CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202100Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM TO NDA 202100

Office of New Drug Quality Assessment

Division of Psychiatry Products
Chemistry, Manufacturing, and Controls

DATE:	15-AUG-2012
TO:	NDA 202100 Resubmission dated 30-MAR-2012: Response to FDA Complete Response Letter dated 30-AUG-2011
FROM:	Chhagan G. Tele, Ph.D., CMC Reviewer, ONDQA/Branch 1
SUBJECT:	Final CMC Recommendation for NDA 202100, (Quillivant™) Methylphenidate HCl Extended-Release Oral Suspension (25 mg/5 mL), CMC Memos (05-MAY-2011) and (26-AUG-2011)
Applicant:	NextWave Pharmaceuticals
Established Name:	methylphenidate hydrochloride
Dosage Form:	Extended-Release Oral Suspension
Route of Administration:	Oral
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)

For NDA 202100, deficiencies were observed during FDA inspections of the Tris Pharma drug product manufacturing facility. Complete Response (CR) Letter (dated 30-AUG-2011) was issued to the NDA applicant indicating that this single issue of deficiencies observed during FDA inspections of the Tris Pharma drug product manufacturing facility needed to be resolved prior to approval. The applicant indicated that all deficiencies regarding Tris Pharma manufacturing facility for this NDA have been adequately addressed. The CDER Office of Compliance (OC) issued an overall “Acceptable” recommendation for NDA 202100 on 22-JUN-2012. A copy of the establishment evaluation report is attached. From a CMC perspective, the Office of New Drug Quality Assessment recommends **Approval** of the application based on the Office of Compliance recommendation.

Attachment

NDA 202100: Overall Acceptable Recommendation from the CDER Office of Compliance

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 202100/000	**Sponsor:**	NEXTWAVE PHARMS
Org. Code:	130		20450 STEVENS CREEK BLVD STE 150
Priority:	3		CUPERTINO, CA 95014
Stamp Date:	30-JUL-2010	**Brand Name:**	METHYLPHENIDATE HCL ER
PDUFA Date:	30-SEP-2012	**Estab. Name:**	
Action Goal:		**Generic Name:**	METHYLPHENIDATE HCL ER
District Goal:	31-MAR-2011	**Product Number; Dosage Form; Ingredient; Strengths**	001; POWDER, FOR ORAL SUSPENSION; METHYLPHENIDATE HYDROCHLORIDE; 25MG/5ML

FDA Contacts:	T. BOUIE	Project Manager	3017961649
	C. TELE	Review Chemist	3017961762
	T. OLIVER	Team Leader	3017961728

Overall Recommendation:	ACCEPTABLE	on 22-JUN-2012	by A. INYARD	(HFD-323)	3017965363
	PENDING	on 22-SEP-2011	by EES_PROD		
	WITHHOLD	on 22-SEP-2011	by EES_PROD		
	WITHHOLD	on 25-AUG-2011	by EES_PROD		
	PENDING	on 10-AUG-2011	by EES_PROD		
	WITHHOLD	on 10-AUG-2011	by EES_PROD		
	WITHHOLD	on 27-MAY-2011	by EES_PROD		
	WITHHOLD	on 04-MAY-2011	by EES_PROD		

Establishment:	**CFN:**	(b) (4)	**FEI:**	(b) (4)	
				(b) (4)	
DMF No:			**AADA:**		
Responsibilities:	DRUG SUBSTANCE MANUFACTURER				
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS		**OAI Status:**	NONE	
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	01-SEP-2010				
Decision:	ACCEPTABLE				
Reason:	DISTRICT RECOMMENDATION				

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	11-MAR-2011		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:**	**FEI:** 3004712471	
	TRIS PHARMA INC		
	MONMOUTH JUNCTION, , UNITED STATES 088523003		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE PACKAGER		
	FINISHED DOSAGE RELEASE TESTER		
Profile:	POWDERS (INCLUDES ORAL AND TOPICAL)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	22-JUN-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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

/s/

CHHAGAN G TELE
08/15/2012
AP from CMC perspective.

RAMESH K SOOD
08/15/2012

MEMORANDUM
Office of New Drug Quality Assessment
Division of Psychiatry Products
Chemistry, Manufacturing, and Controls

DATE: August 26, 2011
TO: NDA 202,100
FROM: Chhagan G. Tele, Ph.D., CMC Reviewer, ONDQA/Branch 1
SUBJECT: **Overall Compliance and Final CMC Recommendation for NDA 202,100, (Quillivant™) Methylphenidate ER Powder for oral suspension (25 mg/5 mL)**

The CDER Office of Compliance (OC) issued an overall “WITHHOLD” recommendation for NDA 202,100 on August 26, 2011. A copy of the establishment evaluation report is attached. The application cannot be approved from CMC perspective because of the "withhold" overall recommendation from the office of compliance.

ATTACHMENT

NDA 202,100: Overall WITHHOLD Recommendation from the Office of Compliance

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 202100/000	**Action Goal:**	
Stamp Date:	30-JUL-2010	**District Goal:**	31-MAR-2011
Regulatory:	30-AUG-2011		
Applicant:	NEXTWAVE PHARMS	**Brand Name:**	METHYLPHENIDATE HCL ER
	20450 STEVENS CREEK BLVD STE 150	**Estab. Name:**	
	CUPERTINO, CA 95014	**Generic Name:**	METHYLPHENIDATE HCL ER
Priority:	3	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	130	001; POWDER, FOR ORAL SUSPENSION; METHYLPHENIDATE HYDROCHLORIDE; 25MG/5ML	

Application Comment: DRUG PRODUCT IS AN EXTENDED-RELEASE POWDER FOR ORAL SUSPENSION; SIMILAR DOSAGE FORM "PACKAGE" AS IN NDA 22-499 (on 26-AUG-2010 by T. LAMBERT () 301-796-4246)

