

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202100Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202-100 (Resubmission)	Reviewer: Elsbeth Chikhale, PhD	
Submission Date:	March 30, 2012		
Division:	Division of Psychiatry Products	Team Leader: Angelica Dorantes, PhD	
Applicant:	NextWave Pharmaceuticals	Acting Supervisor: Rik Lostritto, PhD	
Trade Name:	Quillivant (methylphenidate HCl) for ER Oral Suspension	Date Assigned:	June 6, 2012
Established Name:	Methylphenidate HCl	Date of Review:	August 16, 2012
Indication:	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older	Type of Submission: Resubmission of New Drug Application – 505(b)(2)	
Dosage form/ strengths	For oral suspension (pediatric formulation)/ 25 mg/5 mL		
Route of Administration	Oral		
Type of Review:	Drug product dissolution method and acceptance criteria submitted under DMF 23870.		
<p><u>SUBMISSION:</u> NextWave Pharmaceuticals originally submitted NDA 202-100 to support the marketing authorization of Methylphenidate HCl Extended-Release Powder for Oral Suspension (25 mg/5 mL) on July 29, 2010. The original NDA was submitted pursuant to Section 505(b)(2) of the FD&C Act; the Reference Listed Drug for this application is Methylin (methylphenidate HCl) Oral Solution approved by FDA under NDA 21-419. Methylphenidate is a central nervous system (CNS) stimulant. The resubmission, which is the subject of this review, contains a complete response to the CR letter dated 8/30/11. In the cover letter of the resubmission, it was noted that DMF 23870 was updated. DMF 23870, held by Tris Pharma, Inc., contains the full Drug Product information (section 3.2.P.) supporting NDA 202-100. Even though the CR letter dated 8/30/11, did not note any issues regarding the DMF, this review will evaluate the dissolution method and acceptance criteria proposed in the DMF, to ensure that all dissolution issues and other Biopharmaceutics issues have been resolved.</p> <p><u>BIOPHARMACEUTIC INFORMATION:</u> The drug product dissolution method and acceptance criteria discussed in DMF 23870 are the subject of this review. The original NDA Biopharmaceutics review by Angelica Dorantes, Ph.D., (dated 3/23/11 in DARRTS) evaluated:</p> <ul style="list-style-type: none"> • The originally proposed dissolution method and acceptance criteria and responses to 			

comments (DMF 23870)

- The in vitro alcohol dose dumping study (DMF 23870)
- The extended release dosage form classification

Regulatory history of the drug product dissolution method and acceptance criteria:

7/21/10: DMF 23870 was filed in the EDR as an original new electronic DMF.

7/29/10: The original NDA 202-100 was submitted. Section P.3.2, including the proposed dissolution method (Apparatus USP II (paddle), (b) (4) rpm rotation speed, 900 mL of 0.4 M KH₂PO₄, pH 4.5 at 37 °C medium) and proposed acceptance criteria, was provided by reference to DMF 23870 held by Tris Pharma. Inc.

11/12/10: Two Biopharmaceutics comments (along with CMC comments) were conveyed to the DMF holder in an information request letter dated 11/12/10. The letter is entered in DARRTS under DMF 23870:

- The provided dissolution data indicate that tighter acceptance criteria can be set for your product. Note that the proposed dissolution acceptance criteria (*mean value ±15*) for the (b) (4) hours time-points are very wide and the proposed specification value of NLT (b) (4) for the last sampling time point at (b) (4) is not adequate. Provide the dissolution profile data (*i.e., individual, mean, min. max, SD, and dissolution plots. Include the specific testing conditions*) from the clinical and stability batches supporting the selection of the proposed dissolution acceptance criteria (*i.e., specification-sampling time points and specification values*). In general, the selection of the dissolution specification ranges is based on mean target value ±10%. The specification time for the last sampling point should be set when at least (b) (4) of drug is released or a plateau is reached (b) (4). Wider specification ranges may be acceptable, only if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model.
- If your data (*i.e., dissolution, IVIVC, etc.*) cannot support the currently proposed dissolution acceptance criteria, provide revised dissolution acceptance criteria for your product.

12/27/10: DMF 23870 was amended with a response to the Deficiency letter.

3/21/11: A teleconference was held between Tris Pharma (DMF 23870 holder) and ONDQA's reviewing team (Biopharmaceutics and CMC) to discuss the DMF amendment. In this teleconference, the following two Biopharm Reviewer Comments #1 and #2 were discussed with the DMF holder:

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

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= (b) (4) for the (b) (4) time

point if a new dissolution method is developed. The telephone conference with the DMF holder was documented in the Biopharmaceutics review by Angelica Dorantes, Ph.D. dated 3/23/11 which was entered into DARTTS under NDA 202-100 and it was also documented in the CMC review of the DMF by Chhagan Tele, Ph.D. dated 3/24/11 which was entered into DARTTS under DMF 23870.

3/23/11: The NDA Biopharmaceutics review by Angelica Dorantes, Ph.D. was entered in DARRTS under NDA 202-100

The Biopharmaceutics review dated 3/23/11 concluded that:

- The proposed dissolution specifications are not acceptable and the issues were discussed with the DMF holder in the teleconference on 3/21/12
- Although alcohol did increase the in vitro release of drug from the formulation, a dose dumping effect per se was not observed. The results from this study were communicated to OCP.
- The proposed drug product is described as an Extended-Release drug product; however, the applicant did not provide the information required by 21 CFR 320.25(f)(iii) to support the Extended Release designation for their proposed drug product. This issue was communicated to OPP and OCP. After that, the Clinical Pharmacology Reviewer, Huixia Zhang, Ph.D. addressed the ER claim in her review dated 3/21/11. Dr. Zhang concluded that the sponsor's claim about the onset of effect by 45 minutes and sustained effect through 12 hours is justified based on the provided PK information. The Clinical Pharmacology review also discussed the extended release PK characteristics of the proposed drug product and compared these to the IR oral solution (reference product). It was concluded that the overall PK data supported the Extended Release claim for this product.

3/24/11: The CMC review of DMF 23870 by Chhagan Tele, Ph.D. dated 3/24/11 was entered into DARRTS under DMF 23870

4/11/11: DMF 23870 was amended based on the teleconference between FDA and the DMF holder on 3/21/11. In the amended DMF the Applicant proposed the following revised dissolution method and acceptance criteria

Method: Apparatus USP II, 75 rpm paddle rotation speed, 900 mL of 0.4 M KH₂PO₄, pH 4.5 at 37 °C medium

Acceptance Criteria: (b) (4)

4/27/11: The above proposed criteria were not accepted by FDA and on 4/27/11, a TCON was held between the holder of DMF 23870 (Tris Pharma, Inc.) and FDA to discuss the following dissolution acceptance criteria recommended by FDA, which are based on the information provided in the 4/11/11 DMF amendment:

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

An agreement was reached between the DMF holder and FDA and the revised dissolution specifications (method and acceptance criteria) were found acceptable. This TCON was documented in a Memorandum to NDA 202-100 by Chhagan Tele, Ph.D., dated 5/5/11 which was entered into DARTS as a Quality Review under NDA 202-100.

4/29/11: The DMF was amended with the agreed upon dissolution specifications (method and acceptance criteria). See copy of the Finished Product Specification (Certificate of Analysis) with effective date 4/27/11 below (copied from DMF amendment).

8/26/11: A Memorandum to NDA 202-100 was entered in DARRTS under NDA 202-100 by Chhagan Tele, Ph.D., stating that the CDER Office of compliance issued an overall “withhold” recommendation for this NDA, and therefore the application can not be approved from CMC perspective.

8/30/11: FDA issued a CR letter, stating the only reason for the CR action was the unsatisfactory facility inspections. FDA mentioned in the CR letter that comments on the proposed labeling will be reserved until the application is otherwise adequate.

See the Updated Drug Product Specifications in Appendix 1.

CONCLUSIONS AND RECOMMENDATION:

- The in vitro drug release in the presence of alcohol was evaluated by ONDQA-Biopharmaceutics and the results were communicated to the Office of Clinical Pharmacology (refer to the “First Cycle Biopharmaceutics Review” by Dr. Angelica Dorantes, dated 3/23/11 in DARRTS). The Clinical Pharmacology review by Dr. Huixia Zhang, Ph.D., dated 3/21/11, concludes that an in-vivo alcohol dose dumping study is not required, and there is no concern about infrequent alcohol consumption while taking the proposed drug product.
- All issues regarding the drug product dissolution method and acceptance criteria have been resolved under DMF 23870. The following dissolution method and acceptance for Methylphenidate ER Powder for Oral Suspension are acceptable.

