CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209311Orig1s000

PRODUCT QUALITY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 6 AUG 2018

TO: NDA 209311

THROUGH: DPP/OND

FROM: David Claffey, OPQ

SUBJECT: OPQ Second Cycle Approval Recommendation

APPLICATION/DRUG: NDA 209311 Jornay PM
(methylphenidate hydrochloride) extended-release capsules

OPQ made an approval recommendation for NDA 209311 on 13 JUN 2017 after the first review cycle. A reevaluation of the manufacturing sites was made during this review cycle and they were found to be adequate by Steven Hertz on 20 JUL 2018. OPQ provided labeling edits which were accepted by the applicant. Therefore, OPQ recommends approval of this application from a product quality perspective.

Note that discussion took place during this review cycle concerning the dosage form designation. '[redacted]' was proposed by the applicant. The use of 'delayed release' was also discussed due to the product's unique 6-8 hour delayed release characteristics. The use of either of these options would have helped differentiate this product from other marketed products with the same strength and nonproprietary name, but different pharmacokinetics/dosing. However, the draft 'Product Title' guidance, and USP guidelines state that a product with delayed release and extended release characteristics, such as this product, should be labeled as an 'extended release' product. The clinical review team accepted the 'extended release' dosage form designation with additional labeling language to alert HCP and patients that this product needs to be taken only in the evening – not the morning like all other marketed methylphenidate products.

QUALITY ASSESSMENT

Recommendation: Approval

NDA 209311
Review #1

Drug Name/Dosage Form	JORNAY PM Methylphenidate Hydrochloride Extended Release Capsules
Strength	20 mg, 40 mg, 60 mg, 80 mg, 100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Ironshore Pharmaceuticals and Development Inc.
US agent, if applicable	Baker Botts L.L.P., Ms. Margaret Sampson

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD-1	*9/30/2016*	*All*
SD-3	*10/28/2016*	*Drug product (12 month stability)*
SD-22	*02/22/2017*	*Drug product (stability update)*
SD-23	*28 FEB 2017*	*Biopharmaceutics*
SD-26	*04/03/2017*	*Drug product and Process*
SD-31	*06/07/2017*	*Biopharmaceutics*
SD-33	*06/13/2017*	*Biopharmaceutics*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Haripader Sarker	Ben Stevens
Drug Product	Rao Kambhampati	Wendy Wilson-Lee
Process/ Microbiology	Hang Guo	Bo Jiang
Facility	Steven Hertz	Ruth Moore
Biopharmaceutics	Parnali Chatterjee	Angelica Dorantes
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	5/15/2017	Review filed in DARRTS
	Type III			Satisfactory	N/A	Complies with USP <661> and USP (<671>. All components (b) (4) conform to 21 CFR 177 and 178 and specifications and drawings are acceptable.
	Type III			Satisfactory	N/A	Used in packaging of other FDA approved solid oral dosage forms. Specifications and drawings are acceptable.
	Type III			Satisfactory	N/A	Complies with USP <661> and USP (<671>. All components (b) (4) conform to 21 CFR 177 and 178 and specifications are and drawings are acceptable.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Methylphenidate hydrochloride modified release capsules (HFD-200)	118074	IND (Applicant conducted clinical studies under this IND)
Ritalin	NDA 10187	Listed Drug basis for submission

2. CONSULTS: None

Executive Summary

I. Recommendations and Conclusion on Approvability

Recommend approval. Both the drug product process and release testing and controls, especially the dissolution test, were found to support the manufacture of a product of consistent quality.

II. Summary of Quality Assessments

A. Product Overview

Several methylphenidate extended-release dosage forms are currently marketed. Generally, they are administered in the morning, release throughout the day and are designed to leave low serum levels in the evening to avoid insomnia. This product is unique in that it is administered in the evening between 6:30 and 9:30 pm. A delayed-release coating postpones release of methylphenidate until the following morning – providing low overnight serum levels to allow sleep and then adequate serum levels on awakening to allow the patient to complete their morning tasks. An extended-release coating then allows release of the drug to continue through the morning and afternoon hours.

Five dosage strengths are proposed - 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg. The product is a capsule filled with (b) (4) beads with three distinct sequential coatings. The first inner coating is composed of methylphenidate hydrochloride. The middle layer is an extended-release coating. The outer layer is a delayed-release coating – designed to dissolve at pH >7.0.

After ingestion, the capsule dissolves, releasing the beads to travel through the stomach and small intestine. On reaching the higher pH (>7) environment closer to the large intestine, the outer delayed-release coating dissolves. This exposes the extended-release coating to the aqueous environment, causing it to swell, allowing the methylphenidate hydrochloride in the inner coating to dissolve and escape through the coating. This allows for release of methylphenidate to the plasma at a controlled rate following an initial delay of approximately 8 to 10 hours.

The obvious risk associated with this product is the premature dissolution of the delayed release coating resulting in early release of drug causing interrupted sleep. Disruption of the inner extended-release coating could result in dose dumping. Manufacturing process and release controls are in place to reduce this risk.

The benefits of this product appear to be related to administration convenience. This is possibly because the caregiver will be administering the dose while the patient is more compliant, as their serum levels are not at their lowest point during the morning hours. Insomnia was the most frequent adverse event reported in the clinical studies. Labeling includes instructions to adjust the timing of the dose for each patient to optimize efficacy and limit adverse effects.

Proposed Indication(s) including Intended Patient Population	***ADHD in children***
Duration of Treatment	***Chronic***
Maximum Daily Dose	***100 mg***
Alternative Methods of Administration	***None.***

A. Quality Assessment Overview

Five dosage strengths are proposed - 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg. Capsule strengths differ only in their (b) (4) capsule size and color). They are packaged in HDPE bottles (b) (4) with desiccant. The drug product is intended for once-daily oral administration in the evening for patients 6 years of age and older with ADHD.

Adequate drug product release and stability controls were proposed. Three registration batches of each strength were manufactured. Each met specification. The provided 12-month stability data were found to support an 18 month drug product expiry period, rather than the applicant's proposed (b) (4) months.

Manufacturing Process: The drug product phase 1 and phase 2 clinical batches were manufactured using (b) (4), while the phase 3 clinical batches were manufactured using the (b) (4) Clinical studies were conducted to bridge the two different manufacturing processes (b) (4) is the proposed manufacturing process for commercial manufacturing.

The proposed commercial drug product manufacturing process consists of (b) (4) The proposed commercial batch size ((b) (4) kg) is within 10x of the registration batch sizes (b) (4) kg), and the process parameters at the proposed commercial scale are sufficiently justified.

The controls and in-process tests were found adequate after Agency requests for (b) (4) These additional process parameters and in-process controls reduce the risk to the patient of failing assay and dissolution and will result in product of more consistent quality.

In vitro dissolution method: Considering its unique release profile, the dissolution method is a critical drug product control. It ensures that each batch reproducibly has a dissolution profile similar to the clinical drug product batches. The dissolution method development report was extensive. It demonstrated that the applicant developed and validated a robust drug product dissolution control. The dissolution method is an atypical three-stage method where the product spends the first two hours at pH 1 (replicating gastric conditions), the next four hours at pH 6.0 (post gastric conditions) and hours 6 through 24 at pH 7.0. The following are the dissolution acceptance criteria.