FDA Contacts:			
	T. BOUIE	Project Manager	301-796-1649
	C. TELE	Review Chemist	301-796-1762
	T. OLIVER	Team Leader	301-796-1728

Overall Recommendation:					
	WITHHOLD	on 25-AUG-2011	by T. GOOEN	(HFD-320)	301-796-3257
	PENDING	on 10-AUG-2011	by EES_PROD		
	WITHHOLD	on 10-AUG-2011	by EES_PROD		
	WITHHOLD	on 27-MAY-2011	by EES_PROD		
	WITHHOLD	on 04-MAY-2011	by EES_PROD		

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment Comment: DRUG SUBSTANCE MANUFACTURING, TESTING, PACKAGING. (on 09-AUG-2010 by T. BOUIE () 301-796-1649)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	27-AUG-2010				LAMBERTTU
SUBMITTED TO DO	27-AUG-2010	10-Day Letter			STOCKM
DO RECOMMENDATION	31-AUG-2010			ACCEPTABLE	SBERRYMA
A GMP EI WAS CONDUCTEDC (b) (4) AND WAS CLASSIFIED NAI. BASED ON FILE REVIEW, (b) (4) RECOMMENDS APPROVABLE FOR THIS APPLICATION.				BASED ON FILE REVIEW	
OC RECOMMENDATION	01-SEP-2010			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Establishment Comment: THE DMF HOLDER SUBMITTED THIS SITE FOR THE ANALYSIS OF THE DRUG PRODUCT TO PERFORM MICROBIAL LIMIT TESTING AS AN OUTSIDE CONTRACT FIRM IN AN AMENDMENT DATED 26-JAN-11 (RECEIVED 31-JAN-11). (on 09-FEB-2011 by C. TELE () 301-796-1762)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	09-FEB-2011				BOUIET
SUBMITTED TO DO	10-FEB-2011	10-Day Letter			SMITHDE
DO RECOMMENDATION	11-MAR-2011			ACCEPTABLE	AAGRAWAL
BASED ON THE PREVIOUS GMP EI ON 11/10/09 - NAI WITH ACCEPTABLE PROFILE.				BASED ON FILE REVIEW	
OC RECOMMENDATION	11-MAR-2011			ACCEPTABLE	SMITHDE
				DISTRICT RECOMMENDATION	

Establishment: CFN: FEI: 3004712471

TRIS PHARMA INC.

2033 US HIGHWAY 130
MONMOUTH JUNCTION, NJ 088523003

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

Establishment Comment: DRUG PRODUCT MANUFACURING, PACKAGING, TESTING (on 09-AUG-2010 by T. BOUIE () 301-796-1649)

Profile: POWDERS (INCLUDES ORAL AND TOPICAL) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	27-AUG-2010				LAMBERTTU
SUBMITTED TO DO	27-AUG-2010	Product Specific			STOCKM
INSPECTION SCHEDULED	10-JAN-2011		25-FEB-2011		AAGRAWAL
ASSIGNED INSPECTION TO IB	10-JAN-2011	Product Specific			AAGRAWAL
PAI AND GMP INSPECTION					
DO RECOMMENDATION	09-MAY-2011			WITHHOLD	KDORAZIO
GMP INSPECTION OF 4/4 - 5/6/11 FOUND MULTIPLE AND SYSTEMIC GMP DEFICIENCIES.				PEND REG ACTION - WARNING LTR	
OC RECOMMENDATION	27-MAY-2011			WITHHOLD	SMITHDE
CDER OC CONCURS WITH THE DISTRICT¿S WH-RECOMMENDATION BASED ON SEVERE CGMP DEFICIENCIES. FOR EXAMPLE, THE INSPECTION UNCOVERED A PRODUCT BEING CONTAMINATED WITH A YEAST ORGANISM AS PART OF THE ROUTINE STABILITY PROGRAM. THE CAUSE OF THE CONTAMINATION HAS NOT BEEN IDENTIFIED AND THERE WAS NO EVALUATION OF OTHER MARKETED DRUG PRODUCTS. IN ADDITION, OTHER UNCOVERED CGMP ISSUES INCLUDE: (1) INCOMPLETE INVESTIGATIONS OF UNIDENTIFIED FOREIGN PARTICLES IN MULTIPLE LIQUID PRODUCTS, (2) MULTIPLE RETESTS FOR DISSOLUTION AND ASSAY, (3) UNJUSTIFIED RESAMPLING FOLLOWING OOS RESULTS, (4) AN UNCONTROLLED MANUFACTURING PROCESS FOR AN EXTENDED RELEASE ORAL SUSPENSION, (5) LACK OF METHOD RE-VALIDATION, (6) INADEQUATE CLEANING VALIDATIONS, (7) AN INADEQUATELY MONITORED USP PURIFIED WATER SYSTEM, (8) LABORATORY DATA THAT IS NOT SECURE FROM ALTERATION OR DELETION, (9) UNSUPPORTED BATCH REPROCESSING, (10) INADEQUATELY QUALIFIED MANUFACTURING EQUIPMENT, (11) UNSECURED ACCESS TO THE FACILITY DURING CONSTRUCTION AND (12) LATE NDA FIELD ALERT REPORTING.				DISTRICT RECOMMENDATION	
SUBMITTED TO DO	02-AUG-2011	10-Day Letter			SMITHDE
ASSIGNED INSPECTION TO IB	04-AUG-2011	Product Specific			KDORAZIO
PLEASE CONDUCT PAI ONLY. CONTACT PAM FOR MORE INFORMATION					
INSPECTION SCHEDULED	04-AUG-2011		22-AUG-2011		KDORAZIO
DO RECOMMENDATION	16-AUG-2011			WITHHOLD	MKLAPAL
483 ISSUED, WITHHOLD APPROVAL RECOMMENDATIONS ARE MADE FOR NDA 202-100 DUE TO THE FIRM'S INADEQUATE INVESTIGATIONS REGARDING OOS RESULTS, EI COMPLETED 8/16/11				INADEQUATE LAB CONTROLS	
OC RECOMMENDATION	25-AUG-2011			WITHHOLD	TGOOEN
FIRM'S 8/23/11 RESPONSE STATED THAT THEY WILL NEED TO INSTALL AND QUALIFY NEW FILLING EQUIPMENT BECAUSE ORIGINAL EQUIPMENT IS NOT CAPABLE OF PREVENTING OVER- AND UNDER-FILLED BOTTLES.				DISTRICT RECOMMENDATION FIRM NOT READY	