USP Apparatus	Speed (rpm)	Volume (ml) / Temperature	Medium	Acceptance Criteria (% drug Dissolved)
II (paddle)	75	900 mL 37°C	0.4 M KH ₂ PO ₄ , pH 4.5	0.5 hr (b) (4)
				3.0 hr-
				8.0 hr – NLT (b) (4)

From the Biopharmaceutics perspective, there are no pending issues and the Resubmission of NDA 202-100 for Methylphenidate HCl ER Powder for Oral Suspension (25 mg/5 mL) is recommended for APPROVAL

Signature

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

Review in DARRTS under NDA 202-100 and DMF 23870
cc: RLostritto

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/s/

ELSBETH G CHIKHALE
08/16/2012

ANGELICA DORANTES
08/16/2012

Clinical Pharmacology Review Amendment

NDA:	202100
Proposed Brand Name:	QUILLIVANT™
Generic Name:	Methylphenidate HCl
Dosage Form:	Extended-Release Powder for Oral Suspension
Dosage Strength:	25 mg/5 mL
Indication:	Attention Deficit Hyperactive Disorder (ADHD)
Sponsor:	NextWave Pharmaceuticals Inc.
Submission type:	505(b)(2)
Submission dates:	July 29, 2010; Aug 24, 2011
OCP Reviewers:	Huixia Zhang, PhD, Jogarao Gobburu, PhD,

Background:

In the current submission, the Sponsor has submitted the results from one relative bioavailability study (study S09-0238; RLD: Methylin Oral Solution), one single-dose pharmacokinetic study in children and adolescent patients with ADHD (NWP06-PPK-101), and one efficacy and safety Phase III trial in 45 6-12 year-old patients (NWP06-ADD-100) to support their application. PK samples from study S09-0238 and study NWP06-PPK-101 were analyzed by (b) (4)

In a recent investigation, FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by (b) (4). The pervasiveness and egregious nature of the violative practices by (b) (4) has led FDA to have significant concerns that the bioanalytical data generated at (b) (4) from (b) (4) as part of studies submitted to FDA in NDA and sNDA are unreliable. Serious questions remain about the validity of any data generated in studies by (b) (4) during this time period.

In response to the Agency's letter issued on Aug. 2nd, 2011, the sponsor submitted the sample reanalysis report for study S09-0238 and study NWP06-PPK-101 to provide evidence for the reliability of the original bioanalytical data and PK results.

Recommendation:

The Office of Clinical Pharmacology has determined that the reassayed sample data submitted provide sufficient evidence for the reliability of the original bioanalytical data and PK results, based on the following:

1. The efficacy study (NWP06-ADD-100) clearly demonstrated the efficacy of the product in pediatric patients. This renders the PK information supportive.
2. Overall, 193 samples were reassayed, and the retested concentrations on average were within 3-17% of the original concentration values based on linear regression

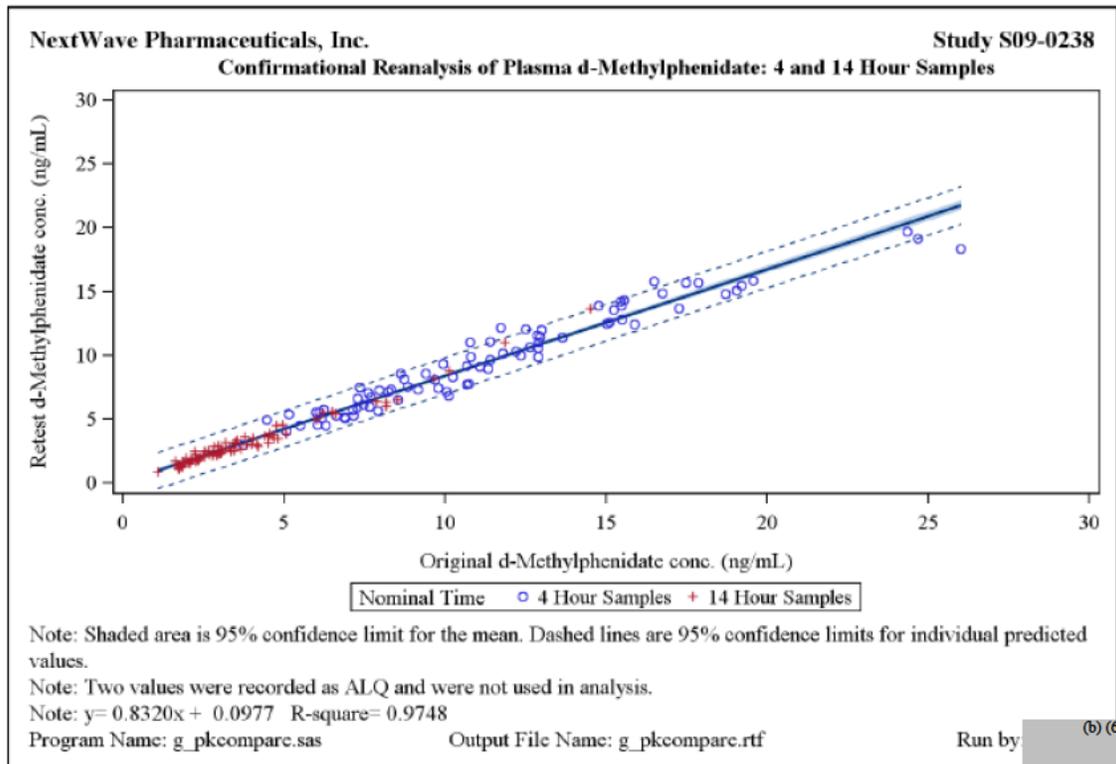
analysis. For study NWP06-PPK-101, the retested concentrations for 27 out of the 29 samples were within 20% of the original values. For study S09-0238, the retested concentrations for 98 out of the 166 samples were within 20% of the original values.

3. The clinical response in the Quillivant arm was superior to placebo between 45 min and 11.5 hrs post-dosing, indicating adequate drug concentrations between those times. The drug concentrations for Quillivant product are in the range of concentrations observed for other products with similar clinical response profiles (e.g. methylin IR, concerta) particularly at the early and late time points.
4. PK parameters for Methylin IR oral solution which was used as the RLD in this application were compared to those from the methylin IR oral solution label and the original NDA 21419. Mean AUC and Cmax values for methylphenidate are quite comparable between NDA 21419 and the current submission. This provides additional evidence for the reliability of the data submitted for this NDA.

Reanalysis Result:

Study S09-0238

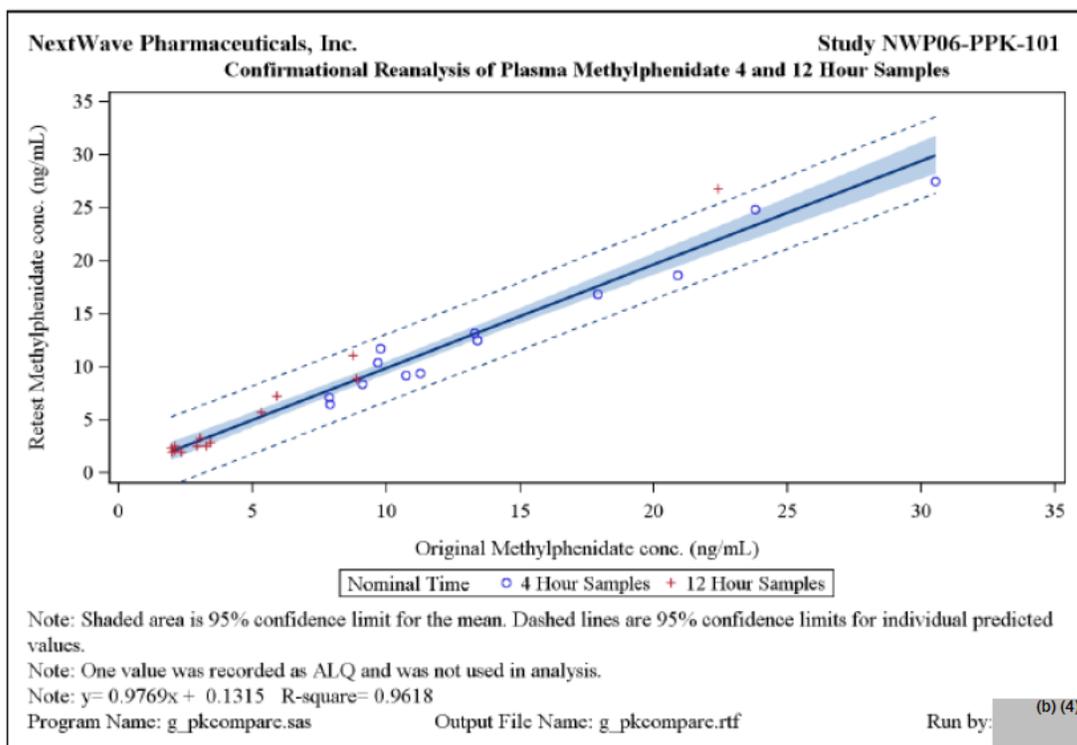
A total of 166 samples from study S09-0238 were reassayed for d-methylphenidate concentration. The samples selected were 4 hr and 14 hr postdose from all three study periods (Quillivant fasting, Quillivant fed, and Methylin IR solution (RLD) fasting) in all subjects. Linear regression analysis of the original vs repeated results is shown in the figure below.



This analysis shows that the original and reassayed sample results are highly correlated ($r^2 = 0.9748$), with slope = 0.832, and intercept = 0.0978. The slope of the regression curve suggests that the reassayed samples are on average approximately 17% lower than original assay values.

Study NWP06-PPK-101

For study NWP06-PPK-101, a total of 29 samples from 4 hr and 12 hr postdose from all subjects and all treatment periods were reassayed for total methylphenidate concentration. Linear regression analysis of the original vs repeated results is shown in the figure below.



This analysis shows that the original and reassayed sample results are highly correlated ($r^2 = 0.9618$), with slope = 0.977, and intercept = 0.1315. The slope of the curve suggests that the reassayed samples are on average approximately 3% lower than original assay values.

Issue identified

Prior to reassay of study S09-0238 samples, an analysis was conducted to assess the long term storage stability of the d-MPH QC plasma samples stored at -20°C . This analysis suggested that plasma d-MPH concentrations are lower on average by 30%. All the QC and study samples were stored at -20°C . Whether this reduction in the QC concentrations is due to degradation or not is unknown.

