CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205831Orig1s000

CHEMISTRY REVIEW(S)

NDA 205831

Aptensio XR™ (methylphenidate hydrochloride) Extended-Release Capsules

10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (b) (4)

Applicant: Rhodes Pharmaceuticals L.P.

Rao V. Kambhampati, Ph.D.

ONDP/DNDP I/Branch I

Quality (CMC) Review

For Division of Psychiatry Products (DPP)

Chemistry Review Data Sheet

1. NDA# **205831**

2. REVIEW #: 1

3. REVIEW DATE: 2-17-2015

4. REVIEWER: Rao V. Kambhampati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	**Document Date**
None	

6. SUBMISSIONS BEING REVIEWED:

Original 0000 (1)	6/18/14
Amendment 0003 (4)	9/5/14
Amendment 0004 (5)	9/18/14
Amendment 0010 (11)	12/19/14
Amendment 0011 (12)	1/8/15
Amendment 0012 (13)	1/12/15
Amendment 0015 (16)	1/16/15

7. NAME & ADDRESS OF APPLICANT:

Name: Rhodes Pharmaceuticals L.P.
Address: 498 Washington Street
Coventry, RI 02816

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Aptensio XR™ Capsules

b) Non-Proprietary Name (USAN): methylphenidate hydrochloride extended release capsules

c) Code Name/#: None

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NDA (21 CFR 314.50), 505 (b)(2)

10. PHARMACOL CATEGORY: A CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity (ADHD) in patients 6 years and older.

11. DOSAGE FORM: Capsules (extended release)

12. STRENGTH/POTENCY: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg [redacted] (b) (4)
capsule.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

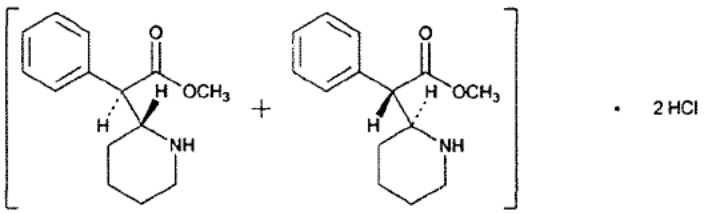
_____SPOTS product – Form Completed

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names:
2-Piperidineacetic acid, α-phenyl-, methyl ester, hydrochloride, (R*,R*)-(±)-;
Methyl α-phenyl-2-piperidineacetate hydrochloride
IUPAC Name: Methyl 2-phenyl-2-piperidin-2-ylacetate hydrochloride
CAS Registry Number: 298-59-9

Structural Formula (per USAN):



Molecular Formula: $C_{14}H_{19}NO_2 \cdot HCl$

Molecular Weight = 269.77 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)	Methylphenidate hydrochloride, USP drug Substance	Adequate	6/11/13 (DARRTS filing date) 9/30/14 (No outstanding deficiencies letter sent to Holder by David Skanchy) No amendments filed after 6/11/13.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	104624	Methylphenidate HCl ER capsules; Rhodes Pharmaceuticals; submission date 2/3/10.

STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Manufacturing and Testing Facilities	Acceptable	1/22/15	Juandria Williams, Office of Compliance/OMQ/DGMPA/NDMAB
ONDP Biopharm	Dissolution method acceptable	2/9/15 (e-mail communication)	Sandra Suarez, Ph.D.
LNC (ONDP) for Established Name	Not applicable. USAN name available.	2/10/15	Rao Kambhampati, Ph.D.
Method Validation	Not necessary per current office Policy	2/10/15	Rao Kambhampati, Ph.D.
Package Insert and Medication Guide	Pending by DPP	2/10/15	Rao Kambhampati, Ph.D.
Container labels and prescribing information	Container labels (9/5/14 and 1/8/15) acceptable. Prescribing information (1/15/15) acceptable with recommended modification to Dosage and Administration section.	1/27/15	Loretta Holmes (DMEPA/OMEPRM/OSE). Review filed in DARRTS .
Proprietary name	Aptensio XR™ acceptable	11/24/15	Loretta Holmes (DMEPA/OMEPRM/OSE). Review filed in DARRTS
EA	Acceptable based on categorical exclusion.	2/9/15	Rao Kambhampati, PhD
Product Quality Microbiology	Microbial limits method acceptable.	1/20/15	John Metcalfe, Ph.D., NDMS/OPS; Review filed in DARRTS

The Chemistry Review for NDA 205831

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry, Manufacturing, and Controls (CMC) review stand point, the NDA# 205831for Aptensio XR™ is recommended for approval provided the revised labeling and labels are acceptable to the DPP and other relevant divisions.