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/s/

CHHAGAN G TELE
08/26/2011
CMC memo-NA

RAMESH K SOOD
08/26/2011

MEMORANDUM

Office of New Drug Quality Assessment

Division of Psychiatry Products
Chemistry, Manufacturing, and Controls

DATE: 05-MAY-2011
TO: NDA 202-100 (Refer Review #1 in DARRTS, 25-MAR-2011)
FROM: Chhagan G. Tele, Ph.D., CMC Reviewer, ONDQA/Branch 1
SUBJECT: Final CMC Recommendation for NDA 202-100, (Quillivant™) Methylphenidate ER Powder for oral suspension (25 mg/5 mL)

In response to the ONDQA biopharm recommendations (refer biopharm review dated 23-MAR-11 by Angelica Dorantes), a teleconference with the DMF holder [Tris Pharma, Inc. (Tris)] was held (27-APR-11) to discuss the following recommended (by biopharm) dissolution acceptance criteria for Methylphenidate ER Powder for oral suspension (25 mg/5 mL) using the newly proposed dissolution conditions (i.e., Apparatus: USP II (Paddle); Speed of Rotation, 75 rpm; Dissolution medium (b) (4) mL of 0.4 M KH_2PO_4, pH 4.5 at 37° C).

Recommended Dissolution Acceptance Criteria for Methylphenidate ER Powder for Oral Suspension	
Time (Hours)	% Drug Dissolved
0.5	(b) (4)
3	
8	NLT (b) (4)

DMF holder accepted (DMF #23870, amendment 0007 dated 28-APR-11) the above recommendations and provided the following: Finished Product Specifications (Attachment 1), Dissolution Method, and Post Approval Stability Protocol and Commitment.