Similar problem was identified for QC samples from study NWP06-PPK-101. QC sample concentrations were reduced on an average by ~17%. This could potentially be

explained by the different storage condition: QC samples were stored at -20°C, while study samples were stored at -80°C.

The cause for this discrepancy with the QC samples is not obvious. An entirely empiric approach might suggest that the reanalyzed concentrations could be 30% lower than the original ones, in which case the reanalysis would not meet the acceptance criteria (to be within 20% deviation). However, based on the totality of evidence (as described under Recommendations), it is unlikely that the QC results would trump study sample results, similarity of methylphenidate AUC and Cmax values from the reference arm in this NDA and the values seen in the original NDA for the reference (see below) and clinical results.

Cross Study Comparison:

PK parameters for Methylin IR oral solution which was used as the RLD in this application were compared to those from the methylin IR oral solution label and the original NDA 21419. Mean AUC and Cmax values for methylphenidate are quite comparable between NDA 21419 and the current submission (Table below). This provides additional evidence for the reliability of the data submitted for this NDA.

NDA	#21419 (approved)	#202100 (current)
Dose (mg)	20	60 (30 mgx2, given 6hr apart)
AUCinf (ng·hr/mL)	51.9±24.7	151±83
Dose-normalized AUCinf(ng·hr/mL/mg)	2.59±1.24	2.52±1.38
Cmax (ng/mL)	9.1±2.6	20.9±12.9
Dose-normalized Cmax(ng/mL/mg)	0.46±0.06	0.35±0.02
T1/2 (hr)	2.7±0.5	3.7±0.6

SIGNATURES

Huixia Zhang, Ph.D.
Reviewer, Psychiatry Drug Team, DCP1
Office of Clinical Pharmacology

RD/FT, Initialized by Jogarao Gobburu, Ph.D.
Acting Team Leader, Psychiatry Drug Team, DCP1
Office of Clinical Pharmacology
Cc: NDA 202100, DCP1 (Mehta, Uppoor, Gobburu, Zhang)

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/s/

HUIXIA ZHANG
08/29/2011

JOGARAO V GOBBURU
08/29/2011

BIOPHARMACEUTICS REVIEW
Office of New Drugs Quality Assessment

Application No.:	NDA 202-100	Reviewer: Angelica Dorantes, Ph.D
Submission Date:	July 29, 2010	Supervisor: Patrick J. Marroum, Ph.D
Division:	Division of Psychiatric Products	Date Assigned: July 30, 2010
Applicant:	NextWave Pharmaceuticals	Date of Review: First Review: Nov 10, 2010 2nd Review: March 23, 2011
Trade Name:	Methylphenidate HCl ER Powder for Oral Suspension	Type of Submission: Original 505(b)(2) NDA
Generic Name:	Methylphenidate HCl	
Indication:	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older	
Formulation/strengths	Powder for oral suspension (pediatric formulation); 25 mg/5 mL	
Route of Administration	Oral	
Review:	<i>Biopharmaceutics - Dissolution Method and Acceptance Criteria</i> <i>- In Vitro Alcohol Dose Dumping Study</i> <i>- Extended Release Dosage Form Classification</i>	

SUBMISSION:

NextWave Pharmaceuticals submitted NDA 202-100 to support the marketing authorization of Methylphenidate HCl Extended-Release Powder for Oral Suspension (25 mg/5 mL). This NDA is submitted pursuant to Section 505(b)(2) of the FD&C Act; the Reference Listed Drug for this application is Methylin (methylphenidate HCl) Oral Solution approved by FDA under NDA 21-419. Methylphenidate is a central nervous system (CNS) stimulant. The mode of therapeutic action in humans is not completely understood. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. This product is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older.

BIOPHARMACEUTICS:

Formulation: The motivation for the development of this new product was to provide a pediatric-friendly formulation of methylphenidate with a fast onset and extended duration of effect.

Methylphenidate HCl Extended-Release Powder for Oral Suspension is a liquid-based, once-daily extended-release formulation of methylphenidate HCl. The motivation for the development of this new product was to provide a pediatric-friendly formulation of methylphenidate with a fast onset and extended duration of effect. The product is supplied as an extended-release powder for oral suspension. After reconstitution, it contains Methylphenidate HCl USP at a concentration of 25 mg/5 mL. Inactive ingredients are: sodium polystyrene sulfonate, povidone, triacetin, (b) (4) sugar, sodium citrate anhydrous, citric acid anhydrous, sodium benzoate, sucralose, poloxamer, (b) (4) food starch, xanthan gum, talc, flavor, and silicon dioxide. An appropriate quantity of the drug product (powder) is filled into glass bottles that are intended to provide a 30-day supply at doses of 10, 20, 30, 40 50, or 60 mg/day.

The qualitative composition, functions, and quantitative composition per dose are provided for each

ingredient used in the manufacture of Methylphenidate ER Powder for Oral Suspension eq. to 25 mg methylphenidate hydrochloride per 5 mL.

Unit Composition		
Ingredients	Function	Quantity (mg/5 mL)
(b) (4)	(b) (4)	(b) (4)
Sodium Polystyrene Sulfonate USP (b) (4)		
Methylphenidate Hydrochloride USP	Active	25
Povidone USP (b) (4)	(b) (4)	(b) (4)
(b) (4)		
Triacetin USP		
(b) (4) Sugar NF (b) (4)		
Sodium Citrate Anhydrous USP		
Anhydrous Citric Acid USP		
Sodium Benzoate NF		
Poloxamer 188 NF (b) (4)		
Sucralose NF		
(b) (4) (Food Starch) (b) (4)		
Xanthan Gum NF (b) (4)		
Talc USP (b) (4)		
(b) (4) Banana Flavor (b) (4)	Flavor	
Silicon Dioxide NF (b) (4)	(b) (4)	(b) (4)
(b) (4)		(b) (4)

Clinical Studies: The current submission includes the results from one relative bioavailability study (study S09-0238, one single-dose pharmacokinetic study in children and adolescent patients with ADHD (NWP06-PPK-101), and one efficacy and safety Phase III trial in 45 6-12 year-old patients (NWP06-ADD-100).

Biowaiver: The bioavailability of the intended commercial Methylphenidate HCl Extended-Release Powder for Oral Suspension product was characterized by the applicant in the above PK studies. Therefore, an in vivo BA/BE waiver is not needed for this 505(b)(2) NDA submission.

In Vitro Dissolution Testing:

Method development: In vitro dissolution studies were conducted to evaluate the effect of paddle speed and pH of the dissolution media; these data were used to select the assay conditions for the proposed dissolution method. In addition, an in vitro dissolution study to evaluate the effect of alcohol on the drug release profile showed that high (20%) concentrations of alcohol may have some impact on accelerating the release of methylphenidate from the formulation.

(b) (4)

After considering all of the above facts, the dissolution method was developed to discriminate between different formulations and manufacturing process change and as a tool to predict the quality of the product.

Reviewer Comment: The applicant states that the tested dissolution method is discriminating on the suspension prepared with (b) (4). However, the data for the (b) (4) show very similar dissolution profiles.

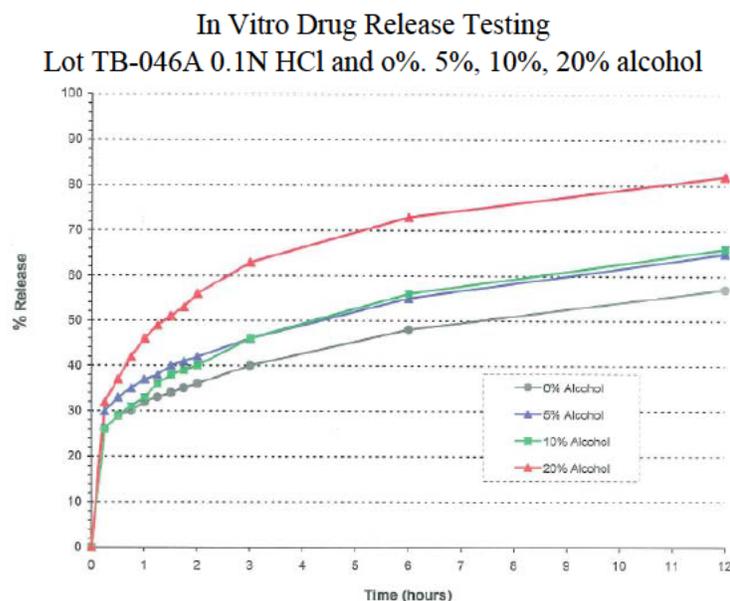
Proposed Dissolution Method and Acceptance Criteria: The proposed dissolution method and acceptance criteria are described below.

Proposed Dissolution method and Acceptance Criteria for Methylphenidate HCl Extended Release Powder for Oral Suspension	
Dissolution Conditions	
Apparatus:	USP Apparatus 2, Paddle
Speed of Rotation:	(b) (4) rpm
Medium:	0.4M KH ₂ PO ₄ pH 4.5 at 37 ± 0.5 ° C
Volume:	900 ml
Sampling Time:	(b) (4) hours
Analytical Test	(b) (4)
Acceptance Criteria	(b) (4)

(b) (4)

Reviewer Comment: It should be noted that at (b) (4) the mean percentage of drug dissolved is (b) (4) (b) (4) therefore, complete dissolution of the drug is not been achieved in this period of time. It is recommended that the sampling time period be extended to 24 hours or the rotation of the paddle be increased (b) (4)

In Vitro Alcohol Dose Dumping Study: An in vitro study was conducted to evaluate if alcohol had an effect on the release characteristics of the ER formulation. The following testing conditions were used; Apparatus 2, 50 rpm, 900 ml of HCl 0.1 N mixed with 0%, or 5%, or 10%, or 20% alcohol at 37°C. The drug release profiles are illustrated in the next figure.