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

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

Drug Substance:

The applicant cross referenced the CMC information for methylphenidate hydrochloride, USP, to the DMF # (b) (4), which was reviewed in June, 2013 and found to be adequate (DARRTS filing date 6/11/13) and also no outstanding deficiencies letter was issued in September, 2014 (DARRTS filing date 9/30/14). Per DARRTS, no amendments to the DMF were submitted after 6/11/13. The drug substance is a monohydrochloride salt with a molecular weight of 269.77 g/mol. It is a white to off-white fine crystalline powder and (b) (4) In addition, the applicant also provided some CMC information directly in the NDA. The drug substance specification include appearance, identification by IR, chloride determination, and HPLC, loss on drying

(water content), residue on ignition, heavy metals, assay by HPLC, residual solvents [redacted], and impurities [redacted]; individual unspecified impurity; and total impurities)] by HPLC. The drug substance is stored at 25°C/60% RH and has a retest period of [redacted] months from the manufacturing date.

Drug Product:

The drug product, Aptensio XR™ (methylphenidate hydrochloride extended release) capsules, are manufactured in the following strengths: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg [redacted] The formulation consists of methylphenidate HCl, USP; sugar spheres [redacted], NF; [redacted] methacrylic [redacted] copolymer, Type B [redacted], NF; methacrylic acid copolymer, Type C [redacted] NF; triethyl citrate, NF; Talc, NF; [redacted] colloidal silicon dioxide (used if necessary). None of the proposed excipients exceed the IID limits for the oral route of administration. All the proposed excipients are commonly used in the oral drug product formulations. The applicant did not observe incompatibilities between the excipients and the drug substance.

The development of the drug product was initiated by [redacted] with a goal to identify formulations with a PK profile that combined both rapid onset and sustained plasma concentrations of methylphenidate (MPH) throughout the day following single dose administration. Formulation utilizing the MLR technology involving approximately 40% IR and approximately 60% ER drug content yielded in vivo plasma profiles matching the prescribed target product profile, and was therefore utilized in clinical efficacy trials. The product was successfully launched in Canada in August 2006. The applicant, Rhodes Pharmaceuticals (RP), [redacted] filed IND# 104624 in February 2010 to support clinical studies and market authorization in the US via 505(b)(2) filing. [redacted] Encapsulation of the beads and packaging of clinical and registration supplies was performed at [redacted] as well as [redacted] in USA. The manufacturing process consists of the following steps:

[redacted]

All the excipients are [redacted], which is tested for appearance and identification by the applicant and accepted on the basis of manufacturer's COA. The final specification for drug product capsules include appearance, identification by HPLC, HPLC-[redacted], and chemical method, [redacted], assay by HPLC [redacted] content uniformity, related substances/degradation products, dissolution (two medium), and microbial limits. Upon comment, the applicant added the [redacted], and microbial limits tests and [redacted] methylphenidate HCl [redacted] content to [redacted]%. Stability data included 24 months long-term, 6 months accelerated data for all strengths of capsules that were stored in HDPE bottles (30 and 100 counts). However, for commercial purpose 90 count bottles only will be used. On the basis of real time stability data and statistical analysis of the data and bracketing of the NDA bottle sizes and counts, 24 months expiration dating period is granted when the drug product bottles are stored at 20°-25°C.

C. Description of How the Drug Product is Intended to be Used

Aptensio XR™ is a CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The recommended starting dose of Aptensio XR for patients, 6 years and above is 10 mg once daily in the morning with or without food. The dose is individualized according to the needs and response of the patient. The dose may be titrated weekly in increments of 10 mg, [redacted]. Daily dosage above 60 mg have not been studied and are not recommended. Aptensio XR may be taken whole, or the capsules may be opened and the entire content sprinkled onto [redacted].