Dissolution Method

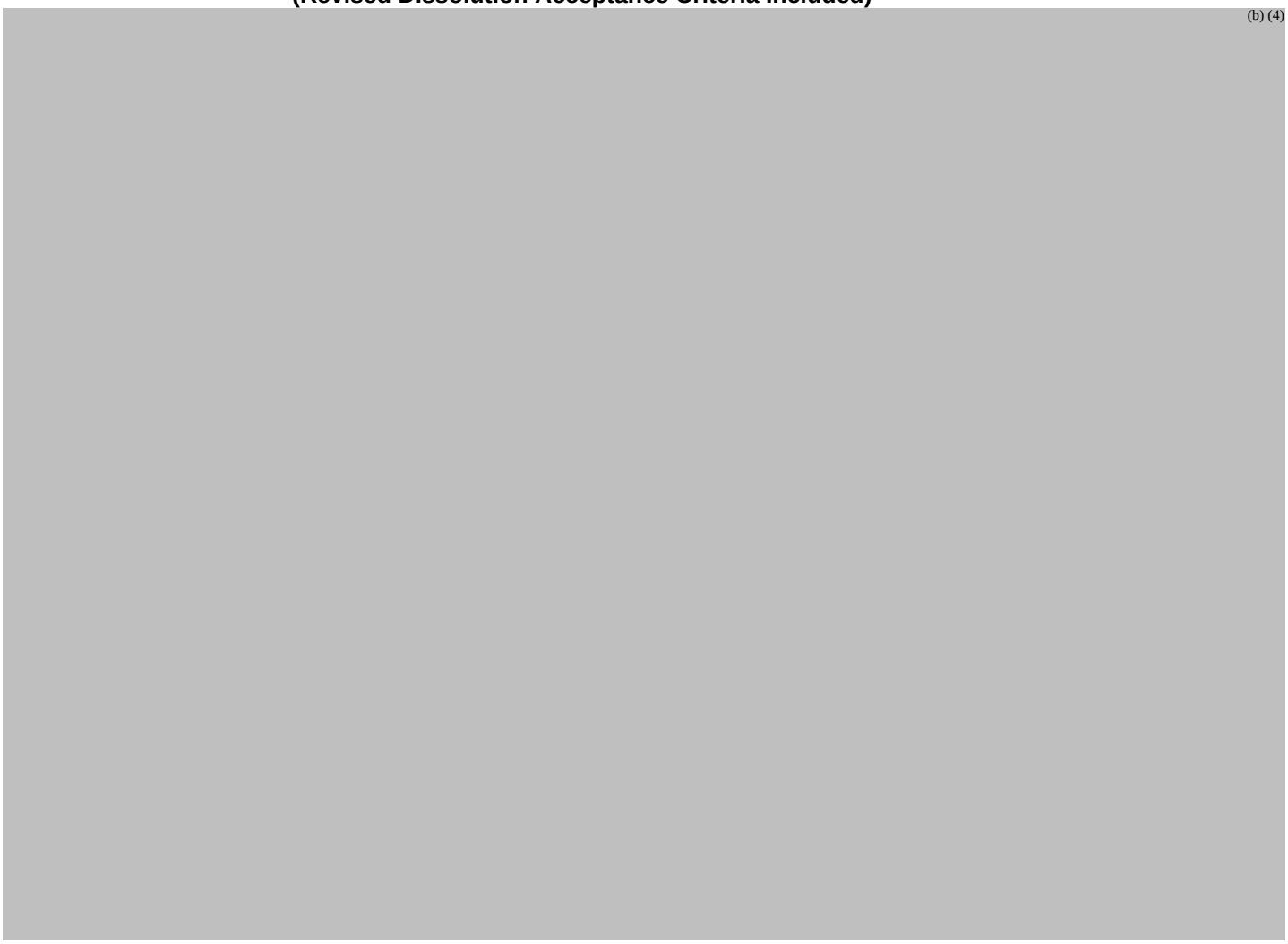
Dissolution Conditions

Apparatus: USP Apparatus II (Paddle)
Speed: 75 rpm
Medium: (b) (4) mL 0.4 M KH_2P0_4 solution
Temperature: 37° C ± 0.5° C
Sampling volume: 5mL
Time interval: 0.5, 3, and 8 hours
HPLC Conditions

(b) (4)

Table 1: Updated Post Approval Stability Protocol and Commitment
(Revised Dissolution Acceptance Criteria Included)

(b) (4)

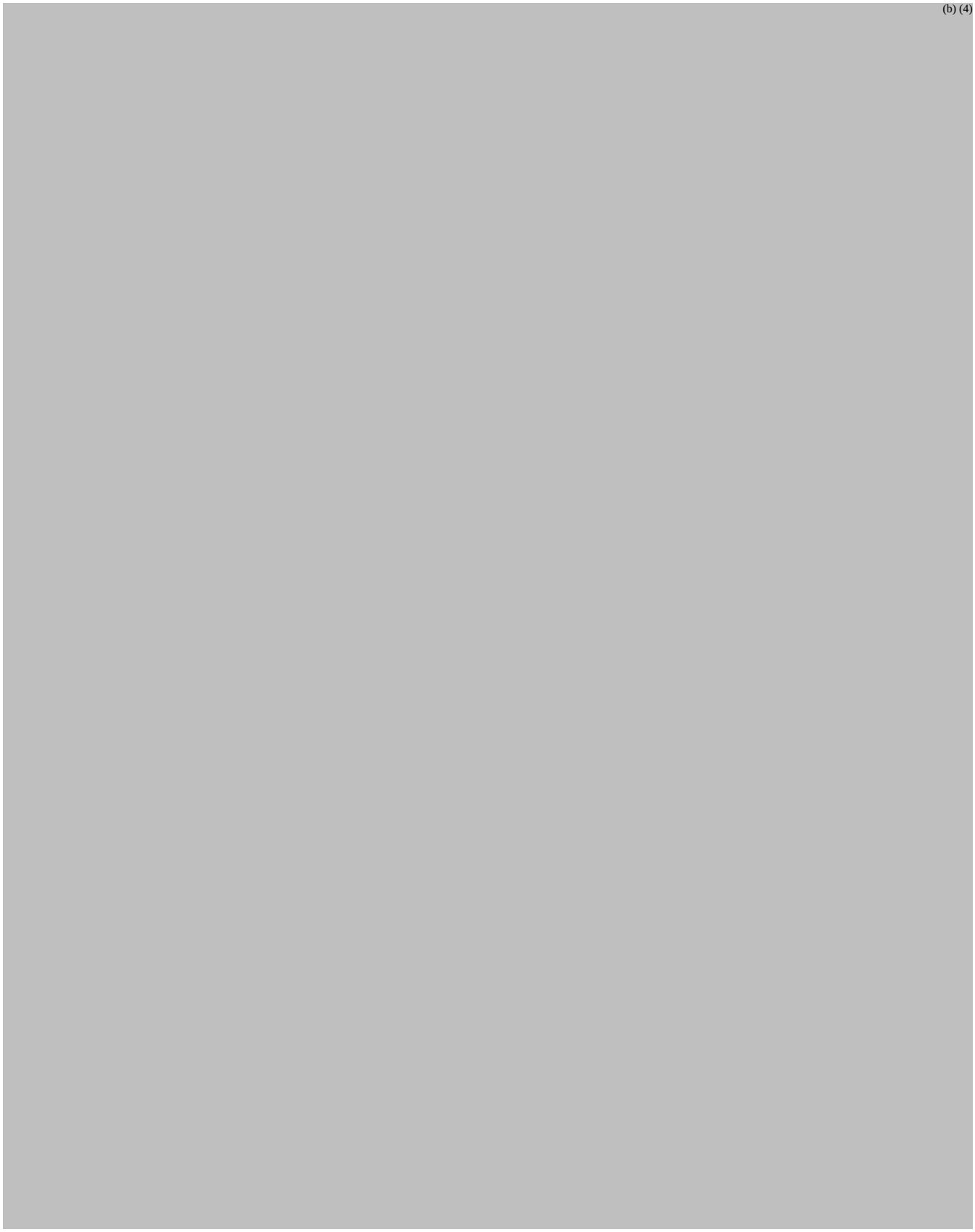


Recommendation: From a CMC perspective, we cannot approve NDA 202-100 for Quillivant™ (methylphenidate HCl) ER Powder for Oral suspension due to **WITHOLD** overall recommendation (dated 04-MAY-11, Attachment 2) from the Office of Compliance for the drug substance and drug product sites.