Parameter	Percent (%) Release Limits of Methylphenidate
Acceptance Criteria	Stage 1 (2 hours) NMT (b)(4)% Stage 2 (6 hours) NMT % Stage 3 (12 hours) (b)(4)% (14 hours) (b)(4)% (24 hours) NLT (b)(4)%

It is designed to ensure that (b)(4)% of the drug releases over the first six hours at pH <7 – this approximates the overnight hours. The 12-hour time point at pH 7.0 ensures that the drug begins to release after the delay. The 14-hour time point ensures that the drug continues to release at a controlled rate, and the final 24-hour time point ensures that at least (b)(4)% of the drug releases.

The method was found to have discriminating power to detect formulation and manufacturing changes and reject batches that do not exhibit similar dissolution profile. An IVIVC was proposed but the applicant was informed that it was unacceptable. It was withdrawn by the applicant. (b)(4)

. The Applicant performed adequate in vitro and in vivo bridging of the formulations across formulation changes, manufacturing site changes, and manufacturing process changes throughout the proposed drug products development process. Dose dumping was found at ethanol concentration of >40% - this information will be added to the label.

The manufacturing sites were found adequate by the OPF facilities reviewer. The drug substance is well known. Its details were referenced to DMF which was found adequate to support this application.

B. Special Product Quality Labeling Recommendations (NDA only)

- Statement about dose dumping at ethanol concentration of >40%
- The product should be administered immediately on mixing with apple sauce. Storage may impact drug product quality and release.

C. Final Risk Assessment (see Attachment)

Appears this way on original

ENVIRONMENTAL ANALYSIS

R Regional Information

Environmental Analysis

In accordance with 21 CFR 25.31(b), the applicant claimed a categorical exclusion from the requirement to prepare an EA as the amount of waste to be generated is expected to be small and also stated that no extraordinary circumstances exist. The applicant stated that Methylphenidate hydrochloride (HCl) Modified Release (MR) Capsules, HLD200, qualifies for a categorical exclusion as the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 ppb. The applicant's claim is supported by performing the calculations as indicated under Section III, Part 2 of the FDA published Guidance for Industry document on EA (July 1998, CMC 6, Revision 1).

Environmental Introduction Concentration (EIC)-Aquatic (ppb) = A x B x C x D where

A = kg/year produced for direct use (as active moiety)

B = 1/liters per day entering POTWs*

C = year/365 days

D = 10^9 µg/kg (conversion factor)

*1.214 x 10^{11} liters per day entering publicly owned treatment works (POTWs), Source: *1996 Needs Survey, Report to Congress.*

In the case of HLD200:

EIC-Aquatic (ppb) = (b) (4) kg/year x 1/1.214 x 10^{11} L/day x year/365 days x 10^9 µg/kg

= (b) (4) µg/liter

= (b) (4) ppb

The amount of HLD200 produced for direct use amounts to (b) (4) kg per year. The amount is based on projected peak sales for the next 5 years.

Reviewer's Assessment: Acceptable on the basis of 21CFR 25.31(b) and 25.15(d). The applicant's calculation of the EIC is reasonable. Methylphenidate hydrochloride is already available in the market and it is marketed by several manufacturers under other approved NDAs and ANDAs. Therefore, the applicant's claim of categorical exclusion is acceptable. No extra ordinary circumstances exist.

QUALITY ASSESSMENT

Primary EA Reviewer Name and Date: Rao V. Kambhampati, Ph.D. 5/31/17

Secondary Reviewer Name and Date: Wendy Wilson-Lee, Ph.D. 5/31/17

Rao Kambhampati

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Wendy Wilson- Lee

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LABELING

R Regional Information

1.14 Labeling

Immediate Container Label

The applicant submitted the following immediate container labels to the NDA on 9/30/2016:

(b) (4)

[redacted]

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(b) (4)

[redacted]

Reviewer's Assessment: The above sample container labels contain most of the required information and they are acceptable after the following recommended changes are incorporated into the final container labels:

1) **Since USP does not allow the use of "** (b) (4) **" in the established name, therefore, it needs to be changed to "extended-release" with a dash in between the "extended" and "release".**
2) **The statement** (b) (4) **" should be changed to as follows: "Each capsule contains 20 mg methylphenidate hydrochloride (equivalent to 17.4 mg of methylphenidate free base)". Similar changes need to be made to the container labels of the other strengths.**
3) **Prominence of the established name that follows the tradename should be at least 50% of the tradename. This comment was also provided by the DMEPA reviewer in her review dated 5/19/17 in DARRTS.**

Carton Labeling: Cartons were not proposed for the packaging of bottles.

Reviewer's Assessment: Acceptable.

QUALITY ASSESSMENT

List of Deficiencies: None

Primary Labeling Reviewer Name and Date: Rao V. Kambhampati, Ph.D. 5/31/2017

Secondary Reviewer Name and Date: Wendy Wilson-Lee, Ph.D. 5/31/2017

Rao Kambhampati

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Wendy Wilson- Lee

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BIOPHARMACEUTICS

NDA: 209311
Drug Product Name / Strength: [redacted]™ **(proposed brand name)**
Methylphenidate Hydrochloride Extended Release Capsules; 20mg, 40mg, 60mg, 80mg, 100mg
Route of Administration: Oral
Applicant Name: Ironshore Pharmaceuticals and Development, Inc.

Background: Ironshore Pharmaceuticals and Development Inc., is seeking approval for Methylphenidate Hydrochloride Extended Release Capsules, 20, 40, 60, 80, and 100 mg to be administered orally for the treatment of [redacted] Attention Deficit Hyperactivity Disorder (ADHD) under the 505 (b) (2) path.

REVIEW SUMMARY:

This Biopharmaceutics Review evaluated the overall dissolution data supporting; **1)** the proposed dissolution method, **2)** the proposed dissolution acceptance criteria, **3)** the bridging of the formulations throughout the product development, due to formulation, manufacturing process, and manufacturing site changes, **4)** the alcohol dose-dumping potential of the proposed drug product, ***5)*** the Biowaiver request for the 40, 60, and 80 mg strengths of the proposed drug product, and **6)** the proposed in vitro-in vivo correlation (IVIVC) model.

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

1) ***Dissolution Method:*** A three-stage dissolution method was developed for the proposed drug product. The proposed dissolution method has the discriminating ability to detect out of limits formulation and manufacturing changes and to reject those batches that do not exhibit similar dissolution profiles. The dissolution method described below is acceptable.

APPROVED Dissolution Method for Methylphenidate HCL ER Capsules; 20, 40, 60, 80, and 100mg	
Apparatus/Speed	USP Type I (Basket) at 75 rpm
Dissolution Media/ Volume	**Stage 1 (0-2 h):** 0.1 N HCl/**700 mL** **Stage 2 (2-6 h):** 0.1 N HCl + Na_3PO_4 (pH 6.0)/ **900 mL** **Stage 3 (6-24 h):** 0.1 N HCl + Na_3PO_4 (pH 6.0)+ NaOH (pH 7.2)/**910 mL**
Bath temperature	37.0±0.5°C
Sampling Times	**Stage 1:** 2 h **Stage 2:** 4 and 6 h **Stage 3:** 8, 10, 12, 14, 16, 20, 22, and 24 h
Analytical Method	HPLC/UV at 205 nm

2) ***Dissolution Acceptance Criteria***: The dissolution acceptance criteria as proposed by the Applicant needed some revision. Therefore, on June 6, 2017, the Applicant was requested to revise the dissolution criteria. The table below includes the originally proposed and the June 6th recommended dissolution acceptance criteria.