Reviewer Comment: *The results from the in vitro alcohol study showed that alcohol increased the release of the drug from the formulation, but a dose dumping effect per se was not observed. The higher release was observed with the higher 20% content of alcohol. These results from this study were communicated to OCP.*

Evaluation of the Extended Release Claim: The applicant classified their proposed Methylphenidate HCl Powder for Oral Suspension product as an Extended-Release drug product. Therefore, to support the ER claim they need to provide drug plasma peak to trough (C_{max}/C_{min}) fluctuation index data from a steady state study comparing their product to that fluctuation index of the reference product and it need to be at least the same or better than that of the reference product. The regulations regarding the specific information that is needed to support an ER claim for a drug product is described in 21 CFR 320.25(f).

21 CFR 320.25

(f)Extended release formulations. (1) *The purpose of an in vivo bioavailability study involving a drug product for which an extended release claim is made is to determine if all of the following conditions are met:*

(i) The drug product meets the extended release claims made for it.

(ii) The bioavailability profile established for the drug product rules out the occurrence of any dose dumping.

(iii) The drug product's steady-state performance is equivalent to a currently marketed non-extended release or extended release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application.

(iv) The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

Reviewer Comment: *The proposed Methylphenidate HCl Powder for Oral Suspension is described as an Extended-Release drug product; however, the applicant did not provide the information required by 21 CFR 320.25(f)(iii) to support the Extended Release designation for their proposed Methylphenidate HCl Powder for Oral Suspension product.*

REVIEWER COMMENTS CONVEYED TO THE APPLICANT:

On November 12, 2010, ONDQA conveyed the following Reviewer Comments to the applicant (Tris Pharma - DMF holder) and under DMF 23-870.

1. The provided dissolution data indicate that tighter acceptance criteria can be set for your product. Note that the proposed dissolution acceptance criteria (*mean value ±15*) for the (b) (4) hours time-points are very wide and the proposed specification value of NLT (b) (4) for the last sampling time point at (b) (4) is not adequate. Provide the dissolution profile data (*i.e., individual, mean, min, max, SD, and dissolution plots. Include the specific testing conditions*) from the clinical and stability batches supporting the selection of the proposed dissolution acceptance criteria (*i.e., specification-sampling time points and specification values*). In general, the selection of the dissolution specification ranges is based on mean target value±10%. The specification time for the last sampling point should be set when at least (b) (4) of drug is released or a plateau is reached (*i.e., NLT (b) (4)*). Wider specification ranges may be acceptable, only if they are supported by an approved In Vitro-In Vivo Correlation (IVIVC) model.
2. If your data (*i.e., dissolution, IVIVC, etc.*) cannot support the currently proposed dissolution acceptance criteria, provide revised dissolution acceptance criteria for your product.

APPLICANT'S RESPONSE TO BIOPHARMACEUTICS COMMENTS :

On December 23, 2010, Tris Pharma provided their response to the Biopharmaceutics comments under DMF 23-870 (Amend 003). For detail information see Attachment 1. ONDQA-Biopharmaceutics has evaluated the information provided in this DMF submission and has the following additional comments:

1. Methylphenidate ER Powder for oral suspension is an extended release product designed to provide therapeutic effect for 12 hours. It is expected that the proposed dissolution method will be able to evaluate the complete dissolution of the drug in the 12 hours time period. However, the provided data from the stability and clinical batches showed that at 12 hours the dissolution of the drug has not reached (b) (4) or a plateau. Therefore, the selected dissolution testing conditions are less than optimal due to the fact that complete dissolution cannot be obtained during the 12 hours sampling time period. It is recommended that the sampling times be extended to 24 hours **or** the dissolution test be modified (b) (4).
2. With respect to the specifications, the provided data do not support the proposed specifications (b) (4). The stability reconstitution (initial) data for times (b) (4) hours indicate that the drug product can meet mean ±10% (USP <724> L1, L2 or L3 criteria as appropriate).
3. Additionally, the applicant is proposing drug release specifications for the ER Powder for oral suspension (b) (4). The applicant's proposal is not acceptable; (b) (4)
4. The proposed Methylphenidate HCl Powder for Oral Suspension is described as an Extended-Release drug product; however, the applicant did not provide any of the information required by 21 CFR 320.25(f)(iii) to support the Extended Release claim for their proposed Methylphenidate HCl Powder for Oral Suspension product. In the absence of this information, NDA 202-100 for Methylphenidate HCl Powder for Oral Suspension is not complying with the CFR Regulations. Therefore, it is recommended that the applicant provide the information described in 21 CFR 320.25(f)(iii) supporting the "Extended Release" claim for their proposed drug product.

TELECONFERENCE WITH THE APPLICANT:

On March 21, 2011, a teleconference was held between Tris Pharma (DMF 23-870 holder) and ONDQA's reviewing team (Biopharmaceutics and CMC). In this teleconference, the above Reviewer Comments 1 and 2 were discussed with applicant and the following agreement was reached:

- ◆ **Dissolution Method** – The applicant has the choice of; **i)** adding an additional sampling time-point at 24 hours for any further stability/batch release dissolution testing of their product **or ii)** develop a new dissolution method for their product (b) (4)

- ◆ ***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 $\pm 10\%$), 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 $\pm 10\%$) and $Q = \text{(b) (4)}$ for the (b) (4) time point if a new dissolution method is developed.

In the teleconference it was concluded that by **April 10, 2011**, the applicant will provide an amendment to the DMF including the necessary additional dissolution data and a proposal for revised dissolution specifications for Methylphenidate HCl Powder ER for Oral Suspension product based on the Agency's above recommendation.

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment

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Office of New Drugs Quality Assessment

ATTACHMENT 1

Applicant Responses to Biopharmaceutics Comments provided in
DMF 23-870 dated 12/23/10

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ATTACHMENT 2

In vitro Dissolution Data for the In Vitro Alcohol Dose Dumping Study

Lot TB-046A (0.1 N HCl dissolution profile)

Apparatus: USP Apparatus II (Paddle)
 Media: 895 mL 0.1 N HCl
 Speed: 50 rpm
 Temp. : 37°C ± 0.5°C
 Sample Vol: 5 mL
 Time Intervals: 0.25, 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 3, 6, and 12 hours

Sample No.	Methylphenidate ER Powder for Oral Suspension Lot: TB-046A (0.1 N HCl dissolution profile)										
	0.25 hr	0.50 hr	0.75 hr	1.0 hr	1.25 hr	1.50 hr	1.75 hr	2.0 hr	3.0 hr	6.0 hr	12.0 hr
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean	26	29	30	32	33	34	35	36	40	48	57
Range	(b) (4)										
%RSD	(b) (4)										

Lot TB-046A (5% v/v Alcohol dissolution profile)

Apparatus: USP Apparatus II (Paddle)
 Media: 895 mL 0.1N HCl containing 5% (v/v) Alcohol
 Speed: 50 rpm
 Temp. : 37°C ± 0.5°C
 Sample Vol: 5 mL
 Time Intervals: 0.25, 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 3, 6, and 12 hours

Sample No.	Methylphenidate ER Powder for Oral Suspension Lot: TB-046A (5% v/v Alcohol dissolution profile)										
	0.25 hr	0.50 hr	0.75 hr	1.0 hr	1.25 hr	1.50 hr	1.75 hr	2.0 hr	3.0 hr	6.0 hr	12.0 hr
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean	30	33	35	37	38	40	41	42	46	55	65
Range	(b) (4)										
%RSD	(b) (4)										

Lot TB-046A (10% v/v Alcohol dissolution profile)

Apparatus: USP Apparatus II (Paddle)
 Media: 895 mL 0.1N HCl containing 10% (v/v) Alcohol
 Speed: 50 rpm
 Temp.: 37°C ± 0.5°C
 Sample Vol: 5 mL
 Time Intervals: 0.25, 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 3, 6, and 12 hours

Sample No.	Methylphenidate ER Powder for Oral Suspension Lot: TB-046A (10% v/v Alcohol dissolution profile)										
	0.25 hr	0.50 hr	0.75 hr	1.0 hr	1.25 hr	1.50 hr	1.75 hr	2.0 hr	3.0 hr	6.0 hr	12.0 hr
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean	26	29	31	33	36	38	39	40	46	56	66
Range	(b) (4)										
%RSD	(b) (4)										

Lot TB-046A (20% v/v Alcohol dissolution profile)

Apparatus: USP Apparatus II (Paddle)
 Media: 895 mL 0.1N HCl containing 20% (v/v) Alcohol
 Speed: 50 rpm
 Temp.: 37°C ± 0.5°C
 Sample Vol: 5 mL
 Time Intervals: 0.25, 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 3, 6, and 12 hours

Sample No.	Methylphenidate ER Powder for Oral Suspension Lot: TB-046A (20% v/v Alcohol dissolution profile)										
	0.25 hr	0.50 hr	0.75 hr	1.0 hr	1.25 hr	1.50 hr	1.75 hr	2.0 hr	3.0 hr	6.0 hr	12.0 hr
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean	32	37	42	46	49	51	53	56	63	73	82
Range	(b) (4)										
%RSD	(b) (4)										

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/s/

ANGELICA DORANTES
03/23/2011

PATRICK J MARROUM
03/23/2011

Clinical Pharmacology Review

NDA:	202100
Proposed Brand Name:	To be determined
Generic Name:	Methylphenidate HCl
Dosage Form:	Extended-Release Powder for Oral Suspension
Dosage Strength:	25 mg/5 mL
Indication:	Attention Deficit Hyperactive Disorder (ADHD)
Sponsor:	NextWave Pharmaceuticals Inc.
Submission type:	505(b)(2)
Submission date:	July 29, 2010
OCP Reviewers:	Huixia Zhang, PhD, Jogarao Gobburu, PhD, Hui Zheng, PhD, Yaning Wang, PhD

OCP Optional Inter-Division Briefing was held on February 14, 2011.