Attachment 1

Updated Drug Substance Specification (Revised Dissolution Acceptance Criteria Included)

(b) (4)



Attachment 2

NDA 202-100: Overall Recommendation (WITHOLD) from the Office of Compliance

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 202100/000	**Sponsor:**	NEXTWAVE PHARMS
Org. Code:	130		20450 STEVENS CREEK BLVD STE 150
Priority:	3		CUPERTINO, CA 95014
Stamp Date:	30-JUL-2010	**Brand Name:**	METHYLPHENIDATE HCL ER
PDUFA Date:	30-MAY-2011	**Estab. Name:**	
Action Goal:		**Generic Name:**	METHYLPHENIDATE HCL ER
District Goal:	31-MAR-2011	**Product Number; Dosage Form; Ingredient; Strengths**	001; POWDER, FOR ORAL SUSPENSION; METHYLPHENIDATE HYDROCHLORIDE; 25MG/5ML

FDA Contacts:	T. BOUIE	Project Manager	301-796-1649
	C. TELE	Review Chemist	301-796-1762
	T. OLIVER	Team Leader	301-796-1728

Overall Recommendation: WITHHOLD on 04-MAY-2011 by EES_PROD

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-SEP-2010
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 11-MAR-2011
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:**	**FEI:** 3004712471	
	TRIS PHARMA INC 2033 US HIGHWAY 130 STE D MONMOUTH JUNCTION, NJ 088523003		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE PACKAGER		
	FINISHED DOSAGE RELEASE TESTER		
Profile:	POWDERS (INCLUDES ORAL AND TOPICAL)	**OAI Status:**	POTENTIAL OAI
Last Milestone:	ASSIGNED INSPECTION TO IB		
Milestone Date:	10-JAN-2011		

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/s/

CHHAGAN G TELE
05/05/2011

RAMESH K SOOD
05/05/2011

NDA 202-100

TRADENAME™ (methyphenidate HCl) Extended Release Powder for Oral Suspension

NextWave Pharmaceuticals

Chhagan G. Tele, Ph.D.
Division I/Branch 1
Office of New Drug Quality Assessment

Division of Psychiatry Products
Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA: 202-100
2. REVIEW #: 1
3. REVIEW DATE: March 23, 2011
4. REVIEWER: Chhagan G. Tele, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	30-JUL-2010
Amendment (0001) warehousing and distribution of DP	18-AUG-2010
Amendment (0006) Response to IR Letter 13-JAN-2011	07-FEB-2011
Amendment (0008) Response to IR (email from PM Sandy Chang 17-MAR-2011)	17-MAR-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	NextWave Pharmaceuticals, Inc
Address:	20450 Stevens Creek Blvd, Suite 150 Cupertino, CA 95014
Representative:	Michael Burdick, Ph.D. Vice President, Product Development
Telephone:	(650) 248-0205

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: TRADENAME™
   b) Non-Proprietary Name: methyphenidate HCl
   c) Code Name/# (ONDC only): NWP06
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 3
      - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2); TRADENAME™ (methyphenidate HCl) ER Powder for Oral Suspension, 25 mg/5 mL.

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY: For the treatment of Attention Deficit Hyperactivity Disorder (ADHD)

11. DOSAGE FORM: Extended Release Powder for Oral Suspension

12. STRENGTH/POTENCY: 25 mg/5 mL

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:

USAN Name: Methylphenidate Hydrochloride

Chemical Name: Methyl α-phenyl-2-piperidineacetate hydrochloride

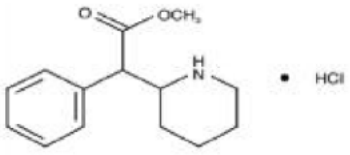
INN Name: 2-piperidineacetic acid, α-phenyl-, methyl ester, hydrochloride, (R*, R*)-(±)-

Chemical Formula: $C_{14}H_{19}N0_2 \cdot HCl$

Molecular Weight: 269.77 (methylphenidate hydrochloride)

CAS registry #: 298-59-9 (assigned to methylphenidate hydrochloride)

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate 09-JUL-10 Dr. Barbara Scott	LOA 28-APR-09
23870	II	Tris Pharma	Drug Product	1	Inadequate	LOA 21- JUL-10

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted

6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	73,856 (effective 18-FEB-2009)	Commercial IND (ADHD), Tris Pharma
NDA	21-419 (effective 19-DEC-2002)	RLD for ADHD, Mallinckrodt Inc.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			John Lawrence
EES	Overall recommendation pending		(HFD-322)
Pharm/Tox	Pending		Ikram Elayan, Ph.D.
Biopharm	Pending	23-MAR-11	Angelica Dorantes, Ph.D. (ONDQA)
Clinical Pharmacology	Acceptable	21-MAR-11	Huixia Zhang, Ph.D.
LNC	N/A		
Methods Validation	Methods are routine. No need to send to FDA labs for validation.		
DMETS	Pending		
EA	Acceptable, categorical exclusion granted as per information from NextWave in this NDA	As per this review	Chhagan G. Tele, Ph.D. (ONDQA-Branch I)
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 202-100

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We have completed the review of NDA 202-100 for Tradename™ (methylphenidate HCl) ER Powder for Oral suspension, and have determined that we cannot approve this application from the CMC standpoint in its present form due to the following pending issues:

1. Pending overall acceptable recommendation by the Office of Compliance for the drug substance and drug product sites.

ONDQA Biopharm Comments:

2. **COMMENT #1: Dissolution Method** – The applicant has the choice of; **i)** adding an additional sampling timepoint at 24 hours for any further stability/batch release dissolution testing of their product **or ii)** develop a new dissolution method for their product [redacted] (b) (4)

3. **COMMENT #2: Dissolution Specifications** – The applicant has the choice of; **i)** provide a proposal for the dissolution specifications ranges at the specification times 1, 3, 6, 12, (based on target mean ±10%), and 24 hours (based on additional dissolution testing for 4 months-stability batches) using the current dissolution testing conditions **or ii)** provide a proposal for new specification times and ranges (based on target mean ±10%) and Q= [redacted] (b) (4) for the [redacted] (b) (4) time point if a new dissolution method is developed.