Originally PROPOSED Dissolution Acceptance Criteria			RECOMMENDED Dissolution Acceptance Criteria		
Stage	**Sampling Time**	**Percent of Drug Dissolved (LC)**	**Stage**	**Sampling Time**	**Percent of Drug Dissolved (LC)**
Stage 1	2 hours	NMT (b) (4)%	**Stage 1**	2 hours	NMT (b) (4)%
Stage 2	6 hours	NMT %	**Stage 2**	6 hours	NMT %
Stage 3	12 hours (b) (4) **hours** 24 hours	(b) (4) % **%** NLT (b) (4)%	**Stage 3**	12 hours **14 hours** 24 hours	(b) (4) % **%** NLT (b) (4)%

On June 7, 2017, the Applicant provided their response, which included a proposed (b) (4)% dissolution range for the 14 hour sampling time point. The FDA agreed with the Applicant's proposal. The table below lists the acceptance criteria **APPROVED** for the dissolution testing of all strengths of the proposed drug product at release and on stability.

APPROVED Dissolution Acceptance Criteria		
Stage	**Sampling Time**	**Percent of Drug Dissolved (LC)**
Stage 1	2 hours	NMT (b) (4)%
Stage 2	6 hours	NMT %
Stage 3	12 hours **14 hours** 24 hours	(b) (4) % **%** NLT (b) (4)%

3) ***Bridging of the Formulations:*** The Applicant provided adequate in vitro and in vivo data to support the bridging of formulations changes, manufacturing site changes, and manufacturing process changes that occurred throughout the IND phases of product development.

4) ***Alcohol Dose-Dumping Potential:*** The results from the in vitro dissolution studies showed no release of methylphenidate in the presence of 0%, 5%, 10% and 20% v/v ethyl alcohol within 2 hours. However, in the presence of 40% v/v ethyl alcohol, complete release of methylphenidate is observed from the 60 mg strength within 120 minutes; indicating that the proposed drug product has the potential for alcohol dose-dumping in vivo at this concentration.

5) ***Biowaiver Request:*** The provided information/data regarding the BA/BE for the highest 100 mg strength, composition proportionality of the formulations for all proposed strengths, PK linearity in the proposed range, and dissolution profile comparison/f2 values is appropriate and fully supports the approval of the biowaiver request; therefore, the biowaiver for the 40 mg, 60 mg, and 80 mg strengths of the proposed Methylphenidate Hydrochloride Extended Release Capsules is granted.

6) ***Proposed IVIVC Model:*** The submission included an IVIVC model, (b) (4) The proposed IVIVC model was found inadequate and not acceptable.

(b) (4)

- ***OVERALL REVIEW RECOMMENDATION:***

Based on the review of the overall information, from the Biopharmaceutics perspective NDA 209311 for Methylphenidate Hydrochloride Extended Release Capsules, 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg is recommended for **APPROVAL.**

- ***SIGNATURES***

Primary Biopharmaceutics Reviewer Name and Date:

Parnali Chatterjee, PhD ***6/1/2017***

Secondary Reviewer Name and Date:

Angelica Dorantes, PhD **6/5/2017**

BIOPHARMACEUTICS ASSESSMENT

➢ LIST SUBMISSIONS BEING REVIEWED:

Submissions Reviewed	Reference ID
Original NDA Submission 209311	\\cdsesub1\evsprod\nda209311\0000\m1\us\12-cover-letters\cover-letter-30sep2016.pdf

➢ DRUG PRODUCT:

The formulation development of the proposed product was driven by the release profile of methylphenidate from the DR and ER coatings. The proposed drug product comprises of immediate-release (IR) methylphenidate HCl spheres as the inner-most core, followed by an extended release (ER) layer. The final layer is a delayed release (DR) layer that is applied to the ER core.

The IR methylphenidate HCl inner-most core is made of (b) (4) . The manufacturing process (b) (4) initially involved (b) (4) . However, (b) (4) , the Applicant modified the process (b) (4)

The ER profile of the proposed HLD200 drug product is achieved by (b) (4)

➢ *BCS DESIGNATION*

The active ingredient in the proposed drug product is Methylphenidate HCl, USP a Schedule II controlled substance. According to the Applicant, Methylphenidate HCl, USP exhibits poor

aqueous solubility (18.6 mg/mL in water) and moderate~high gastrointestinal permeability. Methylphenidate HCl is reported as a BCS-Class 3 drug substance.

- ***Solubility:*** In order to evaluate the aqueous solubility of the proposed drug substance, the Applicant conducted pH dependent equilibrium solubility of Methylphenidate HCl, USP in different buffer solutions (see **Table I**). Based on the data provided by the Applicant, solubility of Methylphenidate HCl, USP is pH dependent with higher solubility in the acidic pH that progressively decreases above pH 6.0.

Table I: pH Dependent Solubility of Methylphenidate HCl

Media or Diluent	pH	% Recovery	Attachment
Hydrochloric Acid	1.2	99.8	API Solubility Report (b) (4)
Sodium Acetate Buffer	4.6	100.4	
Potassium Phosphate Buffer	6.0	100.3	
Potassium Phosphate Buffer	7.2	94.5	
Potassium Phosphate Buffer	7.5	94.8	
Methanol	NA	101.6	
Ethanol	NA	32.1	
Acetone	NA	0.7	

- ***Permeability:*** The current submission did not include any in vitro permeability data. However based on literature evidence and in vivo pharmacokinetic data, the oral absorption of the Listed Drug, Ritalin® is 11-52% in humans, indicating that methylphenidate exhibits moderate~high gastrointestinal permeability.

➢ ***DISSOLUTION INFORMATION:***

Because dissolution testing is a critical quality attribute, the Applicant utilized the dissolution test throughout the drug product development process across the different manufacturing sites and manufacturing processes and for the testing of batches used in the clinical PK studies and stability studies.

The dissolution method was used for bridging formulations due to formulation changes, manufacturing process, and manufacturing site changes, and for developing formulations for their proposed IVIVC model, (b) (4)

➢ ***PROPOSED DISSOLUTION METHOD:***

The Applicant developed the proposed drug product, such that methylphenidate would be released slowly as (b) (4) starts dissolving at pH>7 that delays the release of methylphenidate

by approximately 8 hours, in order to achieve once-daily dosing in the evening for control of ADHD symptoms post-awakening and throughout the day. According to the Applicant, the extended release (ER) and delayed release (DR) coatings control the rate and the time at which the drug is released.

The dissolution method and dissolution acceptance criteria proposed by the Applicant for the proposed drug product are presented below, in **Table II**.

Table II. Proposed Dissolution Method and Dissolution Acceptance Criteria

Parameters	Method
Apparatus/Speed	USP Type I (Basket)/ 75 rpm
Media/Volume	**Stage 1 (0-2 h)**: 0.1 N HCl/**700 mL** **Stage 2 (2-6 h):** 0.1 N HCl + Na_3PO_4 (pH 6.0)/**900 mL** **Stage 3 (6-24 h):** 0.1 N HCl + Na_3PO_4 (pH 6.0)+ NaOH (pH 7.2)/**910 mL**
Bath temperature	37.0±0.5°C
Sampling Time Points	**Stage 1:** 2 h **Stage 2:** 4 and 6 h **Stage 3:** 8, 10, 12, 14, 16, 20, 22, and 24 h
Analytical Method	HPLC/UV at 205 nm
Acceptance Criteria	**Stage 1** (2 h) NMT (b) (4)% **Stage 2** (6 h) NMT % **Stage 3** (12 h) (b) (4) (b) (4)h) % (24 h) NLT (b) (4)%

REVIEWER'S ASSESSMENT *for proposed dissolution Method:*

(b) (4)

