CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205831Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	**205831**
IND:	**104624**
Submission Dates:	**6-18-2014**
Brand Name:	**Aptensio**
Generic Name:	**Methylphenidate**
Dosage & Strength:	**ER Capsules of 10, 15, 20, 30, 40, 50, 60 (b) (4) mg strength**
Indication:	**Treatment for ADHD**
Applicant:	**Rhodes Pharmaceuticals**
Submission:	**Original NDA[505(b)(2)]**
Division:	**DCP1**
Reviewer:	**Andre Jackson, Ph.D.**
Team Leader:	**Hao Zhu, Ph.D.**

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1.0 EXECUTIVE SUMMARY

The sponsor is seeking approval of Aptensio ® as an oral extended-release capsules at dosage strengths of 10mg, 15mg, 20mg, 30mg, 40mg, 50mg, 60mg (b) (4) for the treatment of attention deficit hyperactivity disorder (ADHD) via a 505 b(2) approval route. Aptensio ® is a new solid oral formulation for methylphenidate that can be administered once daily and can achieve adequate biphasic peak concentrations, with its first maximum concentration (C_{max}) being similar to a methylphenidate (MPH) immediate release (IR) formulation.

The clinical development program consisted of 4 pivotal studies, including 2 pivotal pharmacokinetic (PK) studies in healthy adults (a single dose capsule/sprinkles under fast conditions, and a single-and multiple-dose study under fed conditions) and 2 safety and efficacy studies in pediatric and adolescent patients with ADHD. The reference product was Ritalin ® IR. Additionally, the firm conducted a pediatric pharmacokinetic study in children between the ages of 6-12yr. The firm also conducted three studies using pilot formulations to test the effect of food by comparing the Canadian reference product to Concerta ®, and the comparative absorption of two Canadian pilot lots.

Two clinical efficacy and safety studies were conducted. Study EF001 in pediatric patients 6-12 yrs old used the SKAMP score as the clinical endpoint based upon the analog classroom setting showed that Aptensio ® yielded improvement in classroom behavior, written work, and general behavior compared with placebo. Study EF002 which was conducted in 6-18 yr olds with the primary endpoint being measured by the clinician-administered parent version of the ADHD Rating Scale, Version 4 (ADHD-RS-IV) in children and adolescents (aged 6 to 18) diagnosed with ADHD was also positive for effectiveness. The highest dose studied in the efficacy studies was 40mg/day.

OCP's major findings are summarized as follows:

1. An adequate link has been established between Aptensio ® capsule and Ritalin ® immediate release product, the reference list product, through a relative bioavailability study.
2. At mean level, pharmacokinetic profiles in adults and in pediatric patients both show double peaks with similar shape; however, pediatric patients receiving different doses appear to show large variability in the shape of their respective mean pharmacokinetic profiles. The pharmacokinetic findings appear to support the extension of the indication from pediatric patients to adults.
3. (b) (4) Large pharmacokinetic variability in pediatric patients

appears to support a titration-based dosing regimen to target optimal treatment effect for each individual.

4. The pharmacokinetic profile of Aptensio ® is consistent with the expectations for an extended-release formulation and is sufficient to support a once daily dosing.
5. Aptensio ® capsule can be administered as a whole capsule or sprinkled onto applesauce.
6. Aptensio ® may be given with or without food. It is advised that patients should establish a routine pattern with regard to meals.
7. Patients should avoid alcohol while taking Aptensio ®.

1.1 Recommendation

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in the NDA to support a recommendation of approval of Aptensio ®. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP?	Comment
Overall	Yes	Pending labeling agreements with the sponsor.
Evidence of Effectiveness	Yes	2 positive registration trials in pediatric patients
Proposed dose for general population	No	(b) (4)
Labeling	No	Pending satisfactory agreement with the sponsor.

1.2 Post-Marketing Studies

No post-marketing studies are required.

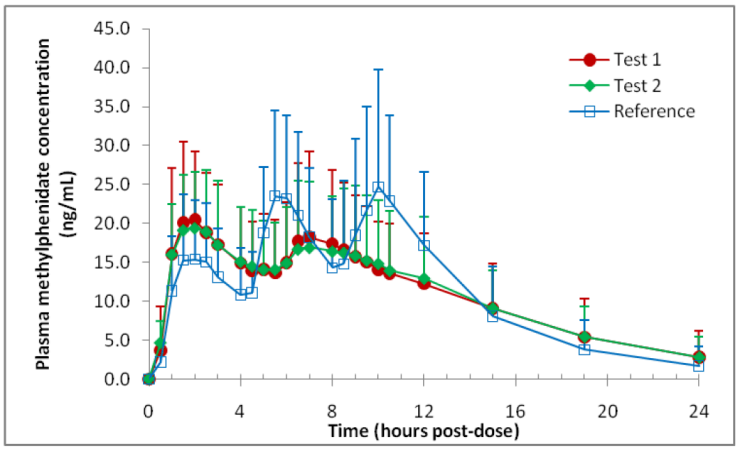
1.3 Summary of Clinical Pharmacology findings

1.3.1 Relative Bioavailability

The link between Aptensio ® capsule and Ritalin ® IR, the reference listed product, has been adequately established through a relative bioavailability study under fasted conditions (Study RP-BP-PK001). Pharmacokinetic profiles and pharmacokinetic parameters between Aptensio ® and Ritalin ® are compared in Figure 1 and Table 1, respectively. As shown in Figure 1, the mean pharmacokinetic profile of Aptensio ® is consistent with the expectations for an extended release formulation and is sufficient to support a once daily dosing.

Study RP-BP-PK-002 was conducted in patients receiving Aptensio ® at steady state under fed conditions. The accumulation ratio was 1.04 indicating no accumulation.

Figure 1: Mean (SD) plasma methylphenidate concentration versus time by treatment after single dose under fasted conditions (linear scale) - PK population



T1: Test: Biphentin 80 mg capsule
T2: Test: Biphentin 80 mg sprinkle
R: RLD (Ritalin) 75 mg daily dose consisting of 25 mg dose administered at time 0, 4, 8 hours.
SD bars shown above the mean represent standard deviation around the mean.

Table 1: Bioavailability Comparisons of Aptensio ® Given as Capsule versus Sprinkled onto Apple Sauce - PK population (T1 Capsule vs. T2 Sprinkles)

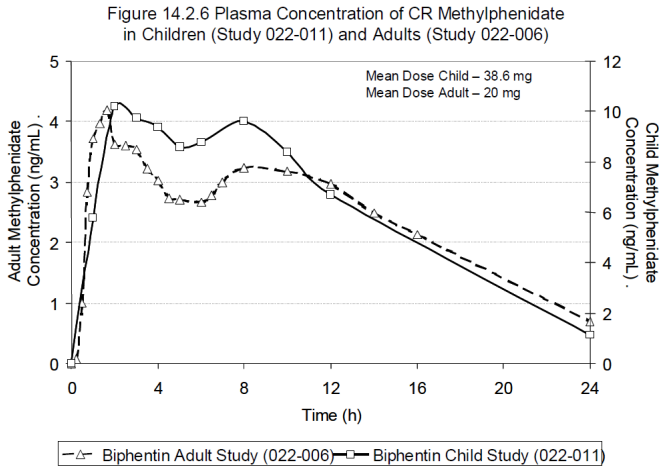
PK parameter (unit)	Geometric means			Ratio (T/R) or (T1/T2)	90% CI (T/R) or (T1/T2)
	Test 1 n=23	Test 2 n=23	Reference n=24		
T1: R					
C_{max} (ng/mL)	21.20		28.52	0.74	68.71, 80.43
$AUC_{0\text{-}inf}$ (ng·hr/mL)	261.91		268.43	0.98	93.94, 101.34
$AUC_{0\text{-}t}$ (ng·hr/mL)	242.28		260.98	0.93	89.26, 96.54
T2: R					
C_{max} (ng/mL)		20.38	28.52	0.71	66.12, 77.20
$AUC_{0\text{-}inf}$ (ng·hr/mL)		264.50	268.43	0.99	94.87, 102.34
$AUC_{0\text{-}t}$ (ng·hr/mL)		244.38	260.98	0.94	90.10, 97.32
T1 : T2					
C_{max} (ng/mL)	21.20	20.38		1.04	96.29, 112.42
$AUC_{0\text{-}inf}$ (ng·hr/mL)	261.91	264.50		0.99	95.33, 102.85
$AUC_{0\text{-}t}$ (ng·hr/mL)	242.28	244.38		0.99	95.39, 103.03

T1: Test: Biphentin 80 mg capsule
T2: Test: Biphentin 80 mg sprinkle
R: RLD (Ritalin) 75 mg daily dose consisting of 25 mg dose administered at time 0, 4, 8 hours.
All calculations based on dose-normalized values.

1.3.2 Pharmacokinetic Profile Comparison between Adults and Adolescents

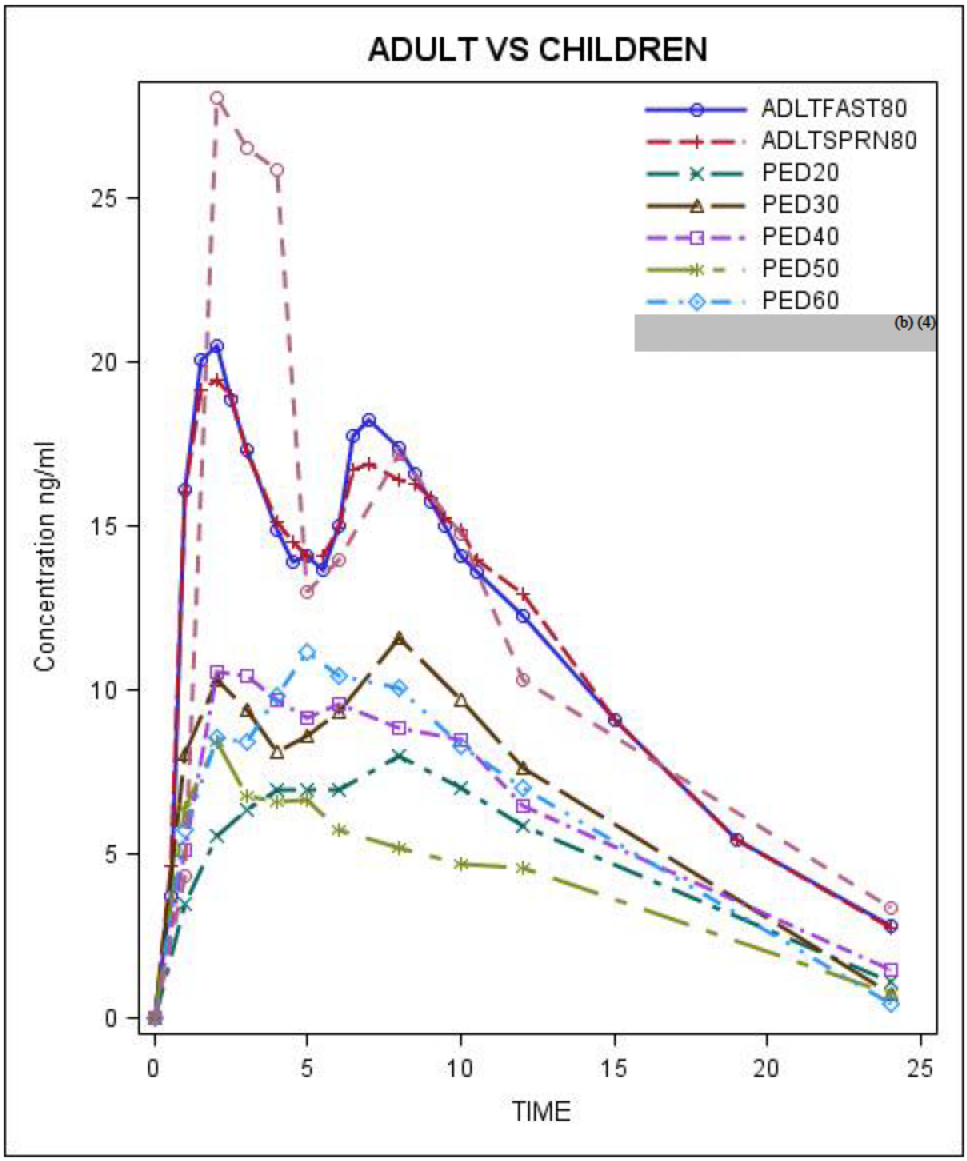
The mean pharmacokinetic profiles of methylphenidate for adults and children 6 years and above following the administration of Apentio ® are shown in Figure 2. Both profiles show double peaks with similar shape. The efficacy and safety information was collected in pediatric patients 6 years and above in the current program. It is anticipated that the similar mean pharmacodynamic effect can be seen in adults if the exposure is reached at appropriate level. As a common practice, dose in adults will be titrated based on each individual's clinical response. Hence the current pharmacokinetic data in combination with the clinical practice and prior experience of methylphenidate appear to support the extension of the indication from pediatric patients to adults.