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

None as per this review

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Methylphenidate HCl Extended-Release Powder for Oral Suspension (25 mg/5 mL) was developed under IND 73,856 (Tris Pharma) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Tris Pharma included outcome of the CMC issues discussed in Pre-IND meetings (08-MAY-06 and 01-OCT-07) and EOP-3 meeting (22-MAR-10) in the drug product DMF #23870. The applicant used Methylin® (methylphenidate HCl) Oral Solution (NDA 21-419) as the Reference Listed Drug (RLD) for this application. Methylphenidate HCl Extended-Release Powder for Oral Suspension was evaluated in five clinical studies: three single-dose PK studies in healthy adult subjects (Studies S07-0079, S07-0443, and S09-0238), one single-dose PK study in pediatric subjects with ADHD (Study NWP06-PPK-101), and one multiple-dose Phase 3 efficacy and safety study in pediatric subjects with ADHD (Study NWP06-ADD-100). Two of these studies (S07-0079 and S07-443) were conducted with prototype formulations (Batch #s RD-0035-068 and RD-0047-185) and the remaining three studies were conducted with the intended commercial formulation (Batch #TB-046A).

Drug Product

Methylphenidate HCl Extended-Release Powder for Oral Suspension will be supplied as a white powder for oral suspension in bottles of 300 mg, 600 mg, 900 mg, 1200 mg, 1500 mg, and 1800 mg. After reconstitution, the product is light beige to tan viscous suspension containing 25 mg/5mL of methylphenidate hydrochloride. The recommended starting dose is (b) (4) 20 mg once daily in the morning for children and adolescents (6 years and over). Dosage may be increased by 10-20 mg/day at weekly intervals. Daily dosage above 60 mg is not recommended. (b) (4) The inactive ingredients include: sodium polystyrene sulfonate, povidone, triacetin, (b) (4) sugar, sodium citrate anhydrous, citric acid anhydrous, sodium benzoate, sucralose, polaxmer, (b) (4) food starch, xanthan gum, talc, flavor, and silicon dioxide. No novel excipients are utilized in drug product. The product contains no overages. The NDA applicant provided LoA (dated 21-JUL-10) which cross-references DMF #23870 [Tris Pharma, Inc.] for information on the drug product, Methylphenidate HCl Extended-Release Powder for Oral Suspension. DMF #23870 was submitted 23-JUL-10 and has been reviewed by Dr. Chhagan Tele and found inadequate due to ONDQA Biopharm issues mentioned above in Recommendation section. Methylphenidate HCl Extended-Release Powder for Oral Suspension will be manufactured, packaged and tested by Tris Pharma, Inc. (Monmouth Junction, NJ). NextWave Pharmaceuticals, Inc. will be responsible for final product release and warehousing distribution. The drug product will be packaged in USP Type III glass bottles, with a CRC cap. The manufacture of the drug product consists of (b) (4) he commercial batch size is about (b) (4) The Methylphenidate HCl ER Powder for Oral suspension will be manufactured at Tris Pharma, NJ site.

Adequate information was provided in DMF #23870 for the manufacturing, release, and stability of the registration batches of the drug product. Information about controls of critical Steps in the manufacture of registration batches of the Tradename™ ER Powder for Oral suspension is provided. In-process controls (b) (4) are performed. The specifications for ER Powder for Oral suspension included description and (b) (4) and for constituted suspension are description, identification (HPLC), pH, preservative (HPLC), microbial limits, assay (HPLC), impurity (HPLC), and dissolution (HPLC). Validated analytical methods are provided in the submission.

Updated data (18 months long term) from the ongoing stability studies are provided in DMF #23870 in accordance with the EOP 3 meeting (IND 73,856, 22-MAR-10). The holder submitted stability data from 3 batches of Methylphenidate (b) (4) ER Powder (b) (4) ill also be commercially available. To support these additional configurations, the holder also provided one batch of updated stability data (6 months long and accelerated storage conditions) (b) (4) The test results for the drug product remained within the shelf-life specifications after 18 months in HDPE bottles of storage at 25° C/60% RH and 30° C/65% RH and after 6 months of storage at 40° C/75% RH. Based on the overall stability data we grant 24 months shelf-life for the

drug product packaged in bottles. The applicant indicated (amendment 0001 dated 18-AUG-2010) that (b) (4) the contract service provider will be the warehousing and distributing the drug product. Methylphenidate (b) (4) ER oral Suspension has shown to be stable at 25° C/60% RH for up to 4 months stored at 25° C/60% RH.

Drug Substance

The only information provided in the drug substance section of the NDA is the chemical name and structure of methylphenidate HCl. The NDA applicant references DMF (b) (4) (b) (4) for information on methylphenidate HCl USP (actual LoA included in drug product DMF #23870). Letter of Authorization to access this DMF was provided for cross-reference. DMF (b) (4) was reviewed and found adequate (see latest review by Dr. Barbara Scott, OGD, 09-JUL-10). Methylphenidate HCl is manufactured and supplied to the applicant by Tris Pharma NJ site according to the process and controls described in their DMF (b) (4). Methylphenidate HCl drug substance is a stable white, fine, crystalline powder with a melting range of 224-226° C.

Batch analysis data of drug substance used in manufacturing of drug product was provided in DMF (b) (4) Validated analytical methods were provided in the DMF. Methylphenidate HCl drug substance is stable. This conclusion is supported by the primary stability results conducted for up to 36 months (see DMF (b) (4), review #10 for details). Methylphenidate HCl drug substance exhibited acceptable stability under storage conditions, 25° C/60% RH and 40° C/75% RH. The accelerated and long-term stability data showed that all stability parameters are well within their respective acceptance criteria after 36 months at 25° C/60% RH. The assay results remain within specification. There is no change in the appearance of the drug substance. The water content remained within the specification. There is no formation of new degradation products, the concentrations of all degradation products remained below the reporting limit (b) (4) during the 36-month study at 25° C/60% RH as well as during the 6-month study at 40° C/75% RH. There are no changes or trends in any tested parameter during long-term stability studies up to 36 months and no changes under accelerated conditions. The proposed storage conditions for the drug substance packaged as described are (b) (4), with a retest period of (b) (4) is proposed and granted.