(b) (4) apple sauce for immediate consumption. The capsules are supplied in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg strengths and are packaged in HDPE bottles of 90 counts. If the daily dose is same as the labeled strength of the capsule, a bottle will provide 90 day supply to the patient. The drug product bottles should be stored at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

D. Basis for Approvability or Not-Approval Recommendation

The applicant provided adequate chemistry, manufacturing, and controls (CMC) information for the drug substance and drug product. The applicant satisfactorily addressed all the deficiencies that were communicated during the review. The established name, methylphenidate hydrochloride, is USAN name and it is acceptable. The tradename, Aptensio XR™ is acceptable to DMEPA and other relevant divisions. The dissolution method and revised acceptance criteria are acceptable to the ONDP Biopharm reviewer. The microbial limits test method is acceptable from the product microbiology reviewer stand point. All the facilities involved in the manufacturing and testing are acceptable to the Office of Compliance. From the quality (CMC) stand point, this NDA is recommended for approval provided revised labeling and labels are acceptable to DPP and other relevant divisions.

III. Administrative

A. Reviewer's Signature

Rao V. Kambhampati, Ph.D.

B. Endorsement Block

Primary Reviewer: Rao V. Kambhampati, Ph.D.
Senior Chemist/ONDP/DNDP I/Branch I

Secondary Reviewer: Olen Stephens, Ph.D.
Acting Branch Chief/ONDP/DNDP I/Branch II

103 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Digitally signed by Rao V. Kambhampati -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300073803, cn=Rao V. Kambhampati -A
Date: 2015.02.17 16:16:14 -05'00'

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2015.02.17 16:21:06 -05'00'

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 205831

DATES AND GOALS:

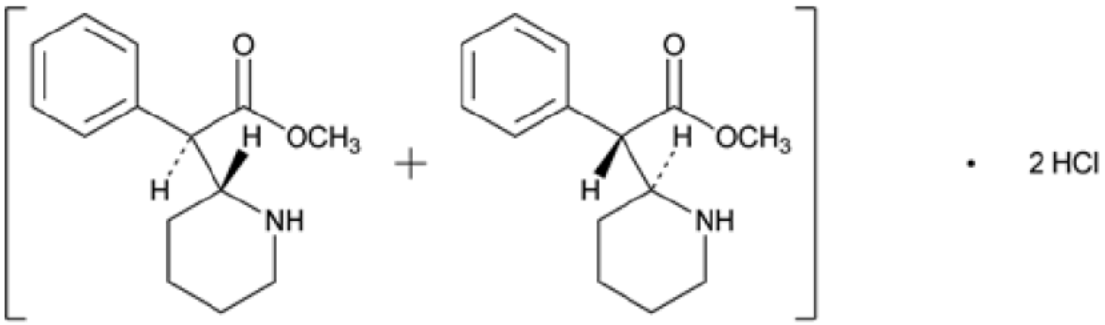
Day 60 (Filing Date): 08/17/2014 (Sunday)
Day 74 (Issue Filing letter): 08/31/2014 (Sunday)
PDUFA: 04/18/2015 (Saturday)

2. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Aptensio XR
Established or Non-Proprietary Name (USAN):	Methylphenidate hydrochloride extended release capsules
Dosage Form:	Extended release capsules
Route of Administration	Oral
Strength/Potency	10, 15, 20, 30, 40, 50, 60 (b) (4)
Rx/OTC Dispensed:	Rx

3. INDICATION: ADHD

4. DRUG SUBSTANCE STRUCTURAL FORMULA:



5. NAME OF APPLICANT (as indicated on Form 356h):

Rhodes Pharmaceuticals

6. SUBMISSION PROPERTIES:

Review Priority:	Standard Priority Expedited Review Requested Expedited Review Granted
Submission Classification (Chemical Classification Code):	
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DPP

7. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		x	
Clinical Pharmacology		x	
Establishment Evaluation Request (EER)	x		
Pharmacology/Toxicology	x		Specified levels of drug product impurities
Methods Validation		x	
Environmental Assessment		x	
CDRH		x	
Other			

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes
CMC Filing Issues: None
1.