Figure 2: Mean Pharmacokinetic Profile of Methylphenidate for Children 6 Years and Above



Pharmacokinetic profiles in pediatric patients are associated with large variability. As shown in Figure 3, different shapes of pharmacokinetic profiles can be observed. The large inter-subject variability in pharmacokinetic profiles appears to support a titration-based dosing regimen to achieve optimal treatment effect for each individual.

Figure 3: Pharmacokinetic Profiles in Pediatric Patients at Different Dose Groups (3-4 Subjects per Group).



1.3.3 Dose for ADHD Patients

OCP's analysis was conducted based on clinical efficacy (QBR 2.2.13) and safety data (QBR 2.2.14) collected in Study EFF001. (b) (4)

[redacted]

1.3.4 Administration of Aptensio ® as a Whole Capsule or Sprinkled onto Apple Sauce

Study RP-BP-PK001 compared the pharmacokinetic profiles (Figure 1) and pharmacokinetic parameters (Table 1) when Aptensio ® was administered either as a whole capsule or sprinkled onto applesauce. The respective ratios of the geometric means and corresponding 90% confidence intervals of C_{max}, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ are within 80%-125%. In addition, the median T_{max} values are 2 hours and the ranges of T_{max} are similar. Furthermore, the mean pharmacokinetic profiles when Aptensio ® was administered as a whole capsule or sprinkled onto apple sauce are superimposable. Therefore, similar mean efficacy and safety profiles are expected when Aptensio ® is given as a whole capsule or sprinkled onto apple sauce.

1.3.4 Food Effect

The effect of a high fat (approximately 50% of total caloric content of the meal), high calorie (approximately 1000 calories) meal on Aptensio ® absorption was compared with Ritalin ® in study RP-BP-PK002. The study results are presented in Table 3. A graphical representation of the pharmacokinetic profiles for Aptensio ® and Ritalin ® under fed conditions is given in Figure 4.

At least one pivotal clinical trial (i.e., Study RP-BP-EF002) has been conducted where patients were dosed without regard to meal. The trial results suggested that Aptensio ® is safe and efficacious. The clinical trial results appear to support that Aptensio ® can be given without regard to meals.

A direct comparison of mean pharmacokinetic profiles when Aptensio ® is given under fast condition (Figure 1) versus under fed condition (Figure 4) showed the second peak of the mean methylphenidate pharmacokinetic profile is reduced or diminished under fed conditions. At individual level, higher percentage of

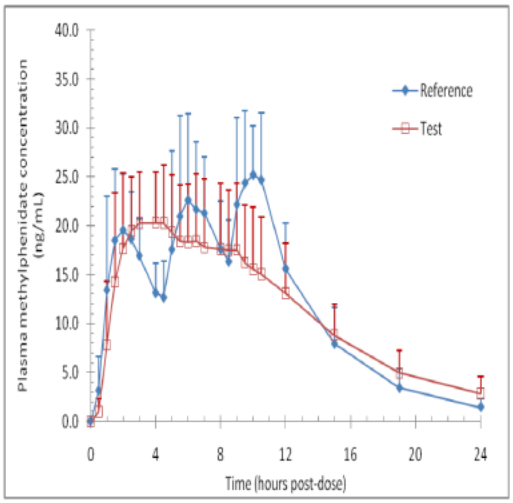
subjects with smaller second peak (< 80% of the first peak) as compared to the first peak can be found in subjects under fed conditions than under fast conditions (Table 4). Pharmacokinetic profile of methylphenidate is known to correlate with its pharmacodynamic effect. Hence, to ensure consistent efficacy and safety experience for a patient receiving Aptensio ®, it is recommended that patients should establish a routine pattern with regard to meals.

Table 3: Statistical analysis of bioavailability of Test (fed) versus Reference (fasting) treatment (PK population)

PK parameter	Geometric means		Ratio (T/R)	90% CI (T/R)
	Test n=21	Reference n=21		
Single dose				
C_{max} (ng/mL)	0.29	0.40	0.71	66.81, 75.66
AUC $_{0\text{-}inf}$ (ng·hr/mL)	3.54	3.82	0.93	88.57, 97.28
AUC $_{0\text{-}t}$ (ng·hr/mL)	3.28	3.72	0.88	84.75, 91.80
Steady-state				
C_{max} (ng/mL)	0.34	0.43	0.80	74.70, 85.51
AUC $_{0\text{-}inf}$ (ng·hr/mL)	3.68	4.19	0.88	84.48, 91.17
AUC $_{0\text{-}it}$ (ng·hr/mL)	3.43	4.08	0.84	81.16, 86.94

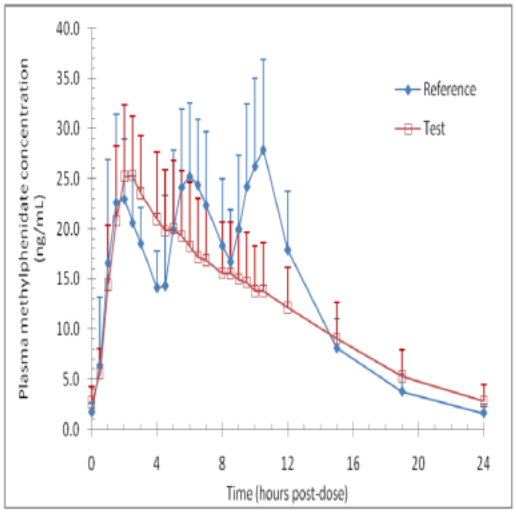
Calculations based on dose-normalized values.
Test: Biphentin (methylphenidate HCl) Extended-Release 80 mg capsule administered at time 0 hours.
Reference: RLD (Ritalin) 75 mg daily dose administered at time 0, 4, 8 hours.
Source:14.2.3 and 14.2.6

Figure 4 Mean (SD) plasma methylphenidate concentration versus time by treatment after single dose under fed conditions on Day 1 (A) and Day 12 (B) (linear scale) - PK population



Test: Biphentin (methylphenidate HCl) Extended-Release 80 mg capsule administered at time 0 hour.
Reference: RLD (Ritalin) 75 mg daily dose administered at time 0, 4, 8 hours.
SD bars represent standard deviation around the mean.
The concentration versus time curves represent the average of each subject's drug level at each time point, and the highest point on each curve, (apparent C_{max}) is actually the maximum average value during time 0 to time 24 hours post-dose. In contrast, mean C_{max} shown in the summary tables represents the average of each subject's maximum drug level, regardless of the time point at which this occurred.

(A)



Test: Biphentin (methylphenidate HCl) Extended-Release 80 mg capsule administered at time 0 hour.
Reference: RLD (Ritalin) 75 mg daily dose administered at time 0, 4, 8 hours.
SD bars represent standard deviation around the mean.
The concentration versus time curves represent the average of each subject's drug level at each time point, and the highest point on each curve, (apparent C_{max}) is actually the maximum average value during time 0 to time 24 hours post-dose. In contrast, mean C_{max} shown in the summary tables represents the average of each subject's maximum

(B)

Table 4: Percentage of Subjects Demonstrated a Smaller Second Peak as Compared to the First Peak

	Treatment Group			
	Fast (PK-001)		Fed (PK-002)	
Condition	Capsule	Sprinkle	Day 1	Day 12
Percentage *(ratio)	46% (11/24)	36% (9/25)	(58%) 12/21	72% (15/21)

*: Percentage of reduced or diminished second peak is defined as the second peak occurs between 5-10 hours and is less than 80% of the first peak which occurs between 0-5 hours.

1.3.5 Alcohol Dose Dumping

Based on *in intro* studies, about 80% of the drug is released within 1 hr in 40% alcohol (Please refer to Biopharm review). Patients should be advised to avoid alcohol while taking Aptensio®.

2.1 Question Based Review

General Attributes

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

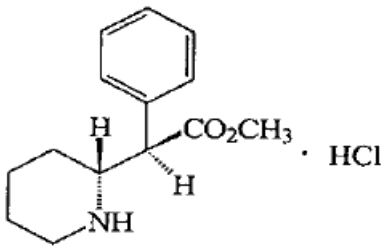
The sponsor submitted a 505(b) (2) application for Aptensio ® Extended Release (ER) capsules. The reference drug for this application is Ritalin ® IR tablet which is currently approved for ADHD.

The application was based on two efficacy and safety studies. Study EF001 was conducted in children 6-12 years of age and Study EF002 was conducted in children and adolescents 6-18 years of age. Both studies demonstrated that the drug is safe and effective. Clinical pharmacology studies were conducted to evaluate the relative bioavailability of Aptensio ® as compare to Ritalin ® IR tablet, to compare pharmacokinetic profiles of Aptensio ® given as a whole capsule versus as sprinkled into apple sauce, to assess the food effect, and to describe pharmacokinetic features in pediatric population.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics?

The structural formula for methylphenidate is given in Figure 5.

Figure 5: Structural Formula for Methylphenidate



The formulation contains a racemic mixture of the stereo pair of methylphenidate (MPH) isomers (d,l - threo methylphenidate). The d-MPH enantiomer is more potent than the l-MPH enantiomer. There is no inter-conversion between the isomers.

2.1.3 What is the proposed dosage form and route of administration?

The proposed dosages are ER capsules containing 10, 15, 20, 30, 40, 50, 60 (b) (4) mg of methylphenidate administered orally.

2.1.4 What is the reported adverse event profile from the pharmacokinetic studies?

For study pk001, a total of 14 (53.8%) subjects experienced at least one treatment-emergent adverse event (TEAE) during the study. Eight (33.3%), 3 (32.0%) and 9 (36.0%) subjects reported at least one TEAE following

administration of Aptensio ® 80 mg capsule, Aptensio ® 80 mg sprinkle, and the RLD, respectively.

In study pk002, a total of 15 (57.5%) subjects experienced at least one treatment-emergent adverse event (TEAE) during the study. Nine (37.5%) and 8 (34.8%) subjects reported at least one TEAE following administration of Aptensio ® 80 mg and RLD 25 mg (three times a day), respectively. There were no serious adverse events reported.

The most common TEAEs for both studies were nausea, headache, decreased appetite and dry mouth. Refer to the medical review for the Agency's assessment of safety.

2.2. General Clinical Pharmacology and Biopharmaceutics

2.2.1 What were the in vivo Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA?

The clinical pharmacology package for Aptensio consists of two pivotal pharmacokinetic studies in adults, a pilot PK study in children and a population PK study. Table 5 summarizes the *in vivo* studies included in the package.