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

Tradename™ (Methylphenidate HCl) ER Powder for Oral suspension will be marketed into bottles. Summary for all of the Methylphenidate HCl stability studies performed by Tris Pharma, NJ site is provided. Stability results obtained from the evaluation of commercial size three site-specific stability batches packaged in the proposed container closure system (bottles) are provided. Results from the stress testing study are described. Overall, stability data concluded to support 24 months expiration dating period for the drug product packaged in bottles stored at controlled room temperature conditions [25° C (77° F); excursion permitted to 15-30° C (59-86° F)]. [See USP Controlled Room Temperature]. Dispense in original container. (b) (4)

Tradename™ ER Powder for Oral suspension are available in (b) (4) (b) (4) bottles of 300 mg (to prepare 60 mL, NDC 24478-200-10), bottles of 600 mg (to prepare 120 mL, NDC 24478-200-20), bottles of 900 mg (to prepare 180 mL, NDC 24478-200-30), bottles of 1200 mg (to prepare 240 mL, NDC 24478-200-40), bottles of 1500 mg (to prepare 300 mL, NDC 24478-200-50), or bottles of 1800 mg (to prepare 360 mL, NDC 24478-200-60). The bottles are closed with a (b) (4) child-resistant closure with a liner sealed by induction.

C. Basis for Approvability or Not-Approval Recommendation

We cannot approve this application from the CMC standpoint in its present form due to the pending issues. The applicant should respond to the deficiencies presented at the end of this review. In resubmission of this NDA new deficiencies may emerge. The overall recommendation for the drug substance and drug product manufacturing sites is pending by the Office of Compliance. This application qualifies for categorical exclusion from environmental assessment under the provisions in 21 CFR §25.31(a).

III. Administrative

A. Reviewer's Signature

See electronic signatures in DARRTS.

B. Endorsement Block

Chemist Name: Chhagan G. Tele, Ph.D.
Branch Chief Name: Ramesh Sood, Ph.D.
Project Manager Name: Shin-Ye Chang, Pharm.D.

C. CC Block

See DARRTS.

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/s/

CHHAGAN G TELE
03/25/2011

RAMESH K SOOD
03/25/2011

CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR A NEW NDA

NDA Number: 202-100	**Applicant:** NextWave Pharmaceuticals	**Stamp Date:** 30-JUL-2010
Drug Name: Methylphenidate HCl ER Powder for Oral Suspension	**NDA Type:** Standard	**Filing Meeting:** 07-SEP-10

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	X		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	NA		

IS THE CMC SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant. **NA**

Chhagan G. Tele, Ph.D. 30-AUG-10
Reviewing Chemist, DPA 1, ONDQA Date

Ramesh Sood, Ph.D.
Branch Chief, DPA 1, ONDQA Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-202100	ORIG-1	NEXTWAVE PHARMACEUTICALS INC	METHYLPHENIDATE HCL ER

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/s/

CHHAGAN G TELE
08/30/2010
CMC section of the application is Fileable.

RAMESH K SOOD
08/31/2010

Initial Quality Assessment
Branch I

OND Division:	Division of Psychiatry Products
NDA:	**202100**
Applicant:	NextWave Pharmaceuticals
Letter Date:	29-JUL-10
Stamp Date:	30-JUL-10
PDUFA Date:	30-MAY-11
Trademark:	Methylphenidate HCl Extended-Release Powder for Oral Suspension (no trade name proposed yet)
Established Name:	methylphenidate hydrochloride
Dosage Form:	Powder for Oral Suspension
Route of Administration:	Oral
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Assessed by:	**Thomas F. Oliver, Ph.D.**

Summary

Methylphenidate HCl Extended-Release Powder for Oral Suspension (25 mg/5 mL) was developed for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The applicant has developed Methylphenidate HCl Extended-Release Powder for Oral Suspension under IND 73,856. The applicant had a Pre-IND meeting (May 8, 2006) with the clinical division to discuss in part the following CMC issues: drug substance and drug product release tests, dissolution testing, and drug product stability testing. The applicant had a second Pre-IND meeting (01-OCT-07) with the clinical division to discuss in part the following CMC issues: (b) (4) The applicant had an EOP-3 meeting (March 22, 2010) with the clinical division to discuss in part the following CMC issues: amount of drug product stability data, (b) (4) oral dispenser, extraction studies of container closure, USAN name, and stability data (b) (4) Minutes for both of these meetings can be found in DARTS and should be read by the reviewer. The sponsor used Methylin® (methylphenidate HCl) Oral Solution (NDA 21-419) as the Reference Listed Drug (RLD) for this application. Methylphenidate HCl Extended-Release Powder for Oral Suspension was evaluated in five clinical studies: three single-dose PK studies in healthy adult subjects (Studies S07-0079, S07-0443, and S09-0238), one single-dose PK study in pediatric subjects with ADHD (Study NWP06-PPK-101), and one multiple-dose Phase 3 efficacy and safety study in pediatric subjects with ADHD (Study NWP06-ADD-100). Two of these studies (S07-0079 and S07-0443) were conducted with prototype formulations (Batch #s RD-0035-068 and RD-0047-185) and the remaining three studies were conducted with the intended commercial formulation (Batch # TB-046A).