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes
CMC Comments for 74-Day Letter:
1. Provide justification for the (b) (4) testing at drug product release and stability with regards to its potential impact on drug product quality (b) (4) 2. Include a second, orthogonal identification test to the drug substance and drug product specifications as the current tests are nonspecific. 3. We request that you lower the drug product acceptance criterion for the (b) (4) to (b) (4)% or provide justification based on the risk to the patient for the proposed (b) (4)% level.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes
Biopharmaceutics Filing Issues:
1. NONE

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes
Biopharmaceutics Comments for 74-Day Letter:
1. The data supporting the proposed dissolution acceptance criteria of your product are insufficient. Therefore, submit the following information/data: a. Dissolution profiles (individual and mean values) in tabular and graphical form from all pivotal clinical and PK studies. b. In general, the selection of the dissolution acceptance criteria limits is based on the mean target value ±10% and NLT (b) (4)% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model or in vivo BE study.

c. Implement a dissolution acceptance criterion for the immediate release portion of your proposed product [*sampling time point (e.g., 30 min) and limit*].

2. Provide the following in support of the extended release designation claim (refer also to CFR 320.25f):
   a. The BA profile established for the drug product rules out the occurrence of any dose dumping;
   b. The drug product's steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed non-controlled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.
   c. The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units;
   d. The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.
3. Provide the data generated on the in vitro dose-dumping study in the presence of alcohol.
   a. The following alcohol concentrations for the in vitro dissolution studies (using 12 units each) are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.
   b. Generally a range of alcohol concentrations in 0.1 N HCl and the QC dissolution medium is recommended. If the optimal dissolution medium has not been identified, then dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.
   c. Submit the dissolution profile comparisons with similarity testing (e.g., f2 values)
      i. Compare the shape of the dissolution profile to see if the modified release characteristics are maintained, especially in the first 2 hours.
      ii. The report should include the complete data (i.e., individual, mean, SD, comparison plots, statistical testing for similarity, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study.

4. Provide Dissolution profile comparisons with similarity testing (e.g., *f2* testing) between the highest and lower strengths of your proposed product in three different media.

5. Provide dissolution profile comparisons with similarly testing between the US clinical trial formulation and the commercial (Canadian) formulation; in addition provide a side-by-side table comparing their manufacturing processes.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes
Microbiology Filing Issues:
See Microbiology Filing Review for details and for Microbiology review issues and comments for 74-Day letter.

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
n	n	n	n

Is a team review recommended?	No
Suggested expertise for team: n	

Summary of Critical Issues and Complexities

Risk Assessment:

Product Property/Impact of change/CQAs	Factors affecting CQA	O	S	D	FMECA RPN	Comment
Appearance	Capsule color fading. Bead agglomeration/delamination	3	3	2	**18**	Bead (b) (4) may impact dissolution
Assay/stability	Coating operation controls	2	2	3	**12**	Drug substance (b) (4)
Identification		1	4	2	**8**	Currently only employs a single non-specific method
Content Uniformity	Coating uniformity controls	2	3	2	**12**	CU test in place
Degradants		2	2	2	**8**	Known degradation on storage
Dissolution	Coating controls and integrity on storage	4	3	4	**48**	
Alcohol Dose Dumping		5	4	4	**80**	Known issue.
Microbial	(b) (4)	1	2	5	**10**	Current release without testing. (b) (4) unknown

RPN < 25 is considered **low** risk;
RPN 25-60 is considered **moderate** risk; RPN > 60 is considered as **high** risk.

Initial Quality Assessment

DRUG SUBSTANCE

Details of the drug substance were cross referenced to DMF (b) (4). This was found to be adequate in June 2013. An Annual Report appears to be overdue for this MF, it will require evaluation on receipt. The drug substance manufacturing site (b) (4) was entered into EES.