Table 5: Overview of *In Vivo* Studies

Study ID, Data Source, Start-End Dates	Pivotal or Supportive	Study Centers	Study Objective	Design & Control	Duration
RP-BP-EF001; Full CSR in this NDA (complete study Synopsis Section 2.7.3.8.1.1)	Pivotal	1 Center; Child Development Center, Univ. of California, Irvine	Efficacy and safety of Biphentin™ in children	Open-Label Titration Followed by Randomized, Double-Blind, Placebo-Controlled Crossover, Open-Label Safety Follow-up; After 1-week of each Double-Blind medication, Patient Underwent a day of Evaluation in a Typical Lab School Day	Titration, up to 4 weeks; Double-blind phase, 1-week on each treatment; 30 day safety follow-up; and up to 21 months allowing compassionate use
RP-BP-EF002; Full CSR in this NDA (complete study Synopsis Section 2.7.3.8.1.2)	Pivotal	16 Centers[a] (see legend for locations)	Efficacy and safety of Biphentin™ in children and adolescents	Randomized, Double-Blind, Placebo-Controlled Forced-Dose, Followed by Open-label Titration and Safety Follow-up	Washout, then one 1-week double-blind treatment; followed by 11-week open-label titration and follow-up and up to 21 months allowing compassionate use
RP-BP-PK001; (Full CSR in Module 5.3.1.2)	Pivotal	1 Center; Frontage Laboratories, Inc., 241 Main Street, Hackensack, NJ	Single-dose Pharmacokinetics and safety of Biphentin™ in healthy adults	Bioavailability Study of a Single 80 mg Dose of Biphentin™ Methylphenidate Hydrochloride ER Capsule, a Single 80 mg Dose of Biphentin™ Methylphenidate Hydrochloride ER Capsule Dosed as Sprinkles vs. Reference 25 mg Ritalin® IR Given Three Times Daily in Healthy Adults under Fasted Conditions	Approximately 3 weeks, including a 21-day screening period and a 1-day treatment period.
RP-BP-PK002; (Full CSR in Module 5.3.1.2)	Pivotal	1 Center; Frontage Laboratories, Inc., 241 Main Street, Hackensack, NJ	Steady-State PK of Biphentin™ vs. Ritalin® IR in Healthy Adults	Bioavailability Study of a Single 80 mg Dose of Biphentin™ Methylphenidate Hydrochloride ER Capsule, a Single 80 mg Dose of Biphentin™ Methylphenidate Hydrochloride ER Capsule Dosed as Sprinkles vs. Reference 25 mg Ritalin® IR Given Three Times Daily in Healthy Adults under Fasted Conditions	Approximately 4 weeks, including a 21-day screening period and 4-day treatment period.
Study 022-001 (Full CSR in Module 5.3.5.4)	Pilot PK	1 Center; Anapharm., 2050 Boul. Rene-Levesque Ouest, Sainte-Foy Quebec, Canada_	Relative Bioavailability of methylphenidate CR (MPH-MLR) under fed and Fasted Conditions	4-Treatment Bioavailability Study to Compare Absorption of One Test Methylphenidate CR 20 mg Capsule and One Reference Comparator Ritalin IR® Under Fasting and Fed Conditions	Approximately 7-weeks, including screening and 22-day treatment period
022-004 (Weiss, et al., 2007)	Supportive	Multicenter[b] (see legend for locations)	Efficacy and safety of methylphenidate CR in children and adolescents	Randomized, Double-Blind, Crossover, study of Controlled-Release Methylphenidate (MPH-MLR) versus IR Methylphenidate in Treatment of ADHD Children 6-17 years of age	Titration, up to 3-weeks; Double-blind phase, 2-weeks on each treatment
RP-PopPK002	Pivotal	Single	PK/PD Modelling	Population Pk Modeling to Bridge the population Pk Model from RP-Poppk001from Adult Subjects to Pediatric Patients and Develops a PK/PD Model to Describe Change From Baseline in the ADHD Total Score as a Primary Efficacy Measure	NA

2.2.2 What are the highlights of the formulation of the drug product?

The compositions of different strengths of Aptensio ® are summarized in Table 6.

Table 6: Composition of 10, 15, 20, 30, 40, 50, 60, (b) (4) mg Capsules

Ingredient (and Test Standard)	10 mg	15 mg	20 mg	30 mg	40 mg	50 mg	60 mg	(b) (4)
Methylphenidate HCl (USP)	10.000	15.000	20.000	30.000	40.000	50.000	60.000	
Sugar spheres (b) (4)							(b) (4)	
Ammonio Methacrylate Copolymer, Type B (b) (4)								
Methacrylic acid copolymer, Type C (b) (4)								
Triethyl citrate (NF)								
Talc (USP) (b) (4)								
Colloidal Silicon Dioxide								
Total Weight of Beads (mg)								
Capsule Shells** (mg)								
Total Finished Dosage Form***	116.3	155.4	204.5	295.8	389.0	487.2	576.5	

(b) (4)

**Average empty capsule weight

***with empty capsule weight (b) (4)

A breakdown of the composition of each of capsule shell is included in the Tables below.

Size 4 CS – 10mg Capsule (White/Light Turquoise Blue)	(b) (4)
Size 4 CS – 15mg Capsule (White/Orange)	
Size 3 CS – 20mg Capsule (White/Yellow)	
Size 2 CS – 30mg Capsule (White/Blue Violet)	
Size 1 CS – 40mg Capsule (White/Pink)	

Size 0 CS – 50mg Capsule (White/Light Green)	Body Composition	(b) (4)
	Cap Composition	
Size 0EL CS – 60mg Capsule (White/Grey)	Body Composition	
	Cap Composition	

(b) (4)

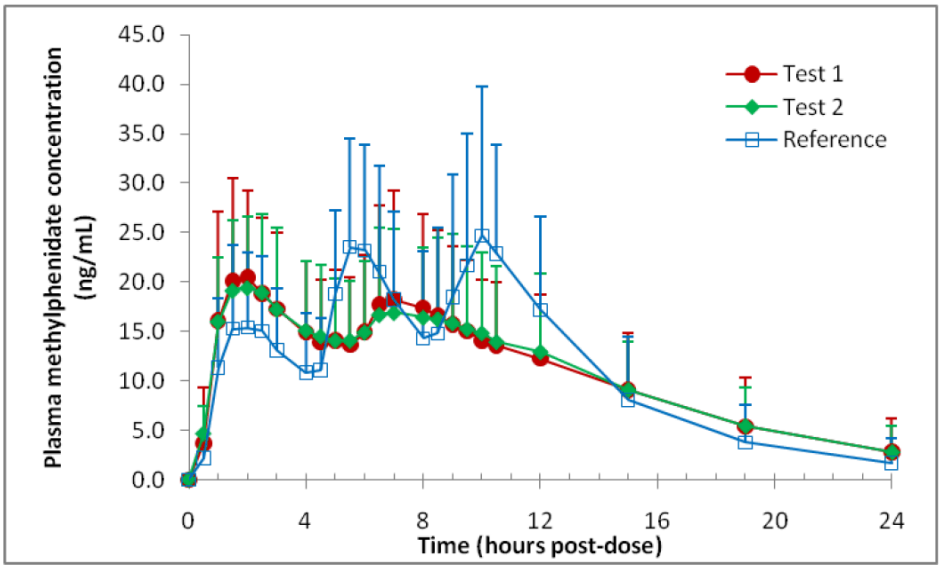
2.2.3 What drugs (substances, products) indicated for the same indication are approved in the US?

Other approved methylphenidate products indicated for the treatment of ADHD are Concerta ®, Ritlain LA ®, Focalin ®, Metadate CD ®, and Quillivant ®.

2.2.4 Does Aptensio show characteristics of an extended-release formulation?

Yes. The pharmacokinetic profile of Aptensio demonstrates the characteristics of an extended release formulation (Figure 6) and supports the once daily dosing.

Figure 6: Plasma Concentrations for an 80 mg Dose of Aptensio in Adults Compared to 25 mg Ritalin IR Tid.



T1: Test: Biphentin 80 mg capsule
T2: Test: Biphentin 80 mg sprinkle
R: RLD (Ritalin) 75 mg daily dose consisting of 25 mg dose administered at time 0, 4, 8 hours.
SD bars shown above the mean represent standard deviation around the mean.

2.2.5 Can Aptensio ® be administered as a whole capsule or as sprinkles into apple sauce?

Yes. A pharmacokinetic study was conducted in adults comparing the administration of the 80 mg capsule administered either as a whole capsule or after the content of the capsule mixed with one teaspoon of applesauce. As shown in Table 7, the respective ratios of the geometric means and corresponding 90% confidence intervals of Cmax, AUC0-inf and AUC0-t are within 80%-125%. In addition, the median Tmax values are both 2 hours with similar ranges. Furthermore, the mean pharmacokinetic profiles when administered as a whole capsule and sprinkled onto apple sauce are

superimposable (Figure 6). Therefore, similar mean efficacy and safety profiles are expected when Aptensio ® is given as a whole capsule or sprinkled into apple sauce.

Table 7: Comparisons of Pharmacokinetic Parameters Obtained from Patients Receiving Sprinkles versus the Whole Capsule

PK parameter (unit)	Geometric means			Ratio (T/R) or (T1/T2)	90% CI (T/R) or (T1/T2)
	Test 1 n=23	Test 2 n=23	Reference n=24		
T1: R					
C_{max} (ng/mL)	21.20		28.52	0.74	68.71, 80.43
AUC $_{0\text{-inf}}$ (ng·hr/mL)	261.91		268.43	0.98	93.94, 101.34
AUC $_{0\text{-t}}$ (ng·hr/mL)	242.28		260.98	0.93	89.26, 96.54
T2: R					
C_{max} (ng/mL)		20.38	28.52	0.71	66.12, 77.20
AUC $_{0\text{-inf}}$ (ng·hr/mL)		264.50	268.43	0.99	94.87, 102.34
AUC $_{0\text{-t}}$ (ng·hr/mL)		244.38	260.98	0.94	90.10, 97.32
T1 : T2					
C_{max} (ng/mL)	21.20	20.38		1.04	96.29, 112.42
AUC $_{0\text{-inf}}$ (ng·hr/mL)	261.91	264.50		0.99	95.33, 102.85
AUC $_{0\text{-t}}$ (ng·hr/mL)	242.28	244.38		0.99	95.39, 103.03

T1: Test: Biphentin 80 mg capsule
T2: Test: Biphentin 80 mg sprinkle
R: RLD (Ritalin) 75 mg daily dose consisting of 25 mg dose administered at time 0, 4, 8 hours.
All calculations based on dose-normalized values.

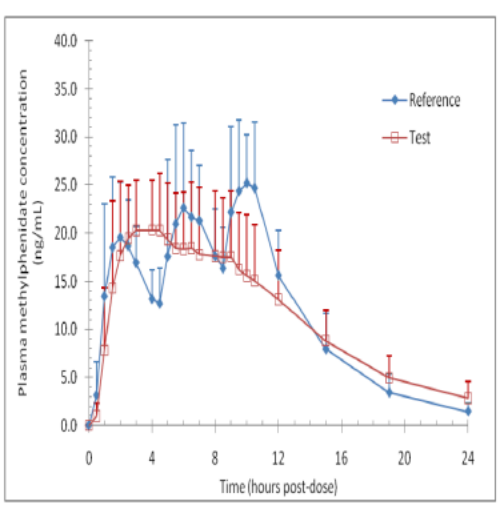
2.2.6 What is the pharmacokinetic feature following multiple doses of Aptensio ® 80 mg ER with a high fat breakfast?

A multiple-dose pharmacokinetic study was conducted comparing an 80 mg dose of Aptensio ® with Ritalin ® IR 25 mg given 3 times a day in healthy adults under fed conditions. The pharmacokinetic profiles on Day 1 and Day 12 are represented in Figure 7. The results comparing methylphenidate exposure on Day 1 and Day 12 under fed condition are presented in Table 8, which showed that there is no accumulation of methylphenidate following repeated dosing of Aptensio ®.

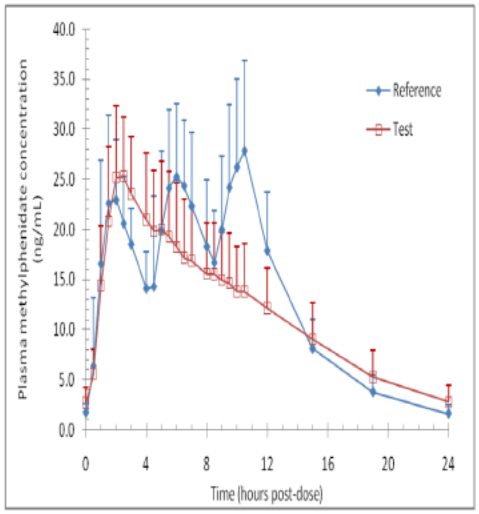
Figure 7 shows the second peak of the mean methylphenidate pharmacokinetic profile is reduced or diminished under fed conditions. At individual level, higher percentage of subjects with smaller second peak (< 80% of the first peak) as compared to the first peak can be found in subjects under fed conditions than under fast conditions (Table 9). Pharmacokinetic profile of methylphenidate is known to correlate with its pharmacodynamics effect. Hence, to ensure

consistent efficacy and safety experience for a patient receiving Aptensio ®, it is recommended that patients should establish a routine pattern with regard to meals.

Figure 7: Mean (SD) Plasma Methylphenidate Concentration versus Time by Treatment after Single Dose under Fed Conditions (linear scale) - PK population Day 1 (A) and Day 12 (B)



Test: Biphentin (methylphenidate HCl) Extended-Release 80 mg capsule administered at time 0 hour.
Reference: RLD (Ritalin) 75 mg daily dose administered at time 0, 4, 8 hours.
SD bars represent standard deviation around the mean.
The concentration versus time curves represent the average of each subject's drug level at each time point, and the highest point on each curve, (apparent C_{max}) is actually the maximum average value during time 0 to time 24 hours post-dose. In contrast, mean C_{max} shown in the summary tables represents the average of each subject's maximum drug level, regardless of the time point at which this occurred.