Drug Substance

The only information provided in the drug substance section of the NDA is the chemical name and structure of methylphenidate HCl. The NDA applicant references DMF (b) (4) for information on methylphenidate HCl USP (actual LoA included in drug product DMF 23870). DMF (b) (4) was found adequate (see latest review by Dr. Barbara Scott, OGD, July 9, 2010).

Drug Product

Methylphenidate HCl Extended-Release Powder for Oral Suspension will be supplied as a powder for oral suspension in bottles of 300 mg, 600mg, 900 mg, 1200 mg, 1500 mg, and 1800 mg. After reconstitution, the product is light beige to tan viscous suspension containing 5 mg per mL of methylphenidate hydrochloride. The recommended starting dose is (b) (4) 20 mg once daily in the morning for children and adolescents (6 years and over). Dosage may be increased by 10-20 mg/day at weekly intervals. Daily dosage above 60 mg is not recommended. (b) (4) The drug product (after reconstitution), will contain methylphenidate HCl USP at a concentration of 25 mg/5 mL. The inactive ingredients include: sodium polystyrene sulfonate, povidone, triacetin, (b) (4) sugar, sodium citrate anhydrous, citric acid anhydrous, sodium benzoate, sucralose, polaxmer, (b) (4) food starch, xanthan gum, talc, flavor, and silicon dioxide. The NDA applicant provided an LoA (dated 21-JUL-10) which cross-references DMF #23870 [Tris Pharma, Inc.] for information on the drug product, Methylphenidate HCl Extended-Release Powder for Oral Suspension. DMF #23870 was submitted 23-Jul-10 and has not been reviewed. Methylphenidate HCl Extended-Release Powder for Oral Suspension will be manufactured, packaged and tested by Tris Pharma, Inc. (Monmouth Junction, NJ). NextWave Pharmaceuticals, Inc. will be responsible for final product release and warehousing distribution. The drug product will be packaged in (b) (4) glass, with a CRC cap.

Critical Issues for Review

· The NDA applicant references DMF (b) (4) for information on methylphenidate HCl USP (actual LoA included in drug product DMF 23870). DMF (b) (4) will need to be evaluated and found acceptable.

· The NDA applicant provided a LoA (dated 21-JUL-10) which cross-references DMF #23870 [Tris Pharma, Inc.] for information on the drug product, Methylphenidate HCl Extended-Release Powder for Oral Suspension. DMF #23870 was submitted 23-Jul-10 and has not been reviewed. It will need to be evaluated.

· The applicant has proposed the following drug product impurity specification: (b) (4) The CMC reviewer and the pharm/tox reviewer will need to determine the acceptability of these limits in conjunction with the related USP monographs. The impurity/degradant specification limits will also need to be evaluated in DMF #23870.

· The applicant utilizes peak retention time by HPLC as the drug product identification method. As this is not a specific method (per ICH Q6A), the applicant will need to add an additional identification test or utilize a specific identification method.

· The inactive ingredients in the drug product include: sodium polystyrene sulfonate, povidone, triacetin, (b) (4) sugar, sodium citrate anhydrous, citric acid

anhydrous, sodium benzoate, sucralose, polaxmer, [redacted] food starch, xanthan gum, talc, flavor, and silicon dioxide. The compatibility of the excipients used in the drug product will need to be evaluated. In addition, for any excipients that are not compendial it will need to be determined whether there is appropriate manufacturing information including adequate controls.

- Sodium polystyrene sulfonate [redacted]

- The applicant utilizes sodium benzoate [redacted] in the drug product formulation. The applicant has a [redacted] with a specification limit of [redacted]. The reviewer will need to determine whether this range is adequate in providing sufficient protection.

- As Methylphenidate HCl Extended-Release Powder for Oral Suspension is designed to release active over time, the attributes [redacted] will need to be evaluated to ensure proper control.

- The applicant has proposed the following [redacted] specification: [redacted]

- The applicant has set a dissolution specification: [redacted] The adequacy of the dissolution method and specification limits will need to be determined in conjunction with the ONDQA biopharm reviewer. The ONDQA biopharn group will need to be consulted (see comment at end).

- The applicant has provided five drug product CoAs (lots TB-072B, TB-072A, TB-046A, TB-033A, and TB-042A) in NDA 202100. The dissolution data for all five lots is reported as a range. It is not clear what the range represents. Getting individual [redacted] data along with the average value at each time point would be useful.

Comments and Recommendation:

The NDA appears to be fileable from a CMC perspective. The NDA cross-references two DMFs (b) (4) for drug substance and #23870 for drug product). As a result, there is very little CMC information submitted in the NDA which has resulted in a terse IQA to protect the proprietary nature of the DMFs. The NDA does not appear to incorporate elements of QbD. My recommendation would be for a single reviewer to be assigned to the NDA. Since Dr. Chhagan Tele reviewed the original IND (1/5/09), he would be a prudent choice as the CMC reviewer. In accordance with 21 CFR §25.31, NextWave Pharmaceuticals claims a categorical exclusion [25.31(a)] from the requirement for an Environmental Assessment or Environmental Impact Statement as approval of the drug product will not increase the use of the active moiety. In addition, the applicant states that to the best of their knowledge, no extraordinary circumstances exist that would preclude this claim for categorical exclusion. The dissolution should be consulted to the ONDQA biopharm group. It is not clear whether all drug substance and drug product manufacturing, testing, and packaging sites have been submitted. The sponsor should be asked to provide a list (including name and address, CFN #, contact information) for all of these sites. In addition, the PM should submit all testing, packaging, and manufacturing sites into EES.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-202100	ORIG-1	NextWave Pharmaceuticals, Inc. 20450 Stevens Creek Blvd, Suite 150, Cupertino, CA 95014	METHYLPHENIDATE HCL ER

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/s/

THOMAS F OLIVER
08/09/2010

RAMESH K SOOD
08/09/2010