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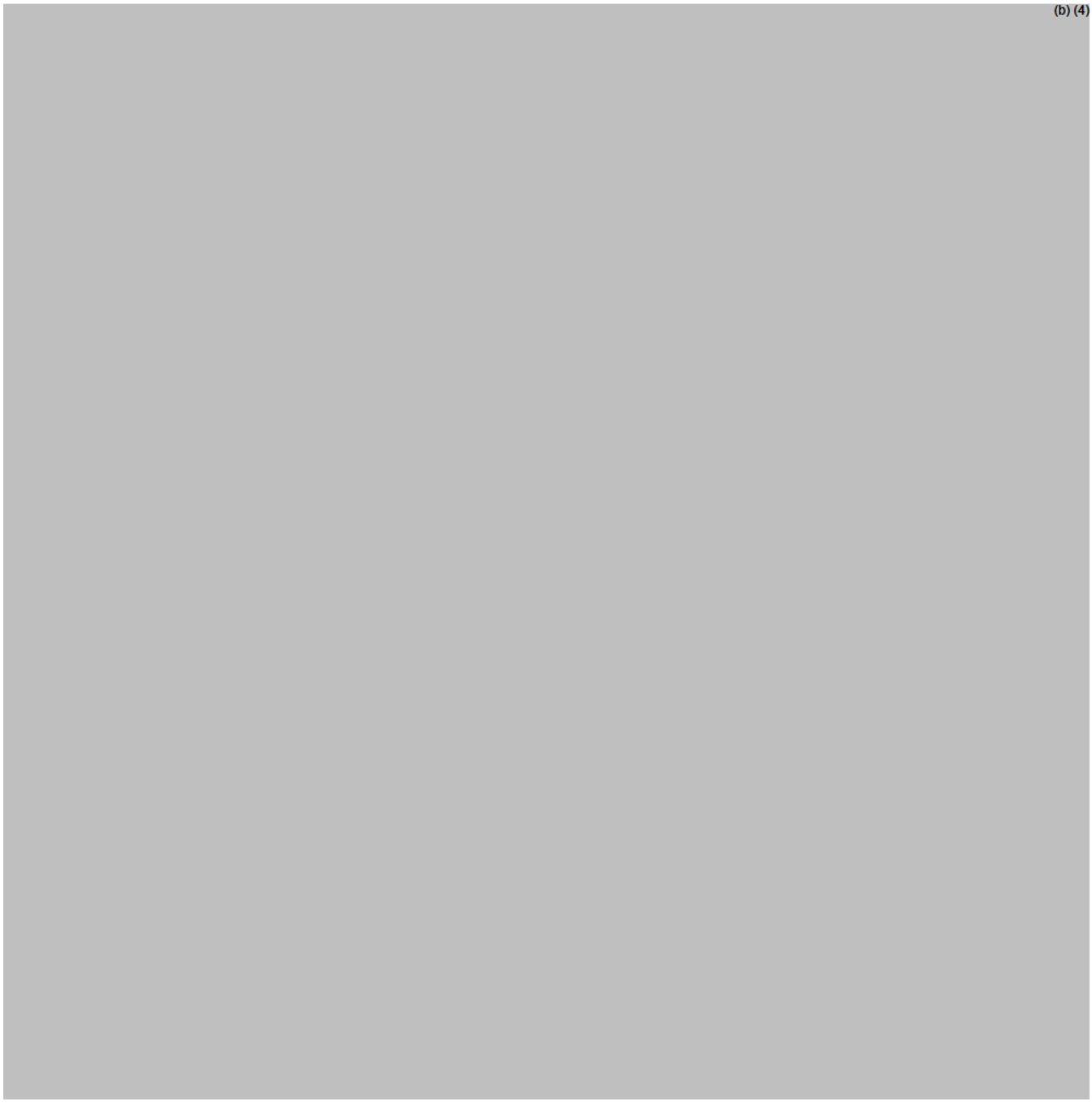
(b) (4)



- ***Discriminating Power of the Proposed Dissolution Method:***

The Applicant evaluated the discriminating power of the proposed dissolution method to ascertain that the developed dissolution method could detect formulations containing different (b) (4) ER and DR coatings, and formulations with different drug substance particle size, (b) (4), and (b) (4) conditions of the drug product.

- *Effect of ER and DR Coating* (b) (4) *on the In Vitro Release of Methylphenidate from HLD200:*

The Applicant developed a number of formulations with different ER and DR coating (b) (4) and generated the dissolution profiles. The dissolution profiles for formulations containing (b) (4) in pH 6.8 and pH 7.0 dissolution media are shown in **Figure II**. From **Figure II**, it can be seen that by changing the ratio of the ER coating (b) (4), the release rates of methylphenidate from the formulations were distinctly different, with formulation containing (b) (4) exhibiting faster release than the formulation containing (b) (4) at both, pH 6.8 and pH 7.0 dissolution media indicating that the dissolution method has discriminating power towards changes in the ratio of ER and DR coating (b) (4) in pH 6.8 and pH 7.0 dissolution media.

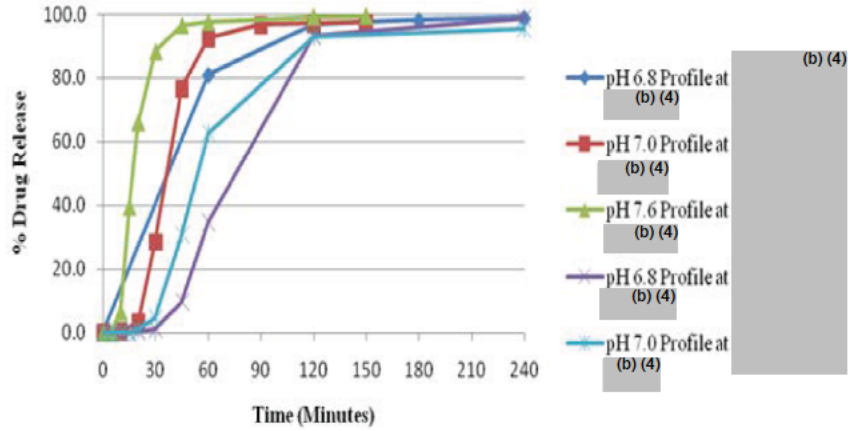


Figure II. Dissolution Profile for the Formulations containing (b) (4) in Different pH Buffers

The Applicant further tested the discriminating power of the proposed dissolution method by evaluating the effect of the particle size, (b) (4) and the (b) (4) on the cumulative percent (%) release of methylphenidate from the proposed HLD200 drug product.

- *Effect of Particle Size of the Drug Coated Inner Cores on the In Vitro Release of Methylphenidate from HLD200:*

The initial formulation was developed at (b) (4) (b) (4)

(b) (4)

Hence, (b) (4) Methylphenidate HCl, USP with particle size in the range as shown in **Table III** was used for product development batches, clinical, and subsequent registration batches of the proposed HLD200 drug product. (b) (4)

Table III. Particle Size of Methylphenidate HCl, USP used for Manufacturing HLD200

Acceptance Criteria	Particle Size Range (µm)
D10: NMT (b) (4) µm	(b) (4)
D50: NMT µm	
D90: NMT µm	
VMD: Report	

VMD = volume mean diameter

As the manufacturing process was transferred from (b) (4) to (b) (4) the Applicant noticed that (b) (4) The effect of the change (b) (4) on the particle size of the drug containing cores that were coated with ER coating was evaluated using the developed dissolution method (see **Figure III**).