Test: Biphentin (methylphenidate HCl) Extended-Release 80 mg capsule administered at time 0 hour.
Reference: RLD (Ritalin) 75 mg daily dose administered at time 0, 4, 8 hours.
SD bars represent standard deviation around the mean.
The concentration versus time curves represent the average of each subject's drug level at each time point, and the highest point on each curve, (apparent C_{max}) is actually the maximum average value during time 0 to time 24 hours post-dose. In contrast, mean C_{max} shown in the summary tables represents the average of each subject's maximum

(A) (B)

Table 8: Statistical Analysis of Bioavailability of Test (Aptensio ®) versus Reference Treatment (Ritalin) (PK population) Day1 and Day 12 under Fed Conditions.

PK parameter	Geometric means		Ratio (T/R)	90% CI (T/R)
	Test n=21	Reference n=21		
Single dose				
C_{max} (ng/mL)	0.29	0.40	0.71	66.81, 75.66
AUC $_{0\text{-}inf}$ (ng·hr/mL)	3.54	3.82	0.93	88.57, 97.28
AUC $_{0\text{-}t}$ (ng·hr/mL)	3.28	3.72	0.88	84.75, 91.80
Steady-state				
C_{max} (ng/mL)	0.34	0.43	0.80	74.70, 85.51
AUC $_{0\text{-}inf}$ (ng·hr/mL)	3.68	4.19	0.88	84.48, 91.17
AUC $_{0\text{-}it}$ (ng·hr/mL)	3.43	4.08	0.84	81.16, 86.94

Calculations based on dose-normalized values.
Test: Biphentin (methylphenidate HCl) Extended-Release 80 mg capsule administered at time 0 hours.
Reference: RLD (Ritalin) 75 mg daily dose administered at time 0, 4, 8 hours.
Source: 14.2.3 and 14.2.6

Table 9: Percentage of Subjects that Demonstrated a Smaller Second Peak as Compared to the First Peak

	Treatment Group			
	Fast (PK-001)		Fed (PK-002)	
Condition	Capsule	Sprinkle	Day 1	Day 12
Percentage *(ratio)	46% (11/24)	36% (9/25)	(58%) 12/21	72% (15/21)

*: Percentage of reduced or diminished second peak is defined as the second peak occurs between 5-10 hours and is less than 80% of the first peak which occurs between 0-5 hours.

2.2.7 Do the supportive studies using the Canadian formulation show a food effect?

The sponsor conducted several supportive studies using a Canadian formulation. Study 022-013 looked at the food effect on the Canadian Aptensio ® and Concerta ® (Figure 8). Study 022-006 investigated the 20 mg capsules under fed and fasted conditions vs Ritalin LA (Figure 9), while study 97-147 using a 20 mg Canadian capsule vs 20 mg IR tablet under fed and fasted conditions (Figure 10).

Figure 8: Study 022-013: Methylphenidate Mean Concentration - Time Profile under fed conditions (N = 21 for Concerta and the Canadian Aptensio test product)

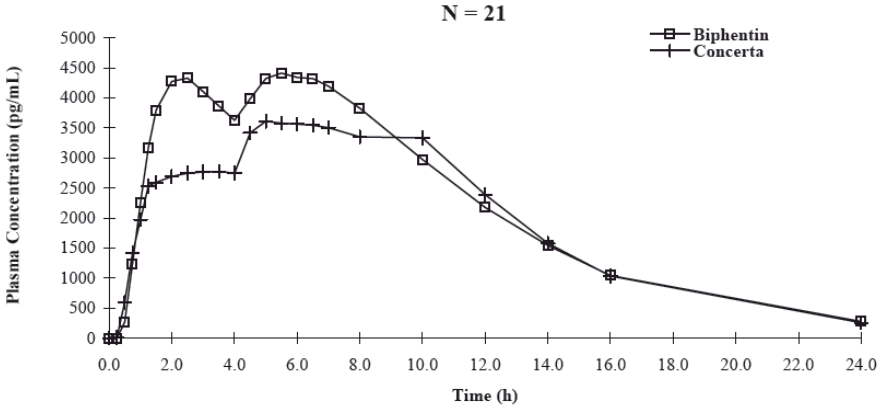


Figure 9. Study 022-006: mean methylphenidate plasma concentrations under fed and fasted conditions. (Test product is Canadian Aptensio)

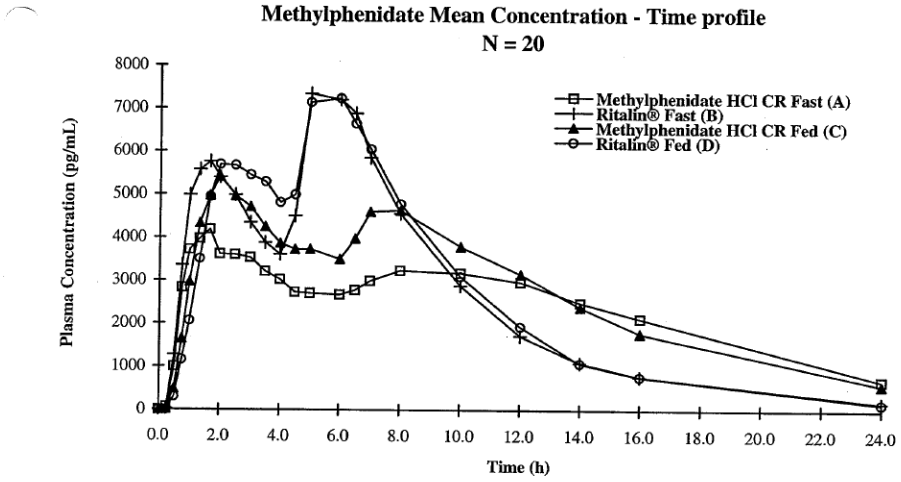
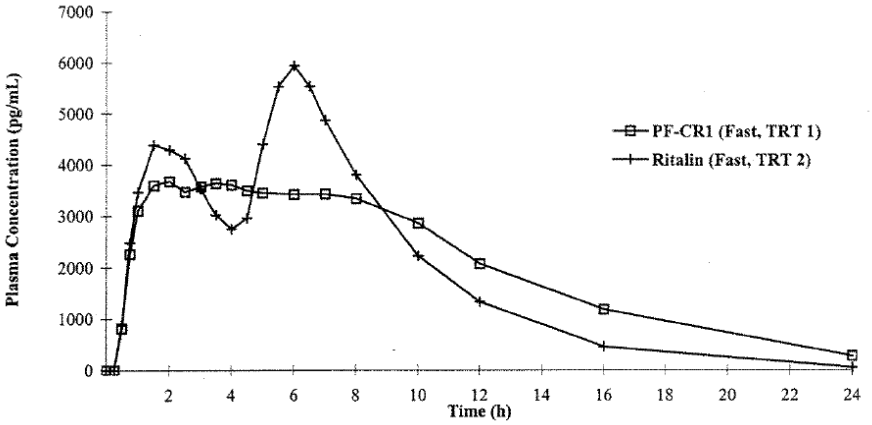
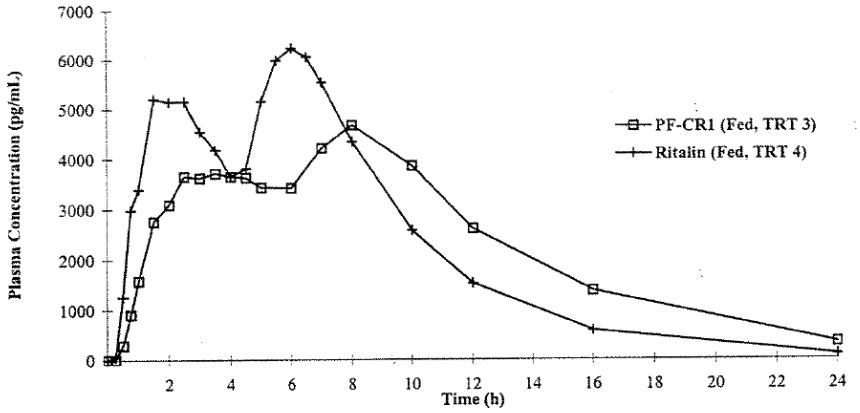


Figure 11. Study 97-147: mean methylphenidate time profiles under fast conditions (A) and fed conditions (B)



(A)



(B)

These results are different from those observed for the US product in the following ways:

1. As shown in Study 022-013, the profile for the Canadain product does not appear to be impacted by food after a single dose in contrast to what is observed for the US product with the second peak and Cmax decreased by food.

2. As shown in study 022-006, the pharmacokinetic curve for the Canadian product looks very similar to the US product. Food appears to make the second peak more prominent for the Canadian product in contrast to the US reference for which food decreases the size of the second peak.

3. The observations from study 022-006 are further supported by study 97-147 which shows the food curve to resemble the US reference curve under fasting conditions.

The three studies are pilot studies using Canadian products. The sponsor conducted a separate food effect study using the U.S. product. The food effect study results based on Canadian products are summarized only for reference.

2.2.8 How was the drug administered with respect to food in the pivotal efficacy and safety trials - Study EF001 and Study EF002?

For Study EF001 breakfast was provided after dosing. For study EF002 the drug was not administered in the fasting state; patients took their medication either before, during, or after meals.

2.2.9 What was the design of the short term efficacy studies and what were the clinical endpoints?

Study EF001 was a randomized, double-blind study of the time course of response to Aptensio ® methylphenidate hydrochloride extended-release capsules as compared to placebo in children 6 to 12 years with Attention Deficit Hyperactivity Disorder in an analog classroom setting. During the open-label optimization phase, all subjects began at an initial Aptensio ® dose of 15 mg and were titrated to an optimal dose using Aptensio ® strengths of 15, 20, 30 or 40 mg, up to the maximum of 40 mg/day. For safety reasons subjects who weighed 25 kg or less were not to be assigned to receive the 40 mg dose. The results are shown in Table 10.

Table 10: Primary Efficacy Endpoint Analysis: SKAMP Total Score Averaged Over All Postdose Time points for the Evaluable and ITT Population

LS	Mean		P-Values[a]			
Total Score	Placebo	Biphentin	Treatment	Covariate	Sequence[b]	Period[c]
Evaluable Population (N = 20)	2.18	1.32	0.0001	0.0003	0.5279	0.0714
ITT Version 1 (N = 22)	2.05 1	.32	0.0005	0.0006	0.8824	0.2570
ITT Version 2 (N = 22)	2.06 1	.33	0.0011	0.0005	0.8524	0.3168
ITT Version 3 (N = 22)	2.05	1.28	0.0002	0.0006	0.9955	0.1664
ITT Version 4 (N = 22)	2.05 1	.29	0.0004	0.0008	0.9966	0.1912

The second study was Study RP-BP-EF002, where the primary efficacy endpoint was the change from baseline (Visit 2) to the end of Week 1 (Visit 3) in the clinician-rated ADHD-RS-IV (ADHD Rating Scale). The design was a parallel, randomized, double-blind, multicenter, placebo-controlled, forced dose, phase 3 study to evaluate the safety and efficacy of Aptensio ® in the treatment of ADHD in children and adolescent patients aged 6 to 18 years. Subjects received their double-blind, randomized dose (10, 15, 20, or 40 mg Aptensio or placebo) for 1 week. Following the double-blind phase, doses were optimized via titration in an open-label manner and subjects continued receiving Aptensio for 11 weeks. During the Double-Blind phase, subjects participated in a Baseline Visit (Visit 2, Day 0) during which they underwent baseline assessments and were dispensed a randomized, double-blind, fixed dose of 10, 15, 20, or 40 mg/day Aptensio or placebo for 1 week. The first dose of double-blind study drug was taken the following morning. The subject's parent/legally authorized representative was required to administer study drug to the subject in the morning each day no later than 10 a.m. The trial results are shown in Table 11.

Table 11: Descriptive Statistics for Decrease in ADHD-RS-IV Total Score from Baseline (Visit 2) to the End of Double-Blind Phase (Visit 3) (Efficacy Population, N = 221)

Statistic	Placebo	10 mg	15 mg	20 mg	40 mg
N	46	48	40	44	43
Mean	5.1	9.3	11.2	12.3	13.2
Median	2.0	8.0	8.0	12.0	13.0
Standard Deviation	10.29	8.86	12.06	9.84	10.29
Min	-22.0	-8.0	-4.0	-5.0	-3.0
Max	32.0	32.0	40.0	45.0	42.0
Data Source: Table 14.2.1.1.1					

2.2.10 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The firm conducted a single-dose 80 mg dose of Aptensio ® dosed as capsule vs 80 mg dose of Aptensio ® dosed as sprinkles vs a reference 25 mg IR under fasted conditions in adults. A second bioavailability study of a single 80 mg dose of Aptensio ® methylphenidate hydrochloride ER capsule dosed under fed

conditions vs. 25 mg Ritalin® IR given three times daily in healthy adults also under fed conditions. They also conducted a PK study in pediatric subjects.