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1. EXECUTIVE SUMMARY

NextWave Pharmaceuticals is seeking approval of NWP06, Methylphenidate Extended-Release Powder for oral suspension, for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older, via 505(b)(2) approach. NWP06 is a new liquid-based, (b) (4) extended-release (b) (4) formulation (20% IR and 80% ER) of methylphenidate (MPH) HCl. This formulation is intended to be used by patients with ADHD who are unable or unwilling to swallow tablets or capsules to allow for improved medication compliance. Methylin oral solution is used as the reference product, which in turn was approved by demonstrating BE to Ritalin tablets (505(b)(2)).

Pharmacokinetics of NWP06 was characterized in children and adolescent with ADHD, as well as in healthy adults. Food and alcohol do not meaningfully interfere with NWP06's PK. The efficacy of NWP06 in ADHD children (6 to 12 years of age) was demonstrated in a double-blind, placebo-controlled laboratory classroom study (NWP06-ADD-100). In addition, based on prior knowledge from Concerta efficacy studies and results from NWP06-ADD-100 study in 6-12 year olds, ADHD indication in adolescents and adults can be given without additional controlled trials.

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 NWP06. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP?	Comment
Overall	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	Pending labeling
Evidence of effectiveness	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	One positive registration trial in 6-12 years; efficacy bridged from Concerta for >13 years.
Duration of clinical response	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	Statistically significant difference was observed from 45 min to 12 hrs post-dose between NWP06 and placebo
Proposed dose for patients 6-17 years	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> NA	(b) (4) we recommend 20 mg starting dose.
Proposed dose for adult patients	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	(b) (4)
BE (NWP06 vs. Methylin Oral Solution)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> NA	Approval will be based on efficacy trial, not BE result. Conventional BE criteria inapplicable.
Labeling	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> NA	Pending satisfactory agreement with sponsor

1.1.1 Labeling Recommendations

Detailed Labeling Recommendations can be found at <\\cdsnas\transfer\OCPB\Reviews\NDA202100>

1.2 Phase IV Commitments

No Phase IV study recommendation.

1.3 Summary of Clinical Pharmacology Findings

In the current submission, the Sponsor has submitted the results from one relative bioavailability study (study S09-0238; RLD: Methylin Oral Solution), one single-dose pharmacokinetic study in children and adolescent patients with ADHD (NWP06-PPK-101), and one efficacy and safety Phase III trial in 45 6-12 year-old patients (NWP06-ADD-100) to support their application.

- NWP06 is efficacious in the treatment of children ages 6-12 years old with ADHD.
- Similar PK parameters were obtained for children and adolescents with ADHD.
- NWP06 and Methylin Oral Solution have different shapes of the concentration-time curves (see Figure 1). Owing to the complex drug release characteristics to match the q6h reference PK profile, conventional BE metrics are not appropriate for NWP06. The test-reference ratio for AUC is 0.95 (90% CI: 0.92-0.99), and C_{max} is 0.69 (90% CI: 0.64 - 0.75). However, the approval decision will be based on the results of the efficacy and safety trial.
- Food increased NWP06's AUC by 20%, C_{max} by 28% and shortened T_{max} (4 hrs vs 5 hrs-fasted). NWP06 can be administered with or without food.

2. QUESTION BASED REVIEW

2.1 Specific Questions

2.1.1 Is there evidence of effectiveness for NWP06 in children aged 6-12 years (prescribability)?

Yes. The efficacy of NWP06 in ADHD children (6 to 12 years of age) was demonstrated in study NWP06-ADD-100.

Study NWP06-ADD-100 was a randomized, double-blind, placebo-controlled, crossover, multicenter, laboratory classroom study. In the open-label dose optimization phase (4 to 6 weeks), the initial methylphenidate dose for all subjects was 20 mg once daily in the morning. The dose was titrated weekly in increments of 10 or 20 mg until an optimal dose or maximum dose (60 mg/day) was reached. After 4 to 6 weeks of dose-optimization, subjects were randomized to one of two double-blind treatment sequences. Subjects were treated with active methylphenidate (with the optimal dose that was established in the open-label, optimization phase) for one week, followed by placebo for one week or vice versa.

The primary efficacy endpoint in this study was the SKAMP-Combined score at 4 hours post-dose, and this endpoint was met. SKAMP combined scores were also obtained for time points of 0.75, 4, 8, 10, and 12 hrs post-dose as secondary end points. The onset of efficacy was determined to be 0.75 hours post-dose, and efficacy was maintained throughout the 12-hour period.

2.1.2 Are sponsor's claim about onset of effect by 45 min and sustained effect through 12 hr justified?

Yes.

1) Time course of concentrations:

The mean concentrations in the first 45 min for both products are similar. Methylin Oral Solution exhibited higher concentrations beyond 5 hrs compared to NWP06. Mean d-MPH plasma concentration-time profiles were compiled from different studies, after oral administration of NWP06 60 mg, Methylin Oral Solution 2x30 mg (NDA202100) and Concerta 54 mg (NDA21121). As shown in Figure 1, different shapes of curves were observed for those products. Concerta has two absorption peaks, Methylin Oral Solution also has two peaks due to q6h administration, while NWP06 only has one peak. Although the concentrations beyond 5 hr for NWP06 and Concerta are similar, Methylin Oral Solution exhibited higher concentrations till 12 hr.

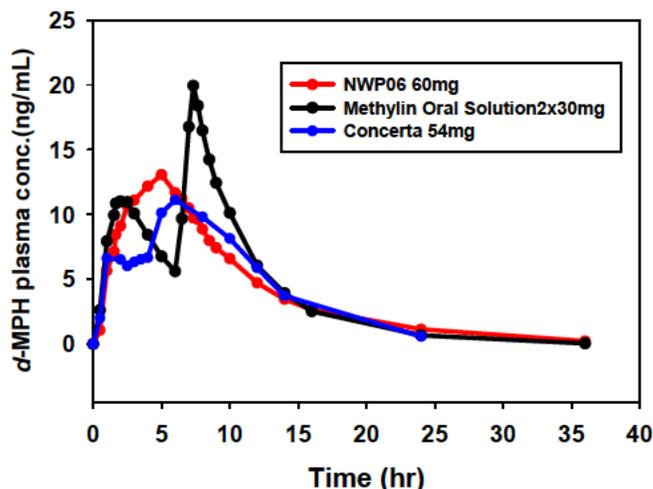


Figure 1. Plasma concentration time profiles of d-MPH after oral administration of NWP06 (60 mg), Methylin Oral Solution q6hr (2x30 mg), and Concerta (54 mg). Total MPH was measured for Concerta (*l*-MPH concentration is 1/40 of *d*-MPH in the circulation). Concerta information source: <\\Cdsub1\evsprod\NDA021121\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\02-160>

Overall AUC for NWP06 and Methylin Oral Solution are similar. Comparison of partial AUCs of NWP06 and Methylin Oral Solution indicates that at the earlier (0-2 hr) and late phases (6-8, 8-12 hr) of the curves, NWP06 has 30-40% lower AUC compared to Methylin Oral Solution (Table 1).

Table 1. Comparison of PK Parameters of NWP06 and Methylin Oral Solution After 60 mg Oral Administration in Healthy Volunteers Under Fasting Conditions (n=28)		
d-MPH PK parameters	Geometric Mean Ratio (%) (NWP06/Methylin Oral Solution)	90% confidence interval (%)
AUC ₀₋₂	70	61-79
AUC ₂₋₄	113	106-121
AUC ₀₋₄	95	88-104
AUC ₄₋₈	108	103-114
AUC ₆₋₈	72	67-77
AUC ₈₋₁₂	62	59-66
AUC _{0-inf}	95	92-100
C _{max}	69	64-75

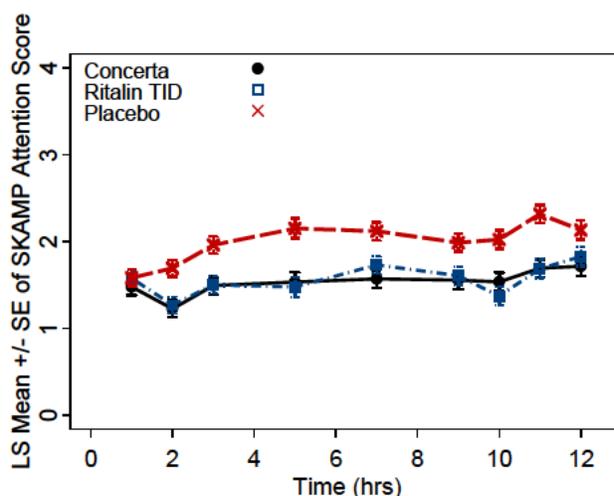
NWP06: 60 mg; Methylin Oral Solution: 2x30 mg, 6 hr apart

The concentration of d-MPH is higher after NWP06 (60 mg) administration than that after Concerta (54 mg) administration, from about 1 hr to 7-8 hrs after dosing. From 8 hr onward, the concentration-time profiles are almost superimposable. Of note, total MPH concentrations were measured in Concerta study, and *l*-MPH concentration was about 1/40 of d-MPH.