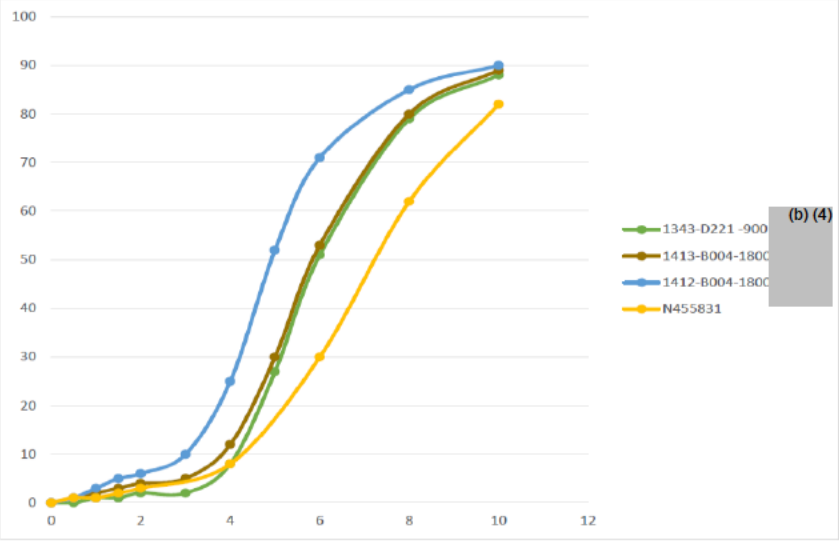


Figure III. Effect of (b) (4) on the Dissolution Profile of Drug Containing Cores Coated with ER Coating

In **Figure III** can be seen that the release of methylphenidate was faster from the optimized batch [redacted] (Batch 1412-B004-1800) than the target clinical batch manufactured at [redacted] (N455831) that exhibits a delay in the release of methylphenidate, thus supporting the discriminating power of the proposed dissolution method.

- *Effect of [redacted] on the In Vitro Release of Methylphenidate from HLD200:*

Furthermore, in order to evaluate the effect of [redacted] on the dissolution profile of the drug containing cores, another batch (Batch 1413-B004-1800) with increased [redacted] was manufactured with [redacted]. As shown in **Figure III**, the release of methylphenidate was faster than the target clinical batch manufactured at [redacted] (N455831). This study further supports the discriminating power of the proposed dissolution method.

- *Effect of [redacted] Process of the DR Coated Cores on the In Vitro Release of Methylphenidate from HLD200:*

[redacted]. The Applicant investigated the effect of [redacted] on the dissolution profile of the DR coated cores. [redacted] for the clinical batches of HLD200 that were used for Phase I, Phase II, and supportive Phase III studies (HLD200-101, HLD200-102, HLD200-103, and HLD200-106). [redacted]

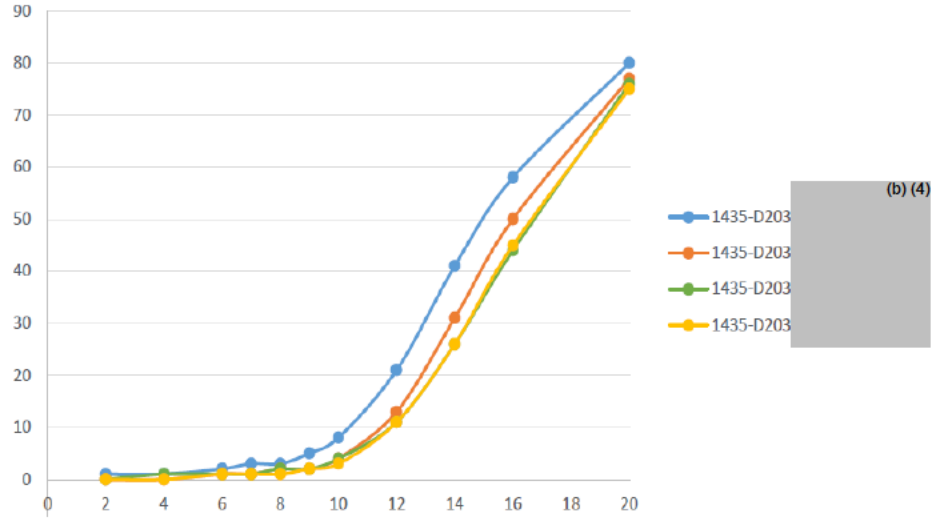


Figure IV. Effect of [redacted] on the Dissolution Profile of Drug Containing Cores Coated with ER Coating

However, the Applicant wanted to evaluate the effect of [redacted] on the dissolution profile of the DR coated cores. From **Figure IV**, it can be seen that [redacted] caused faster release of methylphenidate from the DR coated cores as compared to [redacted] The effect of [redacted] of the DR coated cores on dissolution further supported the discriminating power of the proposed dissolution method.

Based on the dissolution data provided for the evaluation of the effect of the ER and DR coating [redacted] the particle size of the drug layered cores, [redacted], and the [redacted] of the DR coated cores on the cumulative percent (%) release of methylphenidate from the proposed HLD200 drug product, the proposed dissolution method has adequate discriminating power to differentiate formulations with aberrant manufacturing variables and can reject batches that are outside of the acceptance criteria limits of key manufacturing variables. In conclusion, the proposed dissolution method is acceptable.

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

The Applicant proposed the following dissolution acceptance criteria for batch release and stability testing of the proposed Methylphenidate HCL ER Capsules product.

Parameter	Percent (%) Release Limits of Methylphenidate
Proposed Dissolution Acceptance Criteria	Stage 1 (2 hours) NMT [redacted]% Stage 2 (6 hours) NMT [redacted] % Stage 3 (12 hours) [redacted]% [redacted] hours) [redacted]% (24 hours) NLT [redacted]%

REVIEWER's ASSESSMENT for proposed dissolution acceptance criteria:
Since the proposed drug product was formulated such that methylphenidate will slowly release by 8 hours as the [redacted] starts dissolving at pH>7, the Applicant proposed the initial product specifications for 2 hours and 6 hours as NMT [redacted]%, which is acceptable. Once the [redacted] starts dissolving after 8 hours, the Applicant proposed [redacted]% range on the cumulative percent (%) release of methylphenidate at 12 hours, is acceptable.

However, because the proposed drug product was developed to release methylphenidate slowly at pH>7 (*delaying the release of methylphenidate by approximately 8 hours, in order to achieve once-daily dosing in the evening for control of ADHD symptoms post-awakening and throughout the day*), it is recommended that for Stage 3 dissolution testing, a 14 hours sampling time-point be introduced with an acceptance dissolution range of [redacted]% cumulative percent (%) of methylphenidate, and the proposed sampling time point at [redacted] hours be deleted.