2.2.11 What are the sponsor's dosing recommendations for Aptensio?

The sponsor proposed dosing recommendations are shown in table 2 based on simulations using a population pharmacokinetic model.

2.2.12 Did the heavier children in Study EF001 get higher doses?

Study EF001 is designed as a flexible-dosing study. Patients received the final doses through titration based on clinical responses. The results do not appear to suggest that high body weight patients are always titrated to a relatively high dose based on clinical response and patient tolerability, given the caveat that the trends are observed based on small number of subjects and might not be definitive.

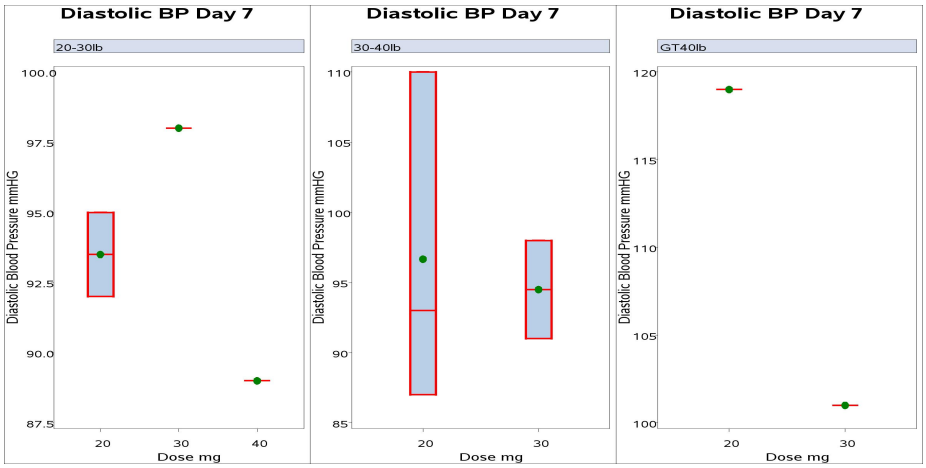
(b) (4)

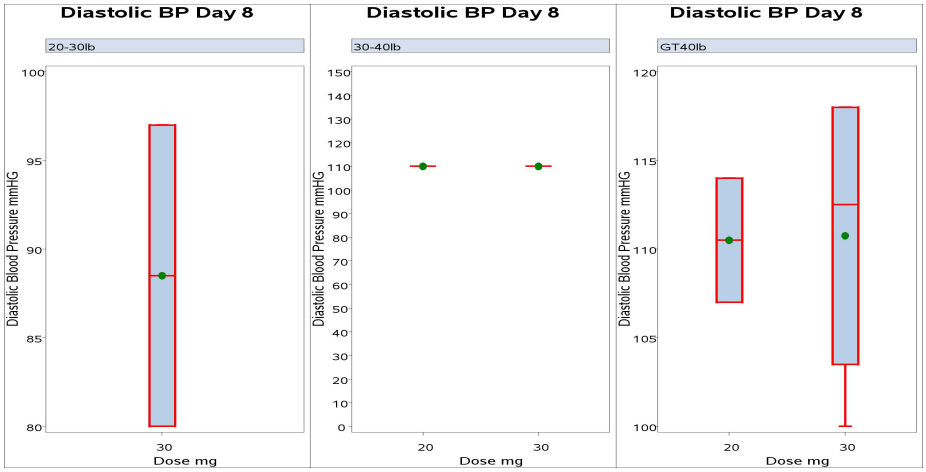
2.2.14 Does the safety data for either sleep, blood pressure or pulse show any increase in low body weight patients receiving the same dose as high body weight patients?

Safety data based on Study EFF001 do not provide conclusive/definitive information to suggest that a detailed body weight based dosing is necessary. The comparison was based on various safety signals observed in children with different body weight receiving the same dose. Due to the small sample size in the study, the results are not conclusive.

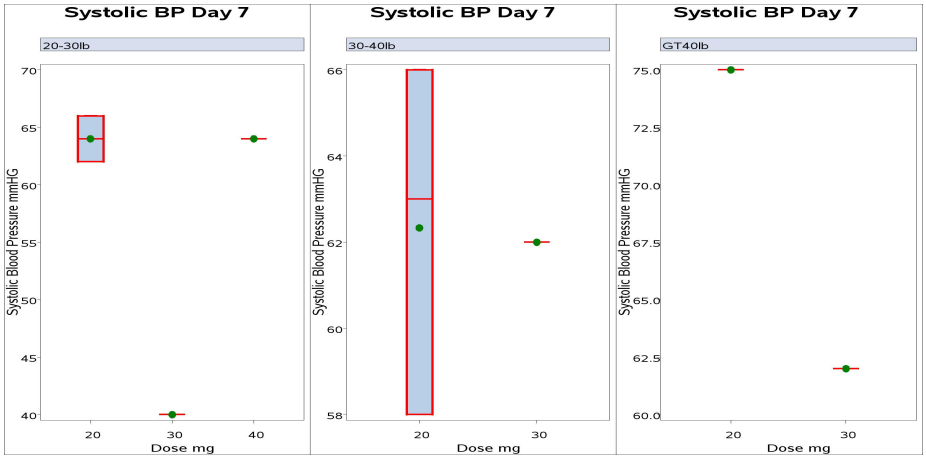
There was no clear trend on observed diastolic blood pressure, systolic blood pressure, plus, and sleep with respect to body weight for any of the dose groups (Figure 13).

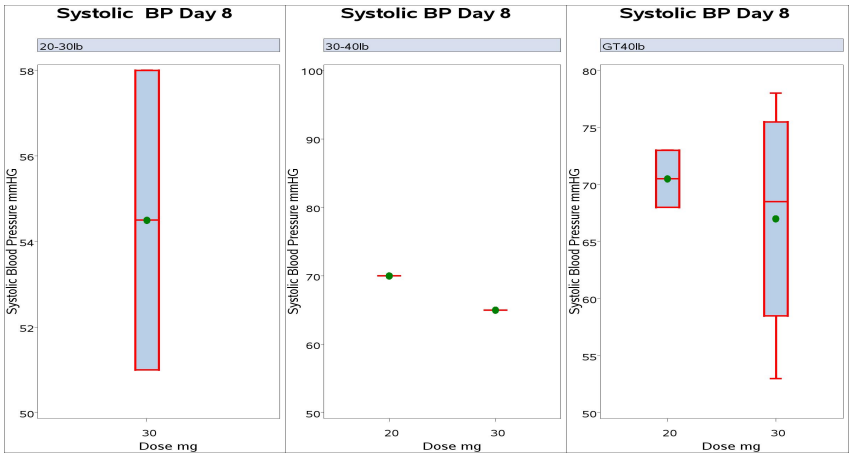
Figure 13: Observed Major Safety Signals for Pediatric Patients Receiving Different Doses of Aptensio ® Stratified by Body Weight

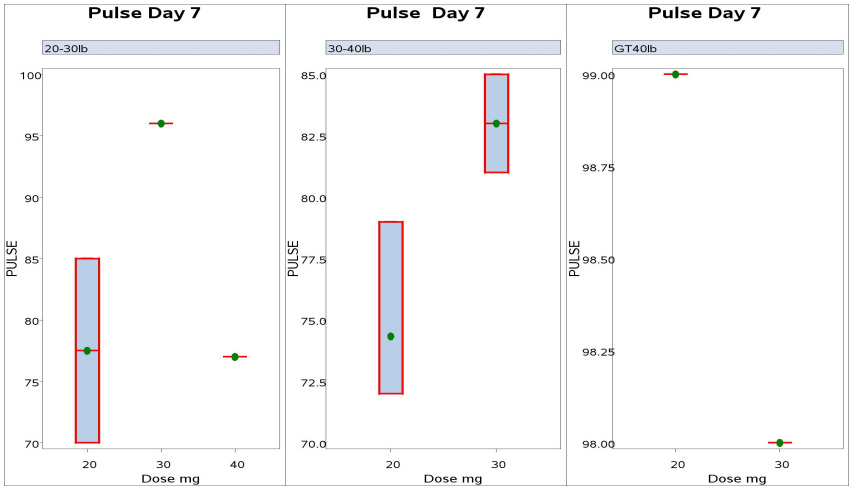


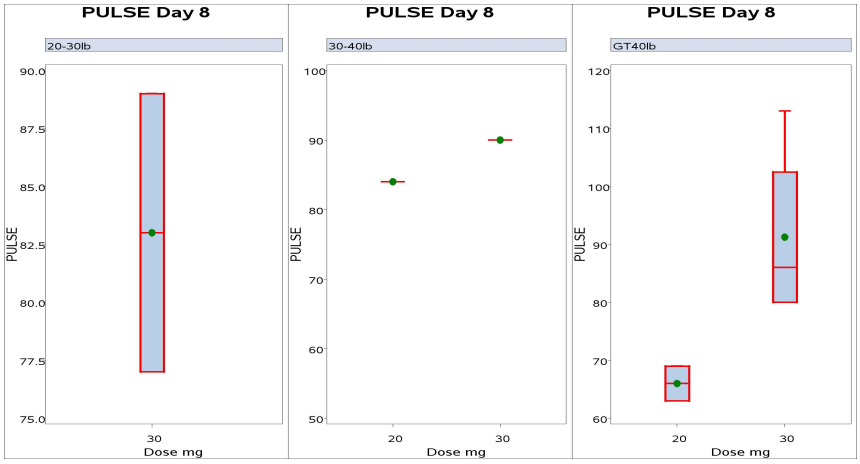


Systolic Blood Pressure

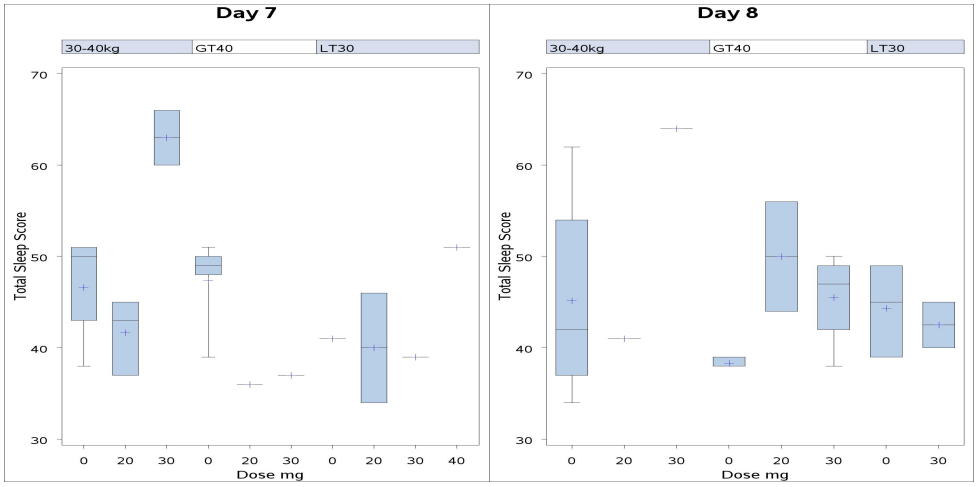



Systolic BP Day 8
20-30lb
30-40lb
GT40lb
Systolic Blood Pressure mmHG
Dose mg


Pulse Day 7
Pulse Day 7
20-30lb
30-40lb
GT40lb
PULSE
Dose mg


PULSE Day 8
PULSE Day 8
PULSE Day 8
20-30lb
30-40lb
GT40lb
PULSE
Dose mg

Sleep-



3.0 Analytical Methods

3.1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes, the active moiety, d- and l-methylphenidate was appropriately measured in biological fluids.

3.2 What bioanalytical methods are used to assess concentrations of d- and l-methylphenidate and is the validation complete and acceptable?

A liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) method was used to analyze the plasma samples from the clinical studies. The method used for the clinical studies was solid phase extraction (SPE) followed by liquid chromatography (LC) based on cation exchange chromatography and tandem mass spectrometric detection (MS/MS), with the mass spectrometer operated in the Multiple Reaction Monitoring mode with positive ion electrospray. The concentrations of dl-methylphenidate in human plasma were determined using a precise and accurate LC-MS/MS method. The calibration range of the method is 2 to 1000 ng/mL using a 50.0 µL aliquot of plasma. The method was sensitive, selective, accurate, and reproducible. Dl Methylphenidate is stable during storage, processing and analysis in human plasma samples. The analytical method was adequately validated and acceptable. The following is a tabular summary of the validation of the bioanalytical method.