(b) (4)

(b) (4)

(b) (4)

DRUG PRODUCT

The drug product consists of bead-filled capsules of (b) (4) dosage strengths. Each strength is a different color and capsule size:

Table 1. Physical Description by Capsule Strength

Drug Product Strength	Description
10 mg	Hard gelatin capsules, size 4 with white opaque body & light turquoise blue opaque cap containing white spherical beads with radial printing "(b) (4)" on the cap and "10mg" on the body of the capsule
15 mg	Hard gelatin capsules, size 4 with white opaque body & orange opaque cap containing white spherical beads with radial printing "(b) (4)" on the cap and "15mg" on the body of the capsule
20 mg	Hard gelatin capsules, size 3 with white opaque body & yellow opaque cap containing white spherical beads with radial printing "(b) (4) on the cap and "20mg" on the body of the capsule
30 mg	Hard gelatin capsules, size 2 with white opaque body & blue violet opaque cap containing white spherical beads with radial printing "(b) (4) on the cap and "30mg" on the body of the capsule
40 mg	Hard gelatin capsules, size 1 with white opaque body & pink opaque cap containing white spherical beads with radial printing "(b) (4) on the cap and "40mg" on the body of the capsule
50 mg	Hard gelatin capsules, size 0 with white opaque body & light green opaque cap containing white spherical beads with radial printing "(b) (4) on the cap and "50mg" on the body of the capsule
60 mg	Hard gelatin capsules, size 0el with white opaque body & grey opaque cap containing white spherical beads with radial printing "(b) (4) on the cap and "60mg" on the body of the capsule
(b) (4)	
(b) (4)	
(b) (4) For commercial product, the trade name and strength will be printed on the cap and the body of the capsule. At the time of filing, the commercial trade name has not yet been established.	

All the strengths (b) (4) composition (b) (4). The beads are composed (b) (4):

1. An inner drug substance layer (60% of total drug)
2. An extended release layer
3. An (b) (4) coating
4. A second outer drug substance layer which acts as the IR portion of the drug (40% of total drug)

The solutions are coated consecutively. It is designed to release 40% of the drug 'immediately' and the remaining 60% after the (b) (4) coated degrades postgastrically. The nature and level of the excipients do not appear to be an issue, but their levels should be checked with IGD:

Table 2. Methylphenidate Hydrochloride Extended-Release Capsules: Quantitative Compositions (mg/capsule)

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)
(b) (4)								
Methacrylic (b) (4) 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)

Note: The drug product is poorly described in the application. The reviewer should ensure that they include a very clear description of the various (b) (4) layers etc. in the executive summary and in P.1.

Much of the development work was carried out by (b) (4) The process was further developed to work with the contracted US manufacturer (b) (4) The reviewer should ensure that all these manufacturing steps were finalized before the production of the clinical and registration batches – or that the differences are justified. The applicant states that (b) (4) (b) (4)

No stability data on the proposed 90-count bottle CCS were provided – (b) (4)

Table P.5.1.1. Specifications for Methylphenidate HCl Extended Release Capsules 10, 15, 20, 30, 40, 50, 60 (b) (4)

Test		Specification						
		10 mg	15mg	20mg	30mg	40mg	50mg	60mg
Appearance* (Visual)	Release/stability	Hard gelatin capsules, size 4 with white opaque body & light turquoise blue opaque cap containing white spherical beads with radial printing (b) (4) on the cap and "10mg" on the body of the capsule	Hard gelatin capsules, size 4 with white opaque body & orange opaque cap containing white spherical beads with radial printing (b) (4) on the cap and "15mg" on the body of the capsule	Hard gelatin capsules, size 3 with white opaque body & yellow opaque cap containing white spherical beads with radial printing (b) (4) on the cap and "20mg" on the body of the capsule	Hard gelatin capsules, size 2 with white opaque body & blue violet opaque cap containing white spherical beads with radial printing (b) (4) on the cap and "30mg" on the body of the capsule	Hard gelatin capsules, size 1 with white opaque body & pink opaque cap containing white spherical beads with radial printing (b) (4) on the cap and "40mg" on the body of the capsule	Hard gelatin capsules, size 0 with white opaque body & light green opaque cap containing white spherical beads with radial printing (b) (4) on the cap and "50mg" on the body of the capsule	Hard gelatin capsules, size 0el with white opaque body & grey opaque cap containing white spherical beads with radial printing (b) (4) on the cap and "60mg" on the body of the capsule
Assay: % label claim (HPLC)	Release/stability	(b) (4)%						
Identification a) HPLC	Release	a) The retention time of methylphenidate HCl in the sample preparation should correspond to that obtained from the standard preparation in the HPLC assay of (b) (4) capsules.						
b) Chemical Method		b) (b) (4)						
Content Uniformity (HPLC)	Release	Meets current USP <905> requirements Initial 10 dosage unit (L1) Acceptance Value (b) (4)						
Degradation/Related Substances (HPLC)	Release/stability	Individual unknown degradation products NMT (b) (4)% Individual known degradation products (b) (4) NMT % NMT % Total degradation products: NMT %						
Dissolution (Two-medium method)	Release/stability	Time (Hrs)	% Methylphenidate HCl Released					
		2	(b) (4)					
		6						
		12						
		18	NLT (b) (4)					