The proposed limit of NLT (b)(4)% at 24 hours is acceptable. The recommended acceptance criteria for the proposed methylphenidate HCl ER Capsules product are as follow:

Parameter	Percent (%) Release Limits of Methylphenidate
Recommended Acceptance Criteria	Stage 1 (2 hours) NMT (b)(4)% Stage 2 (6 hours) NMT % Stage 3 (12 hours) (b) (4) **(14 hours) %** (24 hours) NLT (b)(4)%

On June 6, 2017, an IR comment was conveyed to the Applicant requesting the revision of the dissolution acceptance criteria. However, on June 7th the Applicant responded with a proposed (b) (4)% dissolution range for the 14 hour time point. The FDA agreed to the Applicant's request and the final dissolution acceptance criteria for all strengths of the proposed drug product at release and on stability are as follow:

APPROVED Dissolution Acceptance Criteria		
Stage	**Sampling Time**	**Percent of Drug Dissolved (LC)**
Stage 1	2 hours	NMT (b)(4)%
Stage 2	6 hours	NMT (b)(4)%
Stage 3	12 hours	(b) (4)%
	14 hours	**%**
	24 hours	NLT (b)(4)%

- ***CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo):***

(b) (4)

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(b) (4)

- ***IN-VITRO ALCOHOL DOSE DUMPING***

Since the proposed drug product is a modified release (delayed-release/extended release) drug product, there is the potential for dose-dumping in the presence of alcohol. Therefore, in order to investigate the alcohol dose-dumping potential of the proposed drug product, the Applicant conducted dissolution testing on 12 dosage units of the 60 mg strength of the proposed drug product, in HCl 0.1 N with varying concentrations of ethyl alcohol (0%, 5%, 10%, 20%, and 40% v/v) media for 2 hours (120 minutes) using USP Type-I basket apparatus at an agitation speed of 75 rpm. The release of methylphenidate was assayed by an HPLC/UV method (see **Table V**).

Table V Dissolution Method for In Vitro Alcohol Dose-Dumping Studies

Parameters	Dissolution Testing Conditions
Apparatus/Speed	USP Type I (Basket) at 75 RPM
Media/Volume	700 ml of 0.1 N HCl with 5%, 10%, 20%, or 40% v/v
Bath temperature	37.0±0.5°C
Sampling Time Points	15, 30, 45, 60, 75, 90, 105, 120 minutes
Analytical Method	HPLC/UV at 205 nm

The mean dissolution profile of 12 dosage units of the proposed drug product, 60 mg strength in the presence of ethyl alcohol (0%, 5%, 10%, 20%, and 40% v/v) is shown in below **Figure IX**.

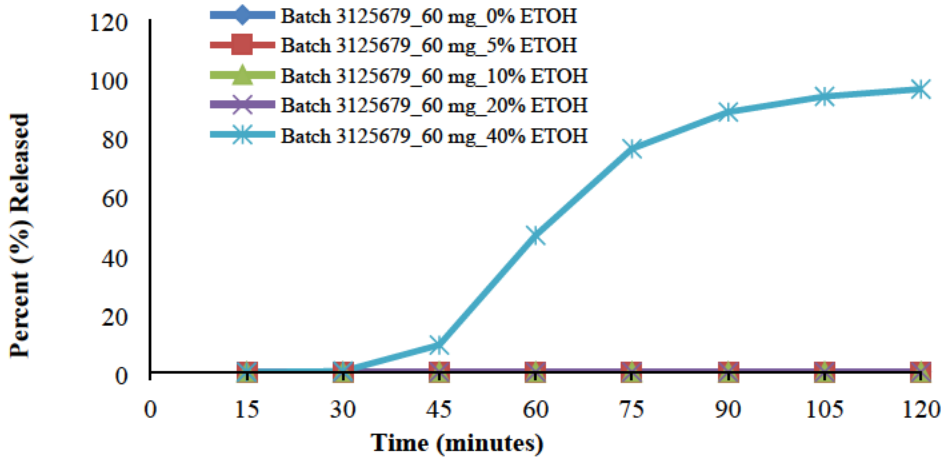


Figure IX. Mean Dissolution Profile of 12 Dosage Units of the 60 mg strength HLD200 in the Presence of Ethyl Alcohol, (0%, 5%, 10%, 20%, and 40% v/v

REVIEWER's ASSESSMENT for alcohol dose dumping:
Based on **Figure IX** dissolution results, no release of methylphenidate is observed in the presence of 0%, 5%, 10% and 20% v/v ethyl alcohol within 120 minutes (2 hours). However, in the presence of 40% v/v ethyl alcohol, complete release of methylphenidate is observed from the 60 mg strength within 120 minutes (refer to **Appendix IV** for the dissolution data).

According to the Applicant, because dose-dumping was observed for the 60 mg strength in the presence of 40% v/v ethyl alcohol (and not at 10% and 20 % v/v ethyl alcohol), which is usually not encountered in a clinical setting, the potential of dose-dumping for 80 mg and 100 mg strength of HLD200 at 10% and 20 % v/v ethyl alcohol does not exist. Therefore, in an IND's meeting held on 11/02/2014, the Applicant requested not conducting the in vitro alcohol dose-dumping studies for the other strengths of the proposed product. The FDA decided that the provided justification was adequate and the Applicant's request of not conducting additional in vitro dose-dumping studies was accepted. Further, at the IND's EOP2 meeting held on 02/04/2015, the Applicant was advised to summarize the results of the in vitro alcohol dose-

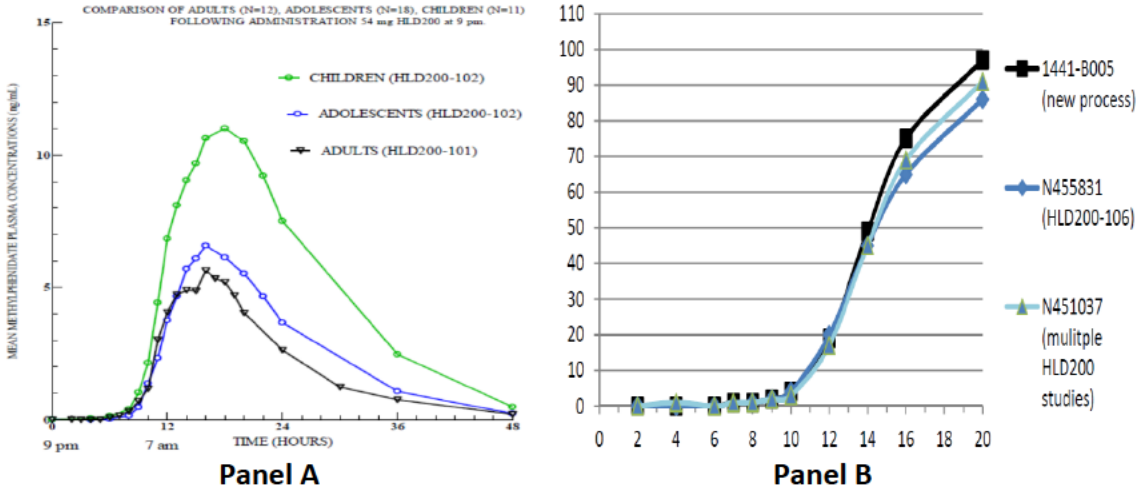
dumping studies in the labeling of the proposed drug product. It is noted that the following statement is included in Section 12.3 of the proposed product's labeling;

Alcohol Effect:

(b) (4)

- ***EXTENDED RELEASE CLAIM:***

To support the 'Extended Release Claim' of the proposed drug product, the Applicant conducted a single-dose pharmacokinetic (PK) study (HLD200-102) comparing the PK profile of B-HLD200, 54 mg strength between adults, adolescents, and children (see **Figure X**, Panel A). In addition, the Applicant performed dissolution studies with the same formulation, N455831 (B-HLD200) and N451037, that was used in the HLD200-102 study and other clinical studies (see **Figure X**, Panel B).



Panel A **Panel B**

Figure X: *Panel A;* Plasma Concentration (Cp) *vs*. Time Profile of B-HLD200, 54 mg strength in Children, Adolescents, and Adults (Study HLD200-102); *Panel B:* Mean Dissolution Profile of Formulation N455831 (B-HLD200) and N451037 (HLD200) used in Multiple Clinical Studies.