Information Requested	**Data**
Bioanalytical report location	**\\cdsesub1\evsprod\nda205831\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\fro-r1524r1\fro-r1524r1-meth-val.pdf**

Analyte	dl-methylphenidate

Method description	Method BTM-1375-R0 is an LC/MS/MS method for the determination of methylphenidate in K_2EDTA human plasma using methylphenidate-D_9 as the internal standard (IS). Methylphenidate and the IS were extracted by protein precipitation from human plasma using acetonitrile. Reversed-phase HPLC separation was achieved with a Thermo Scientific, Hypersil Gold aQ™ column (50 x 3 mm, 3micron). MS/MS detection was set at mass transitions of m/z 234.0→84.0 for methylphenidate and m/z 243.1→93.1 for methylphenidate-D_9 (IS) in TIS positive mode.
Sample volume	100 µL
Regression	Linear Regression
Weighting factor	$1/x^2$
Dynamic range	50-25000 pg/mL for methylphenidate
QC concentrations	150 pg/mL, 7500 pg/mL, and 18750 pg/mL
Analytes	Methylphenidate
Internal standards	Methylphenidate-D_9
Linearity	R^2 ≥0.9983
Lower limit of quantitation (LLOQ)	50 pg/mL
Average recovery of the Analyte (%)	98.6
QC Intra-run precision range (%CV)	Run 1: 1.2-3.6
	Run 2: 1.7-2.9
	Run 3: 1.3-4.3
QC Intra-run accuracy range (%Nominal)	Run 1: 95.3-95.9
	Run 2: 91.7-97.8
	Run 3: 96.4-97.3
QC Inter-run precision range (%CV)	1.8-4.2
QC Inter-run accuracy range (%Nominal)	94.8-96.8
QC sample bench-top stability	At least 5 hours in an ice-water bath under yellow light At least 6 hours at room temperature under white light
Stock solution stability	At least 6 hours at room temperature without light protection for methylphenidate prepared in diluent (50:50 acetonitrile:water) At least 111 days at -20 °C for methylphenidate prepared in diluent At least 17 days at 4 °C for methylphenidate prepared in diluent
Processed sample stability	At least 102 hours at room temperature
QC sample freeze/thaw stability	3 freeze (-70 °C)/thaw cycles
QC sample long-term storage stability	At least 106 days at -70 °C
Dilution integrity	125000 pg/mL diluted 10-fold for methylphenidate
Matrix Effect	Matrix factor = 1.01 ± 0.03 at 150 pg/mL with %CV = 3.0% for methylphenidate
Hemolysis	The hemolysis evaluation met the acceptance criteria.
Selectivity	No interfering peaks were detected at the retention times of methylphenidate and the IS in blank human plasma.
Whole Blood Stability	At least 120 minutes in an ice-water bath (0-4 °C)

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/s/

ANDRE J JACKSON
03/27/2015

HAO ZHU
03/27/2015

BIOPHARMACEUTICS REVIEW

Division of Biopharmaceutics/Office of New Drugs Quality Assessment

Application No.:	NDA 205831	**Reviewers:** Kimberly Raines, Ph.D. Sandra Suarez Sharp, Ph.D.	
Division:	DPP		
Applicant:	Rhodes Pharmaceuticals L.P.	**Secondary Reviewer:** Sandra Suarez Sharp, Ph.D.	
		Acting Branch Chief: Angelica Dorantes, Ph.D.	
Trade Name:	Aptensio XR	**Division Director (acting):** Paul Seo, Ph.D.	
Generic Name:	Methylphenidate Hydrochloride multilayered controlled release capsules	**Date Assigned:**	July 10, 2014
Indication:	Treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years old and older	**Date of Review:**	January 26, 2015
Formulation/strengths	Extended Release Capsules/ 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (b) (4)		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Date	Date of informal/Formal Consult	Primary Review DUE DATE
February 20, 2015 February 4, 2015 January 12, 2015 June 18, 2014	June 20, 2014	March 3, 2015

Type of Submission:	Original NDA
Review key points:	-Dissolution method and acceptance criteria -Data supporting the approval of a biowaiver request for the lower strengths -Extended release designation claim -*In vitro* alcohol dose dumping in the presence of alcohol.

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

NDA 205831 for Aptensio XR, Methylphenidate Hydrochloride multilayer Release (MPH-MLR), Capsules was submitted under a 505 (b)(2) pathway relying on the previous established non-clinical and safety findings for Ritalin. Methylphenidate Hydrochloride multilayer Release (MPH-MLR) is being proposed by Rhodes Pharmaceuticals for once daily treatment of MPH. Ritalin (methylphenidate hydrochloride) immediate release tablets were approved by FDA under NDA 010187 for the treatment Attention Deficit Disorders and Narcolepsy on December 1955.

There are extended release dosage forms of methylphenidate hydrochloride currently approved in the United States, Concerta ER®, Metadate CD®, Focalin XR®, Ritalin LA®, and Quillivant XR®. Rhodes Pharmaceuticals has obtained the rights from Purdue Pharma, to develop and register a MPH-MLR product in the United States. Purdue Pharma markets a product sharing the same formulation under the trade name Biphentin in Canada.

The clinical development program for the proposed drug product consisted of two pharmacokinetic (PK) studies in healthy adults and two safety and efficacy studies in pediatric and adolescent patients with ADHD.

This review focuses on the Biopharmaceutics evaluation and acceptability of: **(1)** The proposed dissolution method and acceptance criteria, **(2)** The data supporting the approval of a biowaiver request for the lower strengths, **(3)** the extended release designation claim, and **(4)** the *in vitro* alcohol dose dumping in the presence of alcohol.

1) Dissolution Method and Acceptance Criteria

The following dissolution method and acceptance criteria have been agreed upon with the Applicant for Methylphenidate Hydrochloride Extended Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (b) (4) for batch release and stability testing (*refer to the Applicant's submission dated January 12, 2015*):

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criteria
Methylphenidate HCl	ER Capsules	I (basket)	100 rpm	**First Stage:** 500ml acidic medium for two hours **Second Stage:** 500 mL potassium phosphate buffer (pH 6.0) with a total of four (4) sampling points: 2, 6, 12, and 18 hours at 37.0 ± 0.5°C.	500 mL/ Stage	**First Stage:** 30 minutes: (b) (4)% 2 hours: (b) (4)% **Second Stage:** 6 hours: (b) (4)% 12 hours: (b) (4)% 18 hours: NLT (b) (4)%

The dissolution acceptance criteria were based on the mean in-vitro dissolution profile for methylphenidate HCl extended release capsules used in the clinical/registration/stability data. Note that the dissolution profile and acceptance criteria reflect the profile of an immediate release, delayed release, and extended release formulation. Since the provided dissolution data supported the discriminating ability of the method, the selected time points and criteria limits were found acceptable.

2) Data supporting the approval of a biowaiver request for the 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg lower strengths

The following information/data were provided in support of the biowaiver:

1. Data from a BE study conducted with the 80 mg strength and reviewed under NDA 205831
2. Clinical safety and efficacy data covering the proposed therapeutic range
3. Information demonstrating the linear elimination kinetics over the therapeutic dose range
4. Evidence of proportional similar composition of the formulations of the lower strengths to the higher 80 mg strength with an appropriate in vivo study
5. Dissolution profile comparisons of all the strengths with statistical testing (i.e. *f2*) in the recommended dissolution testing medium and three additional different media. The *f2* values in the QC media were higher than (b) (4) for all the strengths.

3) Extended Release Designation Claim

The following data were provided to support the extended release designation claim:

1. The drug product's performance is comparable to a currently marketed non-controlled release drug product that contains the same active drug ingredient and that is subject to an approved full NDA (Ritalin);
2. The drug product's steady-state performance is comparable to a currently marketed non-controlled release drug product that contains the same active drug ingredient and that is the subject to an approved full NDA;
3. The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product;
4. The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units (with immediate and extended release properties);

4) Assessment of the In Vitro Alcohol Dose-Dumping

The results of these studies showed that the integrity of the functional coating on the beads is compromised at high ethanol concentrations. This Reviewer presented the above in vitro-alcohol dose-dumping results during the mid-cycle meeting that took place on September 2014, and advised the reviewing team to evaluate the clinical relevance of the in vitro alcohol dose-dumping results. The reviewing team revised the language in Section 17 Patient Counseling to remind prescribers to inform patients of dose-dumping as follows:

> *"Advise patients to avoid alcohol while taking APTENSIO XR. Consumption of alcohol while taking APTENSIO XR may result in a more rapid release of the dose of methylphenidate".*

RECOMMENDATION:

The Division of Biopharmaceutics had reviewed NDA 205831 (000) and its amendments submitted on January 12, 2015, February 4, 2015, and February 20, 2015, for Methylphenidate Hydrochloride Extended Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (b) (4) Based on the review of the overall information, it is concluded that the data supporting the approval of a biowaiver request for the lower strengths is acceptable.

The extended release claim is supported. Waiver of the requirement to submit evidence demonstrating the in-vivo bioequivalence of Aptensio XR (methylphenidate extended release) Capsules 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg is granted. The final dissolution method and acceptance criteria for release and on stability are as follow:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criteria
Methylphenidate HCl	ER Capsules	I (basket)	100 rpm	**First Stage:** 500ml acidic medium for two hours **Second Stage:** 500 mL potassium phosphate buffer (pH 6.0) with a total of four (4) sampling points: 2, 6, 12, and 18 hours at 37.0 ± 0.5°C.	500 mL/ Stage	**First Stage** 30 minutes: (b) (4)% 2 hours: (b) (4)% **Second Stage** 6 hours: (b) (4)3% 12 hours: (b) (4)% 18 hours: NLT (b) (4)%

From Biopharmaceutics perspective, NDA 205831 for Methylphenidate Hydrochloride Extended Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (b) (4) is recommended for **APPROVAL**.

SIGNATURE BLOCK

Kimberly Raines -A
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Date: 2015.03.02 08:39:08 -05'00'

Kimberly Raines, Ph. D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics, ONDP, OPQ

Sandra Suarez -A
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Date: 2015.03.02 08:44:00 -05'00'

Sandra Suarez Sharp, Ph.D.
Acting Biopharmaceutics Lead
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Angelica Dorantes -S
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Date: 2015.03.02 18:08:29 -05'00'

Angelica Dorantes, Ph.D.
Acting Branch Chief
Division of Biopharmaceutics, ONDP, OPQ

c.c.: PSeo, JDuan

BIOPHARMACEUTICS ASSESSMENT

1. BACKGROUND

Submission

Methylphenidate hydrochloride is a central nervous system (CNS) stimulant and is classified as a noncatecholamine sympathomimetic that is a direct and indirect adrenergic agonist. Methylphenidate hydrochloride is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients who are 6 years old and older. Methylphenidate hydrochloride is widely commercialized in many formulations both immediate and extended release. The extended release dosage forms currently approved in the United States include Concerta ER®, Metadate CD®, Focalin XR®, Ritalin LA®, and Quillivant XR®.

Rhodes Pharmaceuticals L.P. has obtained the rights from its Canadian associated company, Purdue Pharma, to develop and register a methylphenidate hydrochloride multilayer release (MPH-MLR) product, Aptensio XR, in the United States. Purdue Pharma has marketed a product sharing the same formulation under the trade name Biphentin in Canada. Rhodes Pharmaceuticals is incorporating data from the Canadian registration in support of this 505(b)(2) New Drug Application (NDA) filing.

In Canada, Biphentin has shown success in modulating ADHD in patients who are 6 years of age and older. It comes in 8 fixed doses, namely 10, 15, 20, 30, 40, 50, 60, and 80 mg, which provides prescribers customized, flexible dosing for dose titration. Additionally, Biphentin's first peak plasma concentration is similar to immediate release methylphenidate dosage forms. Except for the active pharmaceutical ingredient coming from a different source (b) (4) for US clinical and exhibit batches and (b) (4) for the Canadian marketed product), the clinical (MPH-MLR) and commercial (Biphentin) formulations (b) (4)

Review: The Biopharmaceutics review is focused on the acceptability of the following:

- Dissolution method and acceptance criteria
- Data supporting the approval of a biowaiver request for the lower strengths
- Extended release designation claim
- *In vitro* alcohol dose dumping in the presence of alcohol.