Drug product specification is generally adequate. A single non-specific identification test is employed (HPLC retention time). Further the proposed specified limit for the (b) (4) is (b) (4)% - higher than the (b) (4)% limited listed in USP for methylphenidate extended release tablets. A request will be forwarded to the applicant to add a second identification test and to lower the specified limit for the (b) (4) (or provide justification). Note that the USP monograph is for tablets whereas the proposed drug product are capsules – therefore the monograph can only be used as a quality guide.

The dissolution test will be evaluated by biopharm. It includes an initial two hour dissolution in acid which will dissolve the outer immediate release portion of the drug. There appears to be no control

for (b) (4) in the drug product specification. (b) (4) of the drug product components were provided with microbial data from the 18 month time point. These data should be considered. Typical bottles with no dessicant are employed.

Drug product manufacturing sites:

Table P.3.1. Manufacturing, Packaging, and Testing Sites

Name and Address of Site	Documentation	Function	FEI and DUNS Number
(b) (4)	cGMP Certification	Manufacturing of beads. Encapsulation of finished drug product. Testing and release of excipients, drug substance, drug product, and packaging components. Stability testing of the drug product. Method development and validation activities.	FEI No. (b) (4) DUNS No. (b) (4)
(b) (4)	cGMP Certification	Encapsulation and packaging of finished drug product. Testing and release of beads, drug product, and packaging components. Stability testing of the drug product. Method development and validation activities.	FEI No. (b) (4) DUNS No. (b) (4)

Table P.3.1. Manufacturing, Packaging, and Testing Sites

Name and Address of Site	Documentation	Function	FEI and DUNS Number
Rhodes Pharmaceuticals L.P. 498 Washington Street Coventry, Rhode Island 02816 Contact: William Washington Director, Quality Assurance Phone: (401) 262-9438 Fax: (401) 262-9450 William.Washington@pharma.com	cGMP Certification	Sponsor of NDA Method development activities.	FEI No. 3008529213 DUNS No. 831928986
(b) (4)	N/a	Testing of excipients, drug substance, drug product, and packaging components.	FEI No. (b) (4) DUNS No. (b) (4)
	N/a	Microbial enumeration tests, USP <61> and Tests for specified microorganisms USP <62>.	FEI No. (b) (4) DUNS No. (b) (4)
	N/a	Testing of packaging components.	FEI No. (b) (4) DUNS No. (b) (4)

Clarification was sought from the applicant regarding the roles of the (b) (4) sites. Both were entered into EES as drug product manufacturing sites. Only (b) (4) manufactures the beads but both sites carry out the encapsulation and packaging. The (b) (4) testing site was deleted from EES at the request of CDER OC is it is a packaging testing site.

The applicant states that "all bead lots were manufactured at (b) (4). Encapsulation and packaging of all lots took place at (b) (4) except for PAQ100051, PAQ100052, and PAQ100053 (and the corresponding packaged lot numbers). These three lots were encapsulated and packaged at (b) (4)." The majority of the stability data is from batches encapsulated at (b) (4). Stability studies were carried out on the material packaged at (b) (4) (they appear to have lot numbers beginning with "(b) (4)"). Data from 12 to 36 months room temperature storage (and six months accelerated) were provided.
The stability data is volumous and repetitive – it would be helpful if the reviewer could compile a single chart with a very simple summary of the studies (strengths/packaging configuration/site).