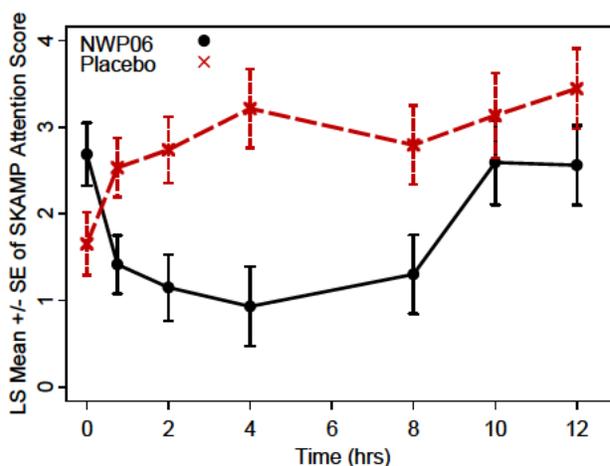
2) Time course of clinical response:

NWP06 exhibited absolute SKAMP scores significantly different from placebo starting from 45 min, and the response sustained up to 12 hr. As Methylin Oral Solution's efficacy was not directly studied, we used Ritalin IR (TID) and Concerta's efficacy results to qualitatively appreciate the time-course of clinical response better (Figure 2). These data suggest that NWP06 is comparable to Concerta and Ritalin IR in terms of effects on SKAMP attention score.

Figure 2: Mean (\pm SE) SKAMP Attention Scores over Time after Treatment with Concerta (Panel A), Ritalin TID (Panel A) or NWP06 (Panel B).



A: Concerta NDA21121, Study C-98-003 3 treatment crossover (n=60, age 6-12)
Dosage: Concerta 18, 36, 54 mg q.d.; Ritalin 5, 10, 15 mg t.i.d.



B: NWP06 NDA202100, Study NWP06-ADD-100

2 treatment crossover (n=45, age 6-12); Dosage: NWP06 20, 30, 40, 50, 60 mg q.d.

2.1.3 Should NWP06 be approved without designated efficacy study in adolescents and adults?

Yes, NWP06 can be approved for adolescents and adults.

- Methylphenidate is shown to be efficacious in several clinical trials across a varied range of formulations in patients 6 years and older.
- Concerta 18 mg was shown to be effective in the treatment of ADHD in children, adolescents and adults. Doses upto 54 mg are approved for children, and upto 72 mg for adolescents and adults. 20 mg NWP06 was shown to be efficacious in children.
- PK of NWP06 in children, adolescents and adults are similar at similar doses.
- MPH concentrations are directly associated with clinical response (Swanson and Volkow 2003: Neuroscience and Biobehavioral Reviews 26: 615-621). Therefore, it is expected that NWP06 is effective in adolescent and adult patients at similar concentrations. Hence 20 mg NWP06 should be efficacious in adolescents and adults.

2.1.4 Is an in vivo alcohol and NWP06 study needed?

An in vitro dissolution study to evaluate the effect of alcohol on the drug release profile showed that high (20%) concentrations of alcohol may have some impact on accelerating the release of methylphenidate from the formulation.

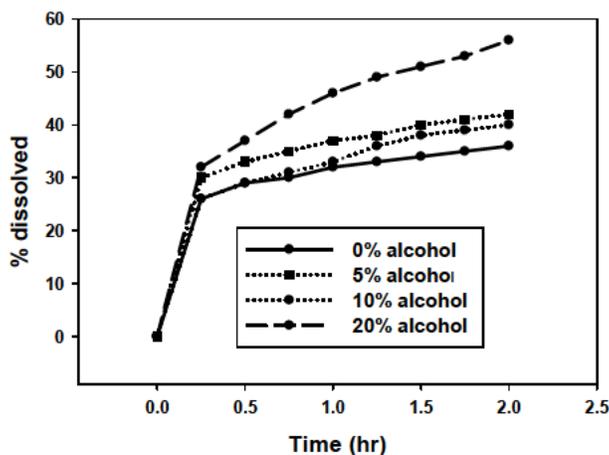


Figure 3: Dissolution profiles of NWP06 in 0.1N HCl with different percentage of alcohol.

Source: \\CDSESUB1\EVSPROD\MF023870

In 0.1 M HCl solution, ~ 36% of the drug powder was dissolved in the medium by 2 hrs; in the presence of 20% of alcohol (v/v), ~ 56% increase in the dissolution of the drug powder was observed. The moderate dose dumping effect with 20% alcohol demonstrates that ~ 60% of the drug powder would be dissolved in 2 hrs.

Clinically, alcohol and medication co-consumption is an unlikely concern for children/adolescents, and is most likely to occur in adults. In the worst case scenario, co-consumption of 20% strength-alcohol might increase the bioavailability and C_{max} by 60%. That means if a patient took 60 mg dose together with a lot of drinking within half an hour, effectively the patient is dosed 96 mg. Doses up to 144 mg were studied for Concerta. No severe adverse events were observed. Therefore, there is no concern about infrequent alcohol consumption, and an in vivo study is not required. However, alcohol is known to impair behavior which might lead to pharmacodynamic interaction with ADHD treatment.

2.1.5 What are the extended release characteristics of NWP06?

NWP06 is a liquid-based, ^{(b) (4)} extended release formulation that contains 20% IR and 80% ER of methylphenidate HCl. Its PK properties are listed in the table below.

Table 2. Pharmacokinetic Parameters (Mean±SD) of d-MPH after oral administration of 60 mg either NWP06 or Methylin IR Oral Solution (30 mg Q6hr) under Fasting Conditions.		
PK Parameters	NWP06	Methylin IR Oral Solution
AUC ₀₋₃₆ , ng·hr/mL	140±71.4	149 ± 82.6
C _{ave} ^a , ng/mL	3.89±2.29	4.14±2.29
C _{max} , ng/mL	13.6±5.79	15.5 ^b
C ₂₄ , ng/mL	1.13±0.81	0.67±0.66
Fluctuation ratio ^c	3.21	3.58
T _{1/2} , hr	5.7±0.85	3.74±0.61
^a C _{ave} is obtained by dividing AUC ₀₋₃₆ with 36; ^b C _{max} is the mean of C _{max1} and C _{max2} ; ^c fluctuation ratio is obtained following equation (C _{max} -C _{min})/C _{ave} using the mean values.		

Because of its half life (~5.7 hr) and once daily dosing regimen, the pharmacokinetic parameters of NWP06 is not expected to change after multiple dosing compared to single dose administration (methylphenidate demonstrates time-independent linear pharmacokinetics). The first dose is almost completely eliminated from the body at the end of 24 hr period, and no significant accumulation of methylphenidate is expected.

2.1.6 Is there any relationship between the final dose and body weight?

Patients in the efficacy study received different doses of NWP06 from 20 mg to 60 mg and the patients had different body weight, from 38 lbs up to 137.5 lbs. To determine if there is a need for body weight-based dosing, an analysis was performed between the final dose and patient body weight. As shown in Figure 4, there is no noticeable relationship between the body weight and the final dose. Hence, there is no need for weight based dosing.

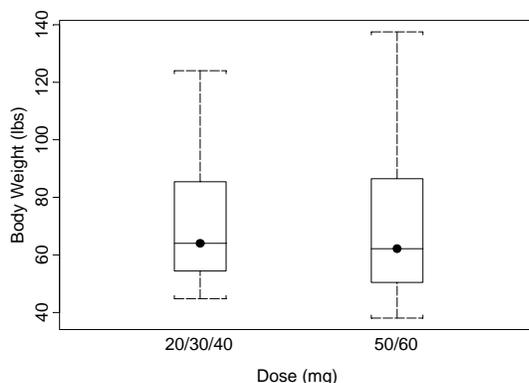


Figure 4: NWP06 Final Dose vs. Body Weight of Subjects

2.2 Standard Questions

2.2.1 Does food affect the bioavailability of NWP06?

High-fat meal increased systemic exposure (AUC_{inf}) of NWP06 by ~ 20%, and C_{max} by ~ 28%. The small increase in exposure is not expected to have a large effect on the efficacy or safety of the product.

PK Parameters	Fed	Fasting	Ratio of Geometric Means (90% Confidence Interval)
AUC_{0-inf}^a , ng·hr/mL	163 (49)	144 (51)	119 (115-123)
C_{max}^a , ng/mL	17 (46)	14 (43)	128 (120-136)
T_{max}^b , hr	4 (1-7)	5 (2-6)	
$T_{1/2}^a$, hr	5 (20)	56(15)	

^aArithmetic Mean (%CV), ^bMedian (Range)

2.2.2. What are the single dose PK parameters of NWP06 in healthy adults and pediatric patients?

Similar PK parameters were obtained for T_{max} and $T_{1/2}$, in children and adolescents with ADHD, and healthy adults after oral administration of 60 mg NWP06 (Table 3). Body-weight corrected clearance values were also similar across the three populations. NWP06 exhibited dose-proportional PK between 20 mg – 60 mg.