Drug Substance

Methylphenidate hydrochloride USP is a white to off-white, odorless, fine crystalline powder. It is freely soluble in water and methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

Drug Product

APTENSIO XR (methylphenidate hydrochloride) Extended-Release Capsules are hard gelatin capsules that work by delivering the immediate-release portion of the methylphenidate dose (b) (4) This technology facilitates once a day dosing before school, work or other start of the day activities without the need for mid-day dosing. The formulation is composed of multi-layer controlled-release beads comprising of approximately (b) (4)% immediate release and approximately (b) (4)% controlled release layers (provided below). The Applicant states that APTENSIO XR and commercial (Biphentin) (b) (4) please see **Figure 1** for a comparative manufacturing process profile. Table 1 summarizes the components and composition of all the proposed strengths of the drug product under review.

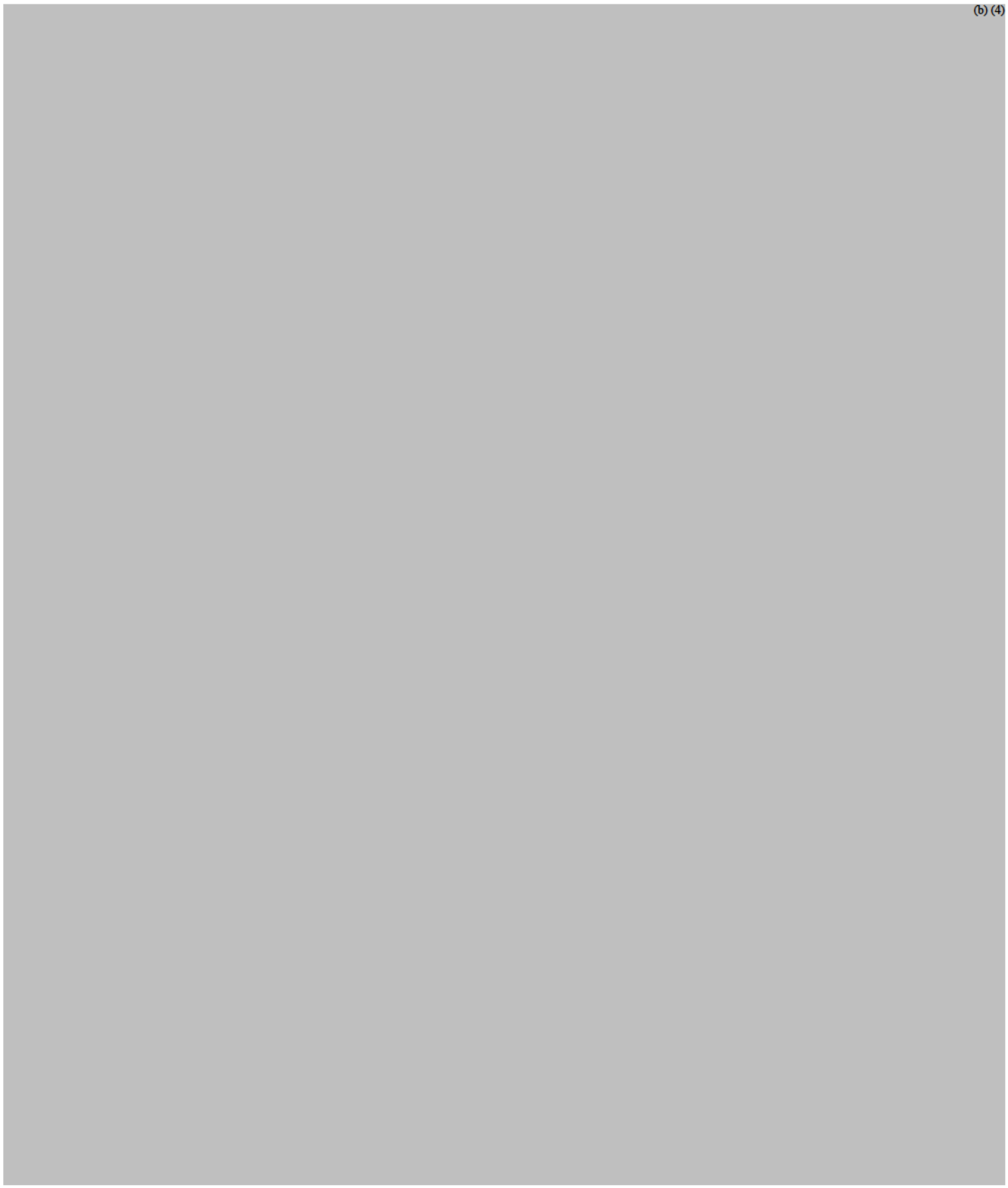
(b) (4)

Table 1: Components and Quantitative Composition of the Formulations for Methylphenidate HCl ER Capsules

Ingredient (and Test Standard)	10 mg	15 mg	20 mg	30 mg	40 mg	50 mg	60 mg
Methylphenidate HCl (USP)	10.000	15.000	20.000	30.000	40.000	50.000	60.000
Sugar spheres	(b) (4)						
Ammonio Methacrylate Copolymer, Type B	(b) (4)						
Methacrylic acid copolymer, Type C	(b) (4)						
Triethyl citrate (NF)							
Talc (USP)	(b) (4)						
Colloidal Silicon Dioxide							
Total Weight of Beads (mg)							
Capsule Shells** (mg)							
Total Finished Dosage Form***	116.3	155.4	204.5	295.8	389.0	487.2	576.5

(b) (4)

**Average empty capsule weight
***with empty capsule weight

(b) (4)

Reviewer's Comments:
As shown in Table 1, all strengths are formulated (b) (4) *are similar in composition to each other.*

Additionally, Rhodes provided dissolution profile comparisons between Aptensio XR Capsules (US clinical trial formulation) and Biphentin Capsules Extended Release (Canadian commercial formulation). Individual profile data of (b) (4) dosage units (individual, mean, SD and graphic-profiles) for Aptensio XR (Methylphenidate Hydrochloride Extended-Release) Capsules, 10 mg and (b) (4) mg strengths and for Biphentin Capsules Extended Release, 10 mg and 80 mg strengths were summarized and the *f2* calculation of each strength relative to Biphentin Capsules Extended Release in response to the FDA's filing communication letter for NDA 205831 dated on 08/28/2014. The following summarizes the Applicant response to this inquiry:

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2. DISSOLUTION METHOD

The dissolution method being proposed for Methylphenidate Hydrochloride Extended-Release Capsules is summarized below:

USP Apparatus	Agitation Speed	Medium	Volume
I (basket)	100 rpm	**First Stage:** 500ml acidic medium for two hours **Second Stage:** 500 mL potassium phosphate buffer (pH 6.0) with a total of four (4) sampling points: 2, 6, 12, and 18 hours at 37.0 ± 0.5°C.	500 mL/ Stage

The dissolution method was evaluated to determine the effect varying dissolution parameters would have on the *in vitro* drug release (for more details refer to dissolution method report under \\CDSESUB1\evsprod\NDA205831\0000\m3\32-body-data\32p-drug-prod\aptensio-xr\32p5-contr-drug-prod\32p52-analyt-proc). The following method parameters were evaluated: the effect of media pH, dissolution apparatus, HPLC detection wavelength, dissolution media volume, agitation rate, and degradant correction.

(b) (4)

[redacted]

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3. DISSOLUTION ACCEPTANCE CRITERIA

Reviewer's comments:
There is no IVIVC being proposed or approved for the proposed drug product. Therefore, the selection of the dissolution acceptance criteria limits should be based on mean target values ± 10% and NLT (b)(4)% for the last specification time-point. The original provided dissolution data did not support the proposed acceptance criteria and was deemed unacceptable. Specifically, the first point should reflect an acceptance criterion for the IR component of NLT(b)(4)% dissolved In 30 min which in this case is (b)(4)% variation rather than NLT (b)(4)% and the last time point should be the time point where at least (b)(4)% of drug has been released. Rhodes Pharmaceuticals was requested to implement the following dissolution acceptance criteria for its proposed product and to provide the revised specification table with the updated acceptance criterion for the dissolution test.

Proposed Acceptance Criteria	Recommended Acceptance Criteria
	(b)(4)

January 12, 2015, Rhodes Pharmaceuticals revised the dissolution acceptance criteria for its methylphenidate hydrochloride multilayer release capsules in response to Filing Communication Letter dated September 18, 2014. The 30 minute time point was added and other time points were revised.

Revised Recommended Acceptance Criteria	
First Stage	30 min: (b)(4)% 2 hrs: (b)(4)%
Second Stage	6 hrs: (b)(4)% 12 hrs: (b)(4)% 18 hrs: NLT (b)(4)%

The selected time points and criteria limits were found acceptable.

4. BIOWAIVER FOR LOWER STRENGTHS

Pursuant to 21 CFR 320.22, Rhodes Pharmaceuticals L.P. requests a waiver of the requirement to submit evidence demonstrating the in-vivo bioequivalence of Aptensio XR (methylphenidate extended release) Capsules 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg. This biowaiver request is supported by the following data:

1. The lower strengths are in the same dosage form and their formulations are proportionally similar in the active and inactive ingredients to the 80 mg strength drug product used in the bio-study. All strengths are manufactured from common multi-layer beads filled at different fill weights to obtain the requisite dose strengths.

2. An acceptable pharmacokinetic study demonstrating the bioequivalence (b) (4) (b) (4) with once daily dosing (QD) versus the 25 mg Ritalin IR Capsules, with three times a day dosing (TID).

3. A population pharmacokinetic model developed on the 80 mg strength in which simulations of methylphenidate concentrations for Biphentin™ doses of 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg were predictive (refer to OCP review for the assessment of this information).

4. Dissolution profile comparisons with statistical testing (*f2* testing) in the proposed stage 1/stage2 release media and three additional media (submitted February 20, 2015) to support the approval of the lower strengths. Rhodes provided dissolution profile comparisons for the all strengths (Figure 6A, 6B, 6C, and 6D).

Figure 6A: Dissolution Profiles of Aptensio in the final release media (b) (4)

(b) (4)

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Reviewer's Comments:
The explanation provided is acceptable given that all capsule strengths are manufactured (b) (4) *. The information provided supports the biowaiver request for the lower strengths.*

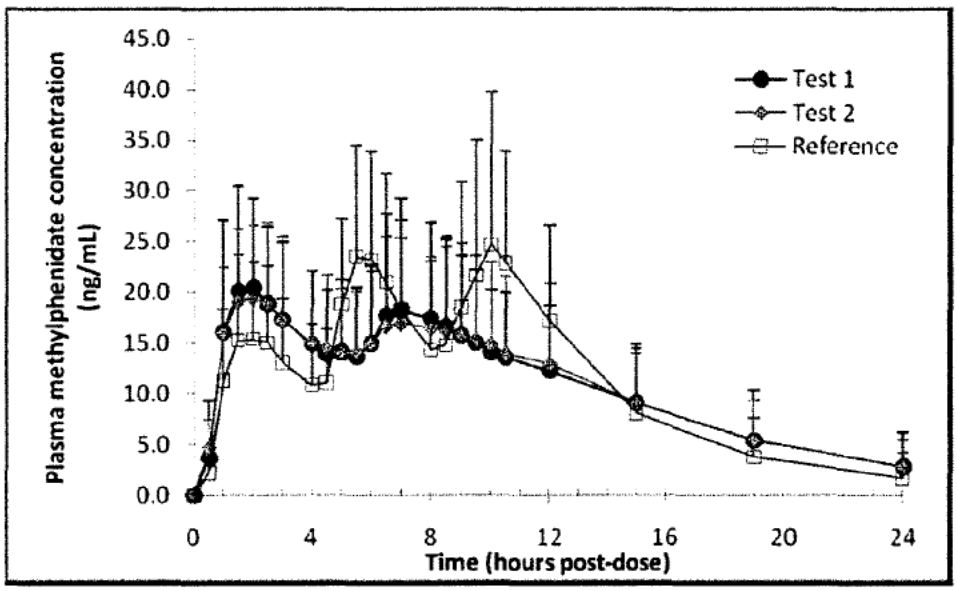
5. EXTENDED RELEASE-DESIGNATION CLAIM

The following data were provided to support the extended release designation claim:

- The drug product's performance is comparable to a currently marketed non-controlled release drug product that contains the same active drug ingredient and that is the subject to an approved full NDA;
- The drug product's steady-state performance is comparable to a currently marketed non-controlled release drug product that contains the same active drug ingredient and that is subject to an approved full NDA;
- The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product;
- The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units (with immediate and extended release properties).

