at the two Supply Chains (Study 063-018) were superimposable and two products are deemed bioequivalent.

Based on the totality of the evidence, the proposed drug product fulfills the requirement of an extended-release dosage form, consisting of both immediate-release and delayed-release components.

Figure 10. Mean pharmacokinetic profile for *d,l*-methylphenidate following single oral administration of 45 mg and 55 mg (b) (4) drug product and 20 mg Ritalin® IR (LD) three times a day in healthy subjects from the Study 063-004



➢ ***BIOPHARMACEUTICS RISK ASSESSMENT:***

From a Biopharmaceutics perspective, the proposed drug product is a modified-release product; therefore, the risk of dissolution failure during batch release and stability testing is considered high. To mitigate dissolution failures, a tighter acceptance criteria is recommended at 6- and 8-hour sampling time-points to ascertain that the (b) (4) is not compromised. Furthermore, this Reviewers recommends that labeling

include mitigation strategy for the effect of alcohol on co-admininstration with the drug product in view of the significant increases in drug release in vitro at higher alcohol concentrations.

- ***POST-APPROVAL COMMITMENTS:*** **None**

- ***LIST OF DEFICIENCIES:*** **None**

- ***OVERALL REVIEW RECOMMENDATION:***

From the Biopharmaceutics perspective, NDA 212038 for Adhansia XR™ (PRC-063; methylphenidate hydrochloride extended-release capsules) containing 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg of methylphenidate hydrochloride is recommended for **APPROVAL**.

APPENDIX I

Table 1. Dissolution Profile Data for the 25 mg Proposed Drug Product (PRC-063 ER) in 900 mL Dissolution Medium using USP Apparatus 2 at (b) (4) rpm at 37 C

(b) (4)

(b) (4)

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Table 4. Effect of varying concentrations of ethanol (0%-40% v/v) on mean dissolution profile data for the 70 mg strength drug product manufactured at Purdue Pharma Canada, Lot No. MPGC 1302-70

Time Point (min)	Mean Cumulative Percent (%) Methylphenidate Released at Sampling Time (%RSD)							
	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
Control (0% ethanol)	20 (1.5)	21 (1.2)	21 (1.1)	21 (1.2)	21 (1.3)	21 (1.3)	21 (1.2)	21 (1.0)
5% v/v ethanol	20 (1.9)	21 (1.1)	21 (1.1)	21 (1.3)	21 (1.4)	21 (1.3)	21 (1.5)	21 (1.3)
20% v/v ethanol	19 (2.5)	20 (1.2)	21 (1.4)	21 (1.3)	21 (1.2)	21 (1.5)	21 (1.2)	22 (1.0)
35% v/v ethanol	20 (1.5)	21 (1.2)	23 (1.1)	26 (1.1)	28 (1.3)	31 (1.7)	34 (2.3)	38 (3.4)
40% v/v ethanol	20 (1.9)	25 (6.6)	33 (16.1)	42 (18.8)	50 (18.7)	58 (16.4)	65 (15.0)	71 (14.5)

Parnali Chatterjee

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Ta-Chen Wu

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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	(b) (4) of drug substance in drug product.	L	(b) (4) release and stability testing	Acceptable	
Content uniformity		L	(b) (4) controls	Acceptable	
Microbial limits	(b) (4)	L	Release testing	Acceptable	
dissolution	(b) (4)	M	Release and stability testing	Acceptable	
Alcohol dose dumping		H	Language in labeling	Acceptable	

David Claffey

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