REVIEWER's ASSESSMENT for extended release claim:
The PK data from the HLD200-102 study show an approximately 8 hour delay in the drug release with therapeutic plasma levels throughout the daytime hours following administration

of the proposed formulation-Product, HLD200, which was substantiated by the sigmodial delayed release dissolution profile for the same formulation, N455831 (B-HLD200).

The Applicant provided further evidence of 'Extended Release Claim' of the proposed HLD200 drug product by conducting several PK studies (Studies HLD200-101, HLD200-102, HLD200-103, HLD200-104, and HLD200-109) that exhibited minimal release of the proposed drug product during the first 8-10 hours following dosing under fasted and fed conditions, with the drug concentration decreasing gradually by following evening. In addition, the Applicant provided relative dose-normalized bioavailability data (mean of individual ratios of AUC_{0-t}) for B-HLD200, 54 mg strength and LD, Ritalin, 20 mg strength, indicative of a once daily (qd) dosing for the proposed drug product as against twice or thrice dosing interval for the LD, Ritalin, 20 mg strength. In conclusion, the extended release claim for the proposed Methylphenidate HCL ER Capsules, is fully supported.

- ***BRIDGING OF FORMULATIONS***

- ***Manufacturing Site Changes***:

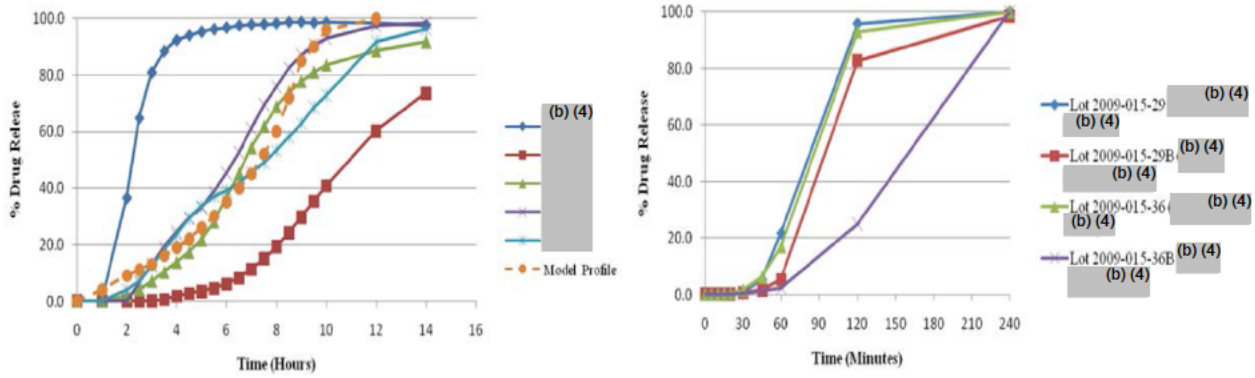
The manufacturing site changes for the product development activities of the proposed drug product are summarized in **Figure XI**.

(b) (4)

Figure XI. Manufacturing Site Changes for Product Development Activities

- (b) (4)

The proposed drug product was initially developed at (b) (4), where the ER and DR coating formulations were developed and tested. After that, the formulation development activities were transferred from (b) (4) to (b) (4) for manufacturing Phase I clinical batches (cGMP). The dissolution profiles for the formulations with different (b) (4) developed at (b) (4) are shown below in **Figure XII** (Panel A and Panel B).



Panel A **Panel B**

Figure XII. Dissolution Profile of the Formulation with (b) (4) (Panel A) (b) (4) (Panel B) Developed at (b) (4)

- (b) (4)

The drug product for Phase I (HLD200-101 and HLD200-103), Phase II (HLD200-102), and supportive Phase III (HLD200-106) clinical studies was manufactured at (b) (4) Based on the ER and DR coating formulations developed at (b) (4), two clinical formulations were developed at (b) (4) B-HLD200, 54 mg, which represented the "slow release" and C-HLD200, 54 mg that represented the "fast release" formulation. The two formulations, B-HLD, 54 mg and C-HLD, 54 mg were bridged to the Listed Drug (LD) product, Ritalin, 20 mg dosage form in the Phase I study HLD200-102 as shown in **Figure XIII** (**Panel A and Panel B**). The Concentration (Cp) vs. time profile for the two formulations, B-HLD and C-HLD and the LD are shown in **Figure XIII** (Panel A), whereas the dissolution profile for the two formulations, B-HLD and C-HLD, are shown in **Figure XIII** (Panel B).

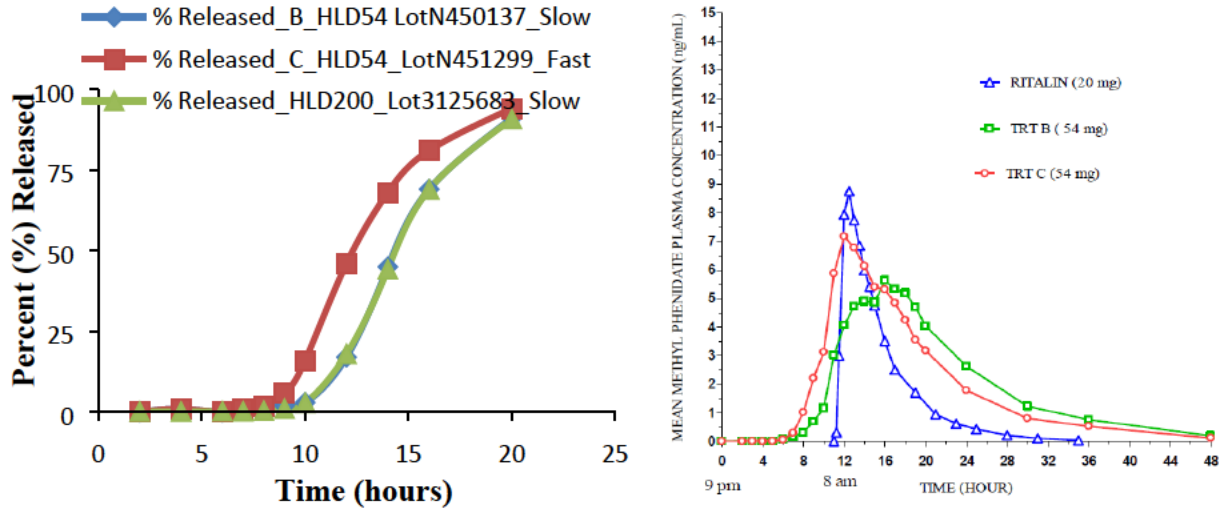


Figure XIII. Plasma Concentration (Cp)-Time profile for the Formulations B-HLD and C-HLD and LD, Ritalin (Panel A); Mean Dissolution Profile of the Formulations, B-HLD and C-HLD (Panel B) Developed at (b) (4)

- (b) (4)

The manufacturing was then transferred from (b) (4) to (b) (4) in order to scale-up the manufacturing process for the pivotal Phase 3 clinical studies (HLD200-107, HLD200-108, clinical material HLD200). (b) (4) The Phase I clinical studies conducted with (b) (4) material were bridged in the clinical study HLD200-104 and HLD200-109 along with Phase III clinical studies, HLD200-107 and HLD200-108 using formulations manufactured at (b) (4) In addition, a BA study (HLD200-110) was conducted with the (b) (4) commercial or 'to-be-marketed" formulation in order to demonstrate BA/BE to the LD, Ritalin® IR, 20 mg tablets. The various batches manufactured during the formulation development of the proposed drug product at different manufacturing sites is highlighted in **Table VI**.