The mean concentration versus time profiles for methylphenidate following administration of MPH-MLR 80 mg capsule, MPH-MLR 80 mg sprinkle, and reference comparator from Study RP-BP-PK001 are displayed in Figure 7. Three doses of comparator at 0, 4, and 8 hours resulted in a tri-phasic profile. In contrast, a single dose of MPH-MLR 80 mg, administered either as a capsule or as sprinkles resulted in similar, sustained concentration versus time profile over an approximate 8 hour period, after which a gradual decline in methylphenidate levels was observed.

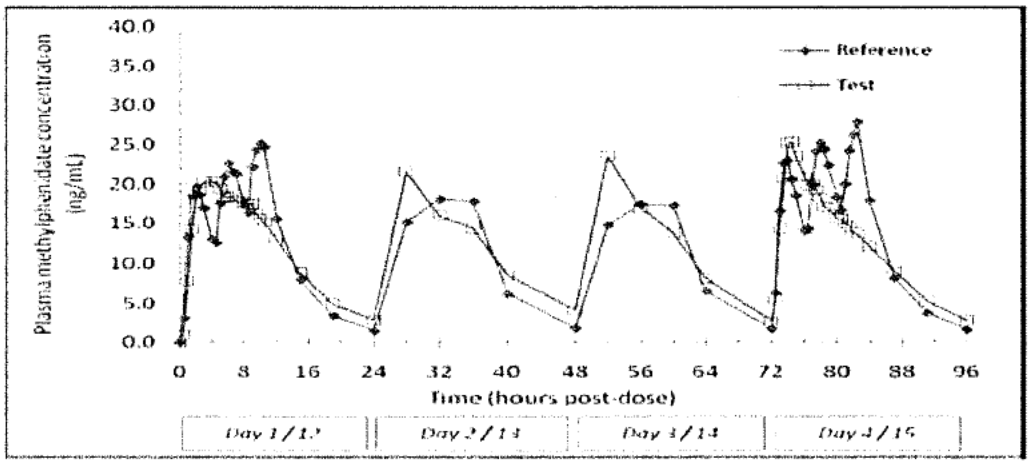
Figure 7: Mean (SD) Plasma Methylphenidate Concentration Verse Time After a Single 80 mg MPH-MLR Capsules (Test 1), MPH-MLR 80 mg Sprinkle (Test 2), and Ritalin® IR 25 mg (Comparator) in Healthy Adult Volunteers Under Fed Conditions (Linear Scale)



Test 1: Methylphenidate multilayer controlled-release 80 mg capsule
Test 2: Methylphenidate multilayer controlled-release 80 mg sprinkle
Reference comparator: Ritalin® 75 mg (administered as 25 mg dose at time 0, 4, and 8 hours)

The mean concentrations versus time profile for MPH following administration of MPH-MLR 80 mg and reference comparator during Day 1 (single dose) through Day 4 (steady-state) from multiple-dose Study RP-BP-PK002 are displayed in Figure 8. Three doses of comparator at time 0, 4, and 8 hours resulted in a tri-phasic profile following one day of dosing and after four days of dosing (steady state). In contrast, a single dose of MPH-MLR 80 mg resulted in a sustained concentration versus time profile over an approximate 8 hour period, after which a gradual decline in MPH levels was observed. Specifically, plasma concentration-time curves following once daily administration have a smoother PK profile (e.g., lower Cmax and similar Cmin) with a decreased fluctuation index at steady-state plasma concentrations over 24 hours as compared with the reference given three times daily.

Figure 8: Mean (SD) Plasma Methylphenidate Concentration Verse Time After Multiple Oral Doses of 80 mg MPH-MLR (Test) Once a Day and Ritalin® IR 25 mg (Comparator) Three Times a Day in Healthy Adult Volunteers Under Fed Conditions – Days 1- 4 (Linear Scale)



Reference comparator: Ritalin® 3 × 25 mg administered at time 0, 4, 8 hours.
Test: Methylphenidate multi-layer controlled release (MPH-MLR) 80 mg capsule administered at time 0 hour

Reviewer's Comments:
In conclusion, the overall data support the extended-release claim for the proposed product and is acceptable.

6. IN VITRO ALCOHOL DOSE DUMPING

The *in vitro* alcohol dose dumping studies were conducted consistent with FDA-requested methodology as outlined below:

Media: Medium 1: pH 1.2 HCl buffer; Medium 2: pH 6.0 phosphate buffer

Alcohol levels: 0%, 5%, 10%, 20%, and 40% v/v ethanol

Samples: n= 12, 10 mg and 80 mg capsules (intended commercial formulation)

Apparatus: USP apparatus 1 (baskets) at 100 rpm

Pull points: Every 15 minutes out to 2 hours

The results of these studies showed that the integrity of the functional coating on the beads is compromised at high ethanol concentrations. The loss of integrity of the functional coating leads to rapid *in vitro* drug release from the beads in the QC method in the presence of 40% ethanol, and to a lesser extent in the presence of 20% ethanol. There was limited/no impact on *in vitro* drug release at the 5% and 10% ethanol level (Figure 9 and 10).

Figure 9: Dissolution Profiles of Aptensio XR (Methylphenidate Hydrochloride Extended-Release) Capsules, 80 mg with and without Alcohol

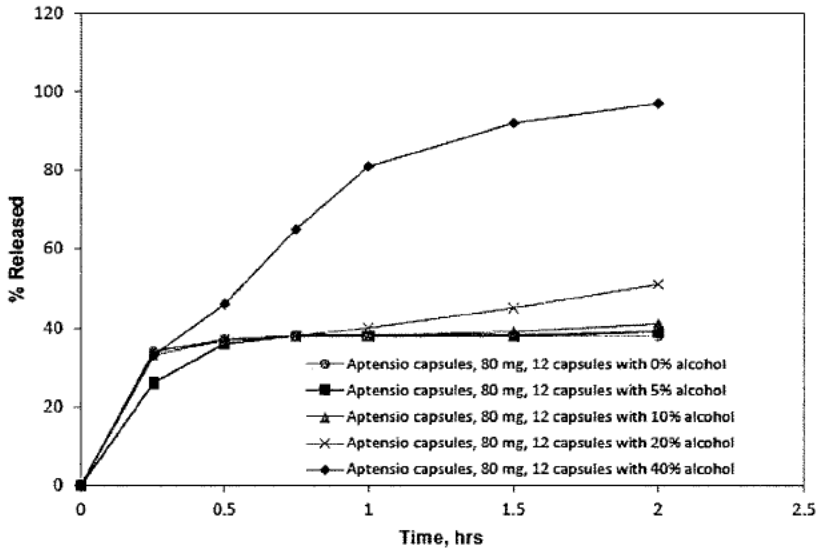
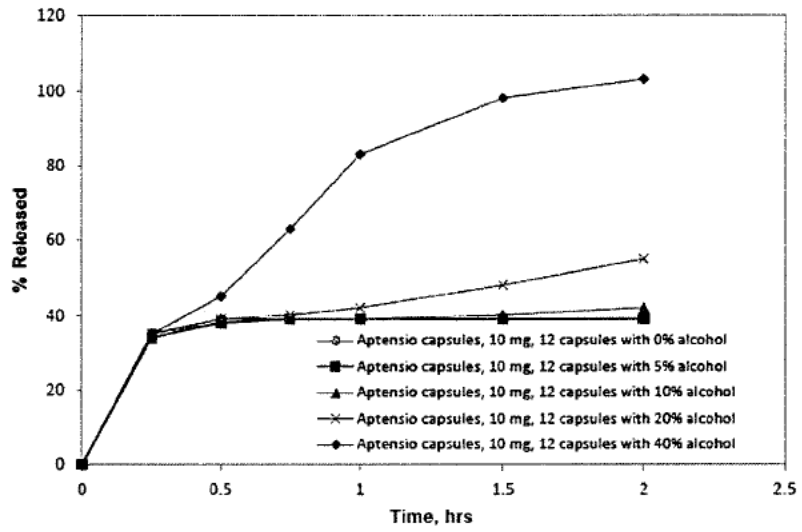


Figure 10: Dissolution Profiles of Aptensio XR (Methylphenidate Hydrochloride Extended-Release) Capsules, 10 mg with and without Alcohol



Reviewer's Comments

This Reviewer presented the above in vitro-alcohol dose-dumping results during the NDA's mid-cycle meeting and conveyed the following comment to the review team during:

- *The clinical relevance of the in vitro alcohol dose-dumping results needs to be evaluated by the ClinPharm and Clinical teams.*
- *Rhodes Pharmaceuticals proposed to include the following language in its product labeling:*

Alcohol Effect

An in vitro study was conducted to explore the effect of alcohol on the release characteristics of methylphenidate from Biphentin® 80 mg capsules. At an alcohol concentration up to 40%, there was 96% release of methylphenidate within two hours. The results with the 80 mg capsule are considered to be representative of the other available capsules strengths.

The review team revised the language in Section 17 Patient Counseling to remind prescribers to inform patients of dose-dumping as follows: "Advise patients to avoid alcohol while taking APTENSIO XR. Consumption of alcohol while taking APTENSIO XR may result in a more rapid release of the dose of methylphenidate".

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**205831**	**Brand Name**	**Aptensio**
OCP Division (I, II, III, IV, V)	**I**	**Generic Name**	**Methylphenidate multilayer controlled release capsules**
Medical Division	DPP	**Drug Class**	**MPH-MLR is a CNS stimulant**
OCP Reviewer	**Andre Jackson**	**Indication(s)**	**Treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years old and older**
OCP Team Leader	**Hao Zhu**	**Dosage Form**	**Capsule**
Pharmacometrics Reviewer	**n/a**	**Dosing Regimen**	**Once-a-day extended-release capsules: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg** (b) (4)
Date of Submission	**June 18, 2014**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**March, 18, 2015**	**Sponsor**	**Rhodes Pharmaceuticals**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**April 18, 2015**		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Summary

Rhodes Pharmaceuticals has submitted this 505(b)(2) New Drug Application (NDA) for Aptensio XR as a new NDA to the Food and Drug Administration (FDA) for treatment of patients with Attention-Deficit Hyperactivity Disorder (ADHD).

The product comes in (b) (4) strengths, namely 10, 15, 20, 30, 40, 50, 60 (b) (4) mg, and may thereby provide prescribers customized, flexible dosing for dose titration. Additionally, MPH-MLR's first C_{max} is similar to MPH IR.

Four pivotal studies, including 2 pharmacokinetic (PK) studies in healthy adults and 2 safety and efficacy studies in pediatric and adolescent patients with ADHD have been completed.

Relative bioavailability study of a single 80-mg dose of Biphentin® capsule, a single 80-mg dose of Biphentin capsule dosed as sprinkles versus reference 25 mg Ritalin® IR administered 3 times daily. This study was a single-center, randomized, open-label, single-dose, 3-period, crossover study; doses administered in fasted state.

The second study was a comparative bioavailability study of a steady-state of Biphentin 80 mg ER capsules versus Ritalin 25 mg IR. This study design was a single-center, randomized, open-label, single- and multiple-dose, 2-period, crossover study; doses administered in the fed state.

Rhodes Pharmaceuticals has also conducted 2 placebo-controlled studies to demonstrate efficacy. One study was a fixed-dose study to characterize the dose-response relationships for both efficacy and safety. The other was a laboratory classroom study in which one could assess efficacy at a number of time points to characterize the pattern of efficacy throughout a single testing day in children 6 to 12 years old.

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE	**505(b)(2) NDA**	**4**		
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
Human PK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology	**x**			
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**x**	**1**		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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multiple dose:	**x**	**1**		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**x**	**1**		**Pilot study 022-011 to compare PK in 6-12 yr olds with ADHD**
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**x**	**1**		**PK/PD modeling of Biphentin ER capsules in Pediatric pateints(PopPk001)**
Population Analyses -				
Data rich:	**x**	**1**		**Population modeling of Biphentin ER capsules(PopPk002)**
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**x**	**2**		**1. BA study 80 mg sprinkles vs Ritalin IR in adults(PK001)** **2. Steady-state comparative BA vs Ritalin IR under fed conditions(PK002)**
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**5**		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	No change in formulation
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Clinical Pharmacology Reviewer	Andre Jackson, Ph.D.	Date
Team Leader/Supervisor	Hao Zhu, Ph.D.	Date

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

/s/

ANDRE J JACKSON
08/11/2014

HAO ZHU
08/11/2014