PK Parameters	Children ² (n=3)	Adolescent ² (n=4)	Adult (n=27)
T_{max} (hr) ³	4 (4-6)	2 (2-4)	4 (1-7)
$T_{1/2}$ (hr)	5±0.1	5±0.2	5±1
C_{max} (ng/mL)	34±14	21±6	17±8
AUC_{inf} (hr*ng/mL)	378±175	178±54	163±80
CL (L/hr/kg)	4±0.7	5±1	6±2

¹Breakfast was given 30min after drug administration ² total MPH measured in children and adolescents, l-MPH<2% of d-MPH in circulation ³data presented as median (range)

SIGNATURES

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Office of Clinical Pharmacology

Yaning Wang, Ph.D.
Team Leader, Pharmacometrics
Office of Clinical Pharmacology

RD/FT, Initialized by Jogarao Gobburu, Ph.D.
Acting Team Leader, Psychiatry Drug Team, DCP1
Office of Clinical Pharmacology
Cc: NDA 202100, DCP1 (Mehta, Uppoor, Gobburu, Zhang)

3. INDIVIDUAL STUDY REPORTS

3.1 Relative Bioavailability and Food Effect Study

An Open-label, Single-Dose, Randomized, Three-Period, Three-Treatment Cross Over, Study Evaluating the Relative Bioavailability and the Food Effect on the PK of Methylphenidate HCl ER Powder for Oral Suspension in Healthy Adult Volunteers.

Study Number: S09-0238

Study Period: 3/15/2010-3/31/2010

Analytical Period: 5/5/2010-5/27/2010

OBJECTIVE

1. To determine the relative bioavailability of 60 mg methylphenidate ER Powder for Oral Suspension vs Methylin IR Oral Solution under fasted conditions.
2. To determine food effect on the pharmacokinetics of NWP06.

FORMULATIONS

	Manufacturer	Formulation	Batch #	Expiration Date
NWP06	Tris Pharma, Inc.	12 mL suspension (5 mg/mL)	TB-046A	05/2010
Methylin® oral solution	Mallinckrodt Inc.	15 mL solution (2 mg/mL)	AML100908	10/2010

STUDY DESIGN

This was an open-label, single-dose, randomized, three-period, three-treatment crossover study under fasting and fed conditions.

A total number of 30 healthy adult subjects (male and female) were enrolled in the study, and twenty eight completed the study. The total duration of the study from screening through study exit was approximately 6 weeks with at least a 7-day washout period between Hour 0 dosing. Each subject received each of the following three treatments in a randomized order.

Treatment A: A single 60 mg (12 mL, 5 mg/mL) oral dose of Methylphenidate ER Oral Suspension under fed conditions (administered at Hour 0, 30 minutes after initiation of a FDA standardized high fat – high calorie meal preceded by an overnight fast of at least 10 hours). The standardized high fat – high calorie meal consisted of the following: 2 eggs cooked in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz. of hash brown potatoes, and 8 fl. oz. of whole milk.

Treatment B: A single 60 mg (12 mL, 5 mg/mL) oral dose of Methylphenidate (b) (4) ER Oral Suspension under fasting conditions (an overnight fast of at least 10 hours) administered at Hour 0.

Treatment C: Two 30 mg oral doses of Methylin® 10 mg/5 ml Oral Solution (the first dose to be administered at Hour 0, after an overnight fast of at least 10 hours, and the second dose to be administered at Hour 6).

Blood sample collection was obtained within 90 minutes prior to each subject's scheduled dose time (Hour 0 only), and after dose administration at post-dose Hours 0.5, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 6.5, 7, 7.33, 7.67, 8, 8.5, 9, 10, 12, 14, 16, 24 and 36 hours post-dose. K₂EDTA was used as the anticoagulant. The actual time of sample collection was documented.

ASSAY

An LC/MS/MS assay (AP LC/MS/MS 416.100) was developed to determine *d*-MPH concentration in human plasma samples. The accuracy (%Bias) and Precision (%CV) of the bioanalytical quality control (QC) samples are summarized in the Table below.

	Quality Control Samples		
	0.3 ng/mL	2.25 ng/mL	15 ng/mL
Accuracy (% bias)	6.8	5.1	5.2
Precision (% CV)	4.4	3.3	-3.3

RESULTS

Demographics:

Demographic and baseline characteristics of the subjects enrolled are summarized in Table 3.

	Test Product A N=27	Test Product B N=28	Reference Product C n=28
Age (mean±SD)	37±14	37±14	37±14
Gender (n, %)	Male 23 (85%) Female 4 (15%)	Male 23 (82.1%) Female 5 (17.9%)	Male 23 (82.1%) Female 5 (17.9%)
Race (n, %)	White 17 (63%) Black 8 (30%)	White 17 (61%) Black 9 (32%)	White 17 (61%) Black 9 (32%)
BMI (mean±SD)	25±3	25±3	25±3

Pharmacokinetics:

A. Relative Bioavailability

The 60-mg dose study comparing the pharmacokinetics of MPH ER oral suspension with Methylin oral solution (2 doses administered 6 hours apart, 30 mg each dose) was conducted under fasting conditions. As shown in Table 4 below, relative bioavailability of NWP06 is 95% of Methylin oral solution, with a 90% CI of 92-100%. Also it was noticed that the

terminal half life for the tested ER product (5.65 hr) is about 1.9 hr longer than that of the reference product (3.74 hr).

PK Parameters	MPH ER Suspension	Methylin IR Solution	Ratio of Geometric Means (90% Confidence Interval)
AUC ₀₋₄ ^a , ng·hr/mL	32(38)	33 (41)	96 (88-104)
AUC _{0-t} ^a , ng·hr/mL	140 (51)	149 (55)	95 (91-99)
AUC _{0-inf} ^a , ng·hr/mL	144 (51)	151 (55)	96 (92-100)
C _{max} ^a , ng/mL	14 (43)	21 (62)	69 (64-75)
T _{max} ^b , hr	5 (2-6)	7 (7-8)	
T _{1/2} ^a , hr	6(15)	4 (16)	

^aArithmetic Mean (%CV), ^bMedian (Range)

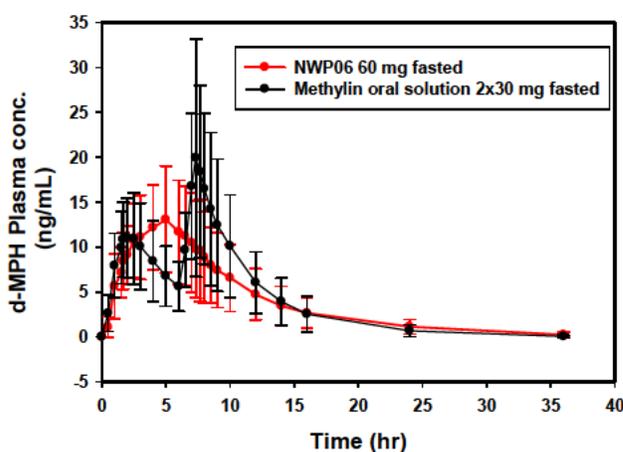


Figure 1. Plasma concentration-time profiles of d-MPH (mean±SD) after 60 mg oral administration of NWP06 and Methylin Oral Solution in healthy volunteers under fasted conditions.

B. Food Effect

The food effect on the pharmacokinetics of the ER tested product was tested after 60 mg oral administration of the drug. In this study, the ratios for the extent of exposure, as indicated by d-MPH AUC_{0-inf} 118.96% (90% CI: 115.23% - 122.82%), were within the standard 80-125% bioequivalence acceptance criteria. However, food significantly increased the rate and extent of the absorption, as indicated by an earlier T_{max} and increased C_{max}. The rate and extent of exposure to d-MPH were approximately 25% higher when MWP06 was administered under fed conditions (standard high-fat, high calorie breakfast), compared to administration under fasting conditions. The 90% confidence interval for the point estimate of geometric means for C_{max} ratio is 115.2-122.8%, out of the acceptance range of 80-125%.

The results of this study indicate that food increased the bioavailability of the NWP06.

Table 5. Pharmacokinetic Parameters of d-Methylphenidate (d-MPH) after oral administration of 60 mg MPH ER oral suspension under Fed or Fasting Conditions			
PK Parameters	Fed	Fasting	Ratio of Geometric Means (90% Confidence Interval)
AUC ₀₋₄ ^a , ng·hr/mL	40 (43)	32 (38)	122 (110-135)
AUC _{0-t} ^a , ng·hr/mL	160 (49)	140 (51)	120 (116-124)
AUC _{0-inf} ^a , ng·hr/mL	163 (49)	144 (51)	119 (115-123)
C _{max} ^a , ng/mL	17 (46)	14 (43)	128 (120-136)
T _{max} ^b , hr	4 (1-7)	5 (2-6)	
T _{1/2} ^a , hr	5(21)	6(15)	

^aArithmetic Mean (%CV), ^bMedian (Range)

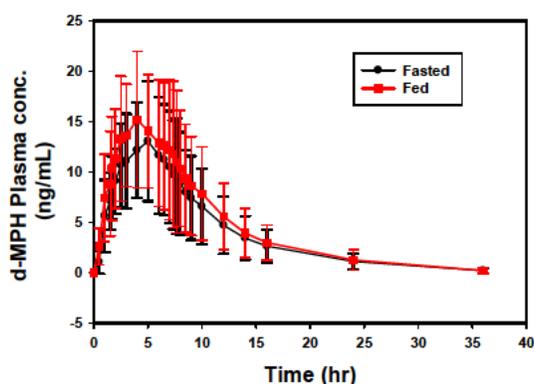


Figure 2. Mean(SD) plasma concentration-time profile of d-MPH after oral administration of 60 mg NWP06 with and without high-fat food.

Safety

Fourteen (14) subjects reported a total of 34 AEs across all treatments over the course of the study. Adverse events were mild in intensity. No SAEs were reported. Overall, the most common AEs reported were headache, dizziness, palpitations, nausea, nervousness, vision blurred, and hot flush.