The (b) (4) testing should be justified. The microbiology reviewer will (b) (4). An environmental exclusion is claimed.

In a preIND meeting (104624) the drug product identification test was recognized as being nonspecific and a second test was recommended. Photostability studies of the capsule color were raised as well as capsule (b) (4). In the preNDA meeting, the Agency found the proposed acceptance criterion for (b) (4) to be acceptable at (b) (4)%. These issues should be revisited over the course of the NDA evaluation.

Note that the salt will likely remain part of the established name, going against current policy, but is in accordance with the USP monograph for the tablet form of this product and currently marketed drugs. This should be discussed with the Labeling and Nomenclature Committee.

Comments for 74-day letter:

1. Provide justification for the (b) (4) testing at drug product release and stability with regards to its potential impact on drug product quality (b) (4).

2. Include a second, orthogonal identification test to the drug substance and drug product specifications as the current tests are nonspecific.

3. We request that you lower the drug product acceptance criterion for the (b) (4) to (b) (4)% or provide justification based on the risk to the patient for the proposed (b) (4)% level.

Biopharmaceutics Assessment

Summary of Critical Issues and Complexities

Submission: Rhodes Pharmaceuticals is seeking approval of Aptensio XR ™ (Methylphenidate hydrochloride, MPH) (referred in here also as MPH-MLR) as an oral extended release (ER) capsules for the once-a-day treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients of age 6 years and older. MPH is a widely used drug and has been commercialized in many formulations both immediate and extended release (IR and ER, respectively). The controlled release products approved in the US include Concerta ER®, Metadate CD®, Focalin XR®, Ritalin LA®, and Quillivant XR®. The Applicant has incorporated data from the Canadian registration in support of this 505(b)(2) Application. MPH-MLR is marketed in Canada as Biphentin.

The clinical development program supporting this NDA is based primarily on four pivotal studies agreed upon with the FDA:

- Two pharmacokinetic (bioavailability/bioequivalence) studies in healthy adults using Retalin® as the listed drug; and
- Two placebo-controlled efficacy and safety studies in children and adolescents diagnosed with ADHD. The PK (BE Studies) studies will be reviewed by OCP since these two studies include an arm conducted under fed conditions.

Product's Description:
MPH-MLR is presented as single, multilayer controlled-release beads comprising of approximately (b) (4)% immediate release (IR) and approximately (b) (4)% controlled release (CR) layers of (MPH) which are filled into capsules to an appropriate fill weight to obtain various strengths of the product. The dosage strengths in this regulatory submission are 10, 15, 20, 30, 40, 50, 60, (b) (4) and all proportionally similar in composition. 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 are (b) (4).

Review: The biopharmaceutics review will be focused on the evaluation and acceptability of the data provided to support: 1) the 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 dissolution data showing absence of dose dumping in the presence of alcohol;

Review Issues Identified:
There are no information/data included in the submission on: 1) in vitro alcohol dose-dumping; and 2) extended release designation claim; 3) Dissolution data supporting a biowaiver for the lower strengths. The Applicant will be requested to provide these data as par at of the 74-day letter. Refer to Biopharmaceutics request comments in pages 3 and 4 of this document.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		x	Drug substance and drug product acceptance criteria do not meet USP minimal standards for some tests. Request for revision will be included in 74-day letter.

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		Clarification was requested on the roles of the drug product sites. Adequate responses received.

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?			

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	x		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?		x	In DMF
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			
14.	Does the section contain information regarding the characterization of the DS?			
15.	Does the section contain controls for the DS?			
16.	Has stability data and analysis been provided for the drug substance?			
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?	x		Waiver of in-vivo bioavailability studies requested
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?			

G. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
30.	Does the application contain dissolution data?	x		**Proposed dissolution method:** USP Apparatus I and 37.0 ± 0.5°C dissolution medium at 100 rpm, first in 500ml acidic medium for two hours followed by 500ml potassium phosphate buffer (pH 6.0) with a total of four (4) sampling points: 2, 6, 12, and 18 hours. See the specific information in the link below. \\CDSESUB1\evsprod\NDA205831\0000\m2\27-clin-sum; \\CDSESUB1\evsprod\NDA205831\0000\m3\32-body-data\32p-drug-prod\aptensio-xr\32p5-contr-drug-prod\32p52-analyt-proc
31.	Is the dissolution test part of the DP specifications?	x		The proposed acceptance criteria are as follows: **Time (hrs) Methylphenidate HCL released** 2 (b) (4) 6 12 18 (b) (4) NLT See detail information in the link below. \\CDSESUB1\evsprod\NDA205831\0000\m3\32-body-data\32p-drug-prod\aptensio-xr\32p5-contr-drug-prod\32p56-justif-spec
32.	Does the application contain the dissolution method development report including data supporting the discriminating ability?	x		There are no data included in this submission on the discriminating ability of the dissolution method.
33.	Is there a validation package for the analytical method and dissolution methodology?	x		These data will be reviewed by the CMC Reviewer.
34.	Does the application include a biowaiver request?		x	
35.	Is there information/data supporting the biowaiver request?		x	
1.	Is there enough information to assess the extended release designation claim?		x	The Applicant is requested to provide this information.
2.	Are there any manufacturing changes implemented to the biobatch/clinical trial formulation?		x	

3.	Are data supporting the manufacturing changes implemented to the clinical trial formulation?		x	
4.	Does the application include an IVIVC model?		x	
5.	Does the application include information/data on in vitro alcohol dose-dumping potential?	x		The Applicant will be requested to provide this information.
6.	Is there any in *vivo* BA or BE information in the submission?	x		The following BA studies are included in the submission: **RP-BP-PK002:** Steady State Comparative Bioavailability Study of Biphentin™ MPH ER Capsule 80 mg versus Comparator Ritalin® IR 25 mg Three Times Daily in Healthy Adults Under Fed Conditions. **RP-BP-PK001**: 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 versus comparator 25 mg Ritalin® IR Given Three Times Daily in Healthy Adults under Fasted Conditions. **Protocol 022-001** compared the bioavailability of the test MPH-MLR 20 mg Versus the comparator product Ritalin® IR 10 mg tablets (Novartis) administered as either 1 × 20 mg MPH-MLR or 2 × 10 mg Ritalin IR tablet under fasted conditions or immediately after a high-fat breakfast. **Protocol 022-011** was a single center, randomized, open-label, 2-way crossover study to compare the PK of MPH-MLR 20 mg and Ritalin® IR 20 mg in young children with ADHD. These studies will be reviewed by OCP.
47.	Is there any design space proposed using in vitro release as a response variable?		x	
48	Is the control strategy related to in vitro drug release?		x	

H. filing conclusion				
	Parameter	**Yes**	**No**	**Comment**
49.	**IS BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		• The NDA is fileable from the Biopharmaceutics Perspective • The acceptability of dissolution method and acceptance criteria will be a review issue. • The Applicant is being requested to provide data supporting: o The ER designation claim o The absence of in vitro dose-dumping in the presence of alcohol o Dissolution profile comparisons supporting the approval of a biowaiver for the lower strengths. o Dissolution data bridging the US clinical trial formulation to the commercial (Canadian) formulation and information on the comparison of the manufacturing processes.
50.	If the NDA is not fileable from the product quality perspective, state the reasons.			Not applicable.
51	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons.			Not applicable.
52	Are there any potential review issues identified?	x		Refer to Biopharmaceutics comments in pages 3 and 4 of this document.
53	Are there any comments to be sent to the Applicant?	x		Refer to Biopharmaceutics comments in pages 3 and 4 of this document.
54.	Are there any internal comment to other disciplines:		x	

I. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
36.	If appropriate, is a separate microbiological section included assuring sterility of the drug product		x	NA (Oral capsule)

J. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
37.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS

K. LABELING				
	Parameter	**Yes**	**No**	**Comment**
38.	Has the draft package insert been provided?	x		
39.	Have the immediate container and carton labels been provided?	x		

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page}
David Claffey
CMC-Lead or CMC Senior Reviewer
Division
Office of New Drug Quality Assessment

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

/s/

DAVID J CLAFFEY
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SANDRA SUAREZ
08/25/2014

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