Table VI. Formulation Batches Manufactured at Different Sites for the proposed Drug Product (HLD2000)

Formulations	Manufacturing Site/ Batch No.		Clinical Trials Study No.
B-HLD200 (54 mg) "slow" release rate (b) (4)	(b) (4)	**Phase I**: MPH004- N450137 **Phase II**: MPH004- N450137 **Phase III:** MPH004-N455831, N455832	**Phase I**: HLD200-101, HLD200-103 **Phase II**: HLD200-102 **Phase III**: HLD200-106
C-HLD200 (54 mg) "fast" release rate (b) (4)	(b) (4)	**Phase I**: MPH005- N451299	**Phase I**: HLD200-101
HLD200 (100 mg) slow dissolution release rate (b) (4)	(b) (4)	**Phase I**: 3135927, 3125683 **Phase III**: 3135927, 3125675	**Repeat Phase I:** HLD200-104, HLD200-109 **Phase III**: HLD200-107, HLD200-108

REVIEWER'S ASSESSMENT *for bridging of formulations:*
Based on **Table VI**, it can be concluded that the Applicant conducted adequate bridging studies to support the manufacturing site changes for the development of the proposed Methylphenidate HCL ER Capsules product.

- ***FORMULATION AND MANUFACTURING PROCESS CHANGES and DISSOLUTION:***

As the formulation development activities (see **Figure XIV**) for proposed drug product proceeded, significant changes were made to the formulation in order to achieve the target dissolution profile (see **Figure XV**).

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(b) (4)

[redacted]

REVIEWER'S ASSESSMENT for bridging of formulations and manufacturing processes:
A comparison of in-vitro dissolution performance for the new manufacturing process (lot 1441-B005) to the old manufacturing process (clinical lots N455831 and N450137) shows an approximate 6-10% difference in drug release at the 20 hour time point and no important difference prior to the 14 hour time point of dissolution. The 6% increase in dissolution only increases the predicted $AUC_{0->\infty}$ by 6%, from 169.2 to 179.4 ng×hr/ml, which is not clinically significant.

Based on the overall dissolution profiles and clinical studies HLD200-101, 102, 103, and 106, it can be concluded that the Applicant conducted adequate bridging studies to support the formulation and manufacturing process changes for the development of the proposed HLD200 drug product.

- ***BIOWAIVER REQUEST for 40, 60 and 80 MG STRENGTHS OF THE PROPOSED PRODUCT:***

To support the approval of the Biowaiver request for the 40, 60, and 80 mg strengths of the proposed product not tested on in vivo PK studies, the Applicant provided BA/BE data for the 100 mg highest strength, information/data demonstrating that all the strengths of the proposed drug product are compositionally proportional (see **Table VI**), that there is PK linearity within the proposed dosing range, and dissolution profile data for the 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg strengths.

Table VI. Qualitative and Quantitative Composition of HLD200 20 mg, 40 mg, 60 mg, 80 mg and 100 mg capsules

Component	Grade and Quality Standard	Function	B-HLD200 (mg)	C-HLD200 (mg)	HLD200 (Proposed Commercial Formulation) (mg)				
			54 mg	54 mg	20 mg	40 mg	60 mg	80 mg	100 mg
		Clinical Studies	HLD200-106[2] HLD200-103[3] HLD200-102 HLD200-101	HLD200-102[4] HLD200-101	HLD200-108 HLD200-107	HLD200-108 HLD200-107	NA	NA	HLD200-109 HLD200-104[1] HLD200-110[5]
Methylphenidate Hydrochloride, CII	USP	Active ingredient	54.00	54.00	20.00	40.00	60.00	80.00	100.00
Microcrystalline Cellulose (b) (4)	NF	(b) (4)							(b) (4)
(b) (4)	USP								
Ethylcellulose (b) (4)	NF								
Hydroxypropyl Cellulose (b) (4)	NF								
Dibutyl Sebacate	NF								
Magnesium Stearate (b) (4)	NF								
Methacrylic Acid Copolymer Type-B	NF								
Mono-and Di-Glycerides	NF								
Polysorbate 80	NF								
Talc (b) (4)	USP								
TOTAL FILL WEIGHT									

The mean dissolution profiles for the 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg strengths are shown in **Figure XIX**. The dissolution data for the 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg strengths are provided in the **Appendix II**.

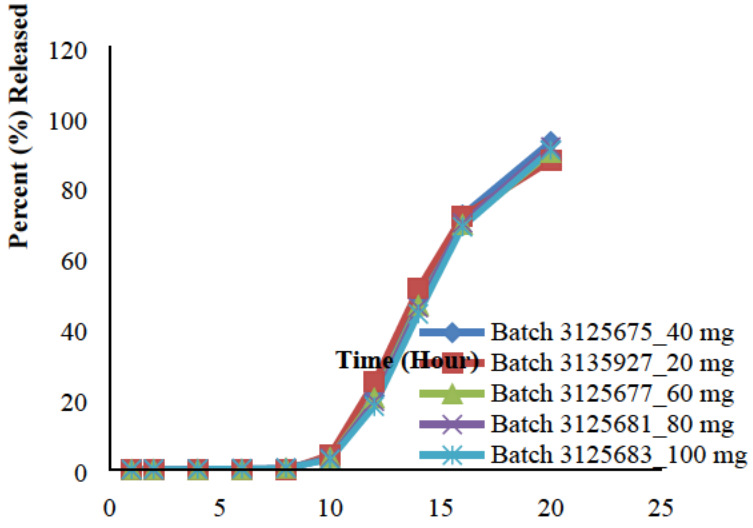

Figure XIX. Mean Dissolution Profile of 6 Dosage Units of HLD200, 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg Strengths

REVIEWER'S ASSESSMENT for Biowaiver request:

The similarity factor '*f2 value*' calculated by this Reviewer between the mean dissolution profiles of HLD200, 20 mg, 40 mg, 60 mg, 80 mg strengths and 100 mg strength is 72.06, 80.63, 91.27, and 93.97 respectively, indicating that the dissolution profiles of the 20 mg, 40 mg, 60 mg, 80 mg, are similar to the highest 100 mg strength. Based on the in vitro dissolution data provided for the different strengths of the proposed HLD200 drug product, it can be concluded that the dissolution profile for the different strengths of the proposed drug product are similar.

The provided information/data for the BA/BE for the highest 100 mg strength, composition proportionality of formulations of all proposed strengths, PK linearity in the proposed range, and dissolution profile comparison/f2 values is appropriate and fully supports the approval of the biowaiver request; therefore, the biowaiver for the 40 mf, 60 mg, and 80 mg strengths of the proposed Methylphenidate Hydrochloride Extended Release Capsules is granted.

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

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

- ***OVERALL REVIEW RECOMMENDATION:***

From the Biopharmaceutics perspective, NDA 209311 for Methylphenidate HCL Extended Release Capsules, 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg is recommended for **APPROVAL.**

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Parnali Chatterjee

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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**
Appearance	Capsule color fading. (b) (4)	L	Release and stability testing. (b) (4)	Acceptable	
Assay/stability	Coating operation controls	L	In-process, release and stability assay testing	Acceptable	
Identification		L	Release testing	Acceptable	
Content Uniformity	Coating uniformity controls	L	Release testing	Acceptable	
Degradants		L	Release testing	Acceptable	
Dissolution	Coating controls and integrity on storage	M	Dissolution release testing	Acceptable	
Alcohol Dose Dumping		H	Known to dump with >40% alcohol. Warning added to labeling.	Acceptable	
Microbial	Limit test	L	Release testing	Acceptable	

David Claffey

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