Reviewers' Comments

Overall AUC for NWP06 and Methylin solution are similar. Comparison of partial AUCs of NWP06 and Methylin oral solution indicates that at the earlier (0-2 hr) and late phases (6-8, 8-12 hr) of the curves, NWP06 has 30-40% lower AUC compared to Methylin oral solution.

High-fat meal increased systemic exposure (AUC_{inf}) of NWP06 by ~ 20%, and C_{max} by ~ 28%. The small increase in exposure is not expected to have a large effect on the efficacy or safety of the product. NWP06 can be administered with or without food.

3.1.2 Single Dose Pharmacokinetics in Children and Adolescents with ADHD

Report # NWP06-PPK-101	Study Period: clinical phase start: April 23, 2010; Study treatment date: May 8-9, 2020	EDR Link
Title	Evaluation of the Single Dose Pharmacokinetics of NWP06 in Children and Adolescents with ADHD	

Study Design: phase 1, open label, children (6-12 years-old) and adolescents (13-17years-old) ADHD patients				
Number of Subjects/ dose group: 7	Drug	Methylphenidate extended release powder for oral suspension	Placebo	NA
Dose: 20 mg; 60 mg				
PK Sampling Times: pre-dose (up to 2 hours before dosing) and 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose on Day 1 (within ±15 minutes of the scheduled time), and 24 hours post-dose on Day 2 (within 24-28 hours post-dose)				
Analytical Method:				
Type	LC/MS/MS (AP LC/MS/MS 070.100)	Range	0.1-40 ng/mL	
The performance of the analytical method is acceptable.			<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
Study Population :				
Randomized/Completed/ Discontinued Due to AE			14/14/0	
Age [Median (range)]			6-17	
Male/Female			11/3	
Race (Caucasian/Black/Asian/other)			10/40/0/0	
Results				

Table 1. Pharmacokinetics Parameters (Mean (%CV)) Per Dose Group in Children and Adolescents with ADHD

PK Parameters	20 mg NWP06		60 mg NWP06	
	6-12 years (n=4)	13-17 years (n=3)	6-12 years (n=4)	13-17 years (n=3)
C _{max} (ng/ml)	11.5 (2.2)	9.2 (0.6)	34.4 (14)	21.1 (5.9)
T _{max} (hr)	3.0 (2.0-4.1)	2.0 (2.0-4.0)	4.1 (4.0-6.0)	2.0 (2.0-4.0)
AUC _{0-inf} (hr*ng/mL)	101 (4.2)	82.4 (4.8)	378 (175)	178 (54.2)
T _{1/2} (hr)	5.3 (0.7)	5.2 (0.2)	5.2 (0.1)	5.0 (0.2)
Cl/F (L/hr/Kg)	5.0 (1.1)	5.1 (0.6)	4.3 (0.7)	5.1 (1.4)

Figure 1. Arithmetic Mean (\pm SD) Plasma Methylphenidate Concentration-Time Profiles following a Single Oral 20-mg or 60-mg Dose of NWP06 given to Children and Adolescents with ADHD (linear and semi-logarithmic scale).

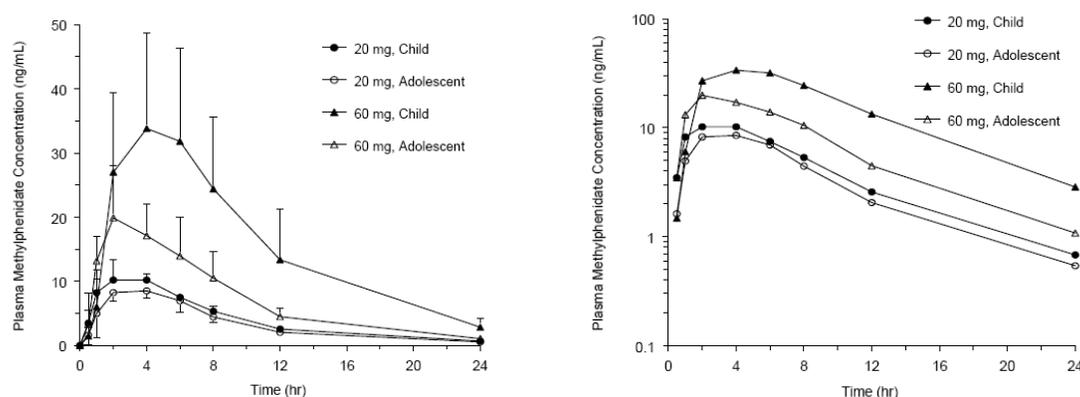
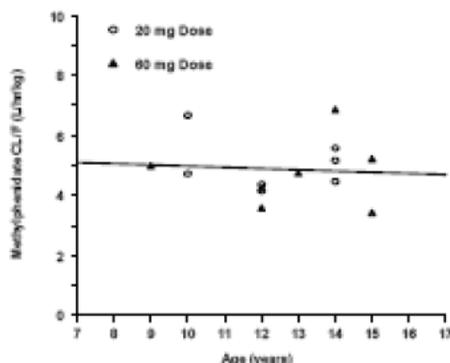


Table 2. Mean (SD) Dose- and Weight-Corrected Plasma Methylphenidate Pharmacokinetic Parameters in Children and Adolescents with ADHD following a Single Oral 20-mg or 60-mg of NWP06.

PK parameters	20 mg NWP06		60 mg NWP06	
	6-12 years (n=4)	13-17 years (n=3)	6-12 years (n=4)	13-17 years (n=3)
C _{max} /D (ng/mL/mg)	0.7 (0.1)	0.5 (0.03)	0.7 (0.3)	0.4 (0.1)
AUC _{0-inf} /D (hr*ng/mL/mg)	5.8 (0.2)	4.8 (0.3)	7.3 (3.4)	3.4 (1.1)
Cl/F (L/hr/Kg)	5.0 (1.2)	5.1 (0.6)	4.3 (0.7)	5.1 (1.4)

Figure 2. Plasma Methylphenidate CL/F (L/hr/kg) versus Age following A Single Oral 20-mg or 60-mg Dose of NWP06 in Children and Adolescents with ADHD.



A poor linear correlation was apparent between body weight-adjusted clearance and age ($r=0.078$), suggesting that when corrected for body weight, methylphenidate oral clearance does not vary with age.

- Was the pharmacokinetics dose proportional? Yes No
- The pharmacokinetics is best described by:
 Mono-exponential decay, Bi-exponential decay, Tri-Exponential Decay
- Was there a lag time in absorption? Yes No

Safety

- Was there any death or serious adverse events? Yes No NA
- What is the maximum tolerated dose?
60mg/day was the highest dose studied in the clinical trial.
- What are the safety profiles of the highest dose?

NWP06 after a single oral dose of 20 or 60 mg was well tolerated. Only a single occurrence of vomiting (mild) was considered possibly related to study medication. No treatment-emergent suicidal thoughts or behaviors were reported.

Comments

The pharmacokinetics of methylphenidate is dose-proportional in the dose range of 20-60 mg in children and adolescents with ADHD. Similar PK parameters were obtained for children and adolescents.

4. NDA FILING FORM

Office of Clinical Pharmacology and Biopharmaceutics			
New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	202100	Brand Name	TBD
OCP Division (I, II, III)	DCP I	Generic Name	Methylphenidate extended-release powder for oral suspension
Medical Division	Psychiatry Drug Products	Drug Class	Stimulant

OCP Reviewer	Huixia Zhang	Indication(s)	Attention Deficit Hyperactivity Disorder
OCP Team Leader	Raman Baweja	Dosage Form	Extended-release powder for oral suspension
		Dosing Regimen	QD
Date of Submission	07/29/2010	Route of Administration	Oral
Estimated Due Date of OCP Review	4/25/2011	Sponsor	NextWave Pharmaceuticals, Inc.
PDUFA Due Date	5/30/2011	Priority Classification	Standard 10 months
Division Due Date	5/2/2011		

Clin. Pharm. and Biopharm. Information

NextWave Pharmaceuticals. submitted an NDA for methylphenidate extended-release powder for oral suspension for the treatment of ADHD in patients aged 6 years and over.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies		3		
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-		1		
single dose:		1		
multiple dose:				
Patients-				
single dose:		1		
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:		1		
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:		1		
geriatrics:				
renal impairment:				

hepatic impairment:			
PD:			
Phase 2:			
Phase 3:		1	
PK/PD:			
Phase 1 and/or 2, proof of concept:			
Phase 3 clinical trial:		1	
Population Analyses -			
Data rich:			
Data sparse:			
II. Biopharmaceutics			
Absolute bioavailability:			
Relative bioavailability -			
solution as reference:			
alternate formulation as reference:		1	
Bioequivalence studies -			
traditional design; single / multi dose:		1	
replicate design; single / multi dose:			
Food-drug interaction studies:		1	
Dissolution:			
(IVIVC):			
Bio-wavier request based on BCS			
BCS class			
III. Other CPB Studies			
Genotype/phenotype studies:			
Chronopharmacokinetics			
Pediatric development plan			
Literature References			
Total Number of Studies		3	
Filability and QBR comments			
	"X" if yes	Comments	
Application filable?	x	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?	
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.	
QBR questions (key issues to be considered)	Is there any exposure-response relationship between plasma concentrations and SKAMP scores?		
Other comments or information not included above			
Primary reviewer Signature and Date	Huixia Zhang	08/17/2010	
Secondary reviewer Signature and Date	Raman Baweja	08/18/2010	

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

/s/

HUIXIA ZHANG
03/21/2011

YANING WANG
03/21/2011

JOGARAO V GOBBURU
03/21/2011