CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202100Orig1s000

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA 202-100

Drug:	Methylphenidate ER suspension (Quillivant ER)
Sponsor:	NextWave
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Submitted Material:	NDA-Class 2 Resubmission
Correspondence date:	30 Mar 2012
Date Received:	30 Mar 2012
Review Date:	30 Sep 2012

I. Executive Summary

With this submission, the sponsor has committed to resolve chemistry, manufacturing and control deficiencies that led to the 30 August 2011 Complete Response letter to the manufacture for the first round of reviews for this new drug application (NDA).

No new clinical data was provided with this submission. Consistent with this reviewer's assessment of the clinical data submitted with the original NDA application dated 30 Jul 2010, this reviewer recommends APPROVAL of this NDA re-submission from a clinical standpoint.

II. Review of Clinical Data

A complete review of the clinical data conducted by myself was completed on 7 Apr 2011 with a recommendation for approval. In brief, the sponsor conducted a seven week double-blind, placebo controlled 2X2 cross-over laboratory classroom study in 45 pediatric patients with flexible dosing for 4-6 weeks followed by one week of dosing (up to 60mg/day) at the optimized dose with cross-over to placebo. The primary efficacy analysis using the SKAMP-combined scores at the 4 hour time-point demonstrated statistically significant reductions with Quillivant treatment when compared to placebo treatment. Key secondary endpoint of duration of efficacy was established from timepoints 0.75hour to 12 hours.

III. Review from Other Disciplines

Pharmacology/Toxicology
There were no new issues related to pharmacology/toxicology and thus APPROVAL was recommended on 15 Aug 2012

Controlled Substance Staff
The following comments from Steven Sun, MD of CSS dated 16 Aug 2012 are recommended to be sent to sponsor:

1. Abuse and dependence sections in the product label should contain the recommended elements as described in the stimulant class label memorandum

2. A discussion in the quarterly periodic safety report should provide numbers and trends based upon MSSO's Standardized MedDRA Query (SMQ): "Drug Abuse, Dependence and Withdrawal" while the drug is marketed. As a new formulation of methylphenidate powder and higher-strength liquid as dispensed, abuse-related adverse events associated with this product should be reported as a 15-day important medical event
3. Sponsor should be actively engaged in the surveillance of the potential known and unknown methods for misuse of this new formulation.
4. Sponsor should highlight all precautions against misused, abuse, and diversion for any materials seen by patients and healthcare professionals.
5. Sponsor should employ safeguards against unintended distribution of the powdered methylphenidate by the pharmacist to the patient, e.g. sponsor should highlight instructions to the pharmacists that the drug should be reconstituted only by the pharmacist and not to permit distribution of the product in powder form to allow patient or caregiver self-reconstitution.

Office of Compliance
Based on the CMC deficiencies noted during the original NDA review, the Office of Compliance provided constant vigilance of the corporation cited (Tris Pharma manufacturing) for the CMC deficiencies. On 22 June 2012, the Office of Compliance issued an overall "acceptable" recommendation for the NDA.

Chemistry, Manufacturing and Controls
With the acceptable recommendation issued by the Office of Compliance, all CMC issues have been resolved. The Office of New Drug Quality and Assessment recommends APPROVAL on 16 Aug 2012.

Biopharmaceutics
With the original submission, issues were noted with drug product dissolution method and acceptance criteria. These issues were resolved and the division recommends APPROVAL for this re-submission.

IV. Labeling

Based on current Division activities related to revisions on-going for the stimulant-class of medications, a brief highlight of labeling changes are provided below:

Highlights
- Warning, Abuse and Dependence boxed warning has been re-worded
- Deletion of (b) (4) as a contraindication
- Deletion of (b) (4) from Warnings and precautions
- Deletion regarding (b) (4)
- Update of drug interactions

Full Prescribing Information

- Deletion of [redacted] (b) (4)
- Abuse and Dependence sections modified
- Patient Counseling section updated to provide information on abuse and dependence, serious cardiac risks, hypertension and tachycardia, psychiatric risks, suppression of growth, use in pregnancy and nursing, [redacted] (b) (4)

V. Conclusions and Recommendations

Based on the reviews from all the disciplines involved, this reviewer recommends APPROVAL of this re-submission

It is recommended that the CSS comments be transmitted to the sponsor. Furthermore labeling revisions consistent with the stimulant-class labeling review currently ongoing within the Division of Psychiatry Products be transmitted to the sponsor.

Mark Ritter, MD
20 Aug 2012

CC: HFD-130 (div File)
HFD-130 Laughren/Mathis/Levin/Ritter/RPM

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

/s/

MARK A RITTER
08/20/2012

ROBERT L LEVIN
09/05/2012
See clinical team leader memo to follow.

M E M O R A N D U M

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

DATE: 29 August 2011

FROM: Mitchell V. Mathis, M.D.
Deputy Director
Division of Psychiatry Products, HFD-130

TO: File NDA 202-100

SUBJECT: Complete Response (CR) Recommendation for Methylphenidate ER Powder (NWP06) for Suspension for the Treatment of Attention Deficit-Hyperactivity Disorder

Background and Summary

Methylphenidate products have been approved for many years to treat Attention Deficit Hyperactivity Disorder (ADHD). There are multiple formulations available, but there is no extended-release oral suspension approved. An extended-release formulation is clinically important because it provides an option for patients (mostly children and adolescents) to be dosed once daily, in the morning, from home—this prevents having to manage a controlled substance in the school setting. The oral suspension provides a practical option for children who cannot swallow pills.

The sponsor, Next Wave Pharmaceuticals, Inc., has submitted this NDA pursuant to Section 505(b)(2) of the FD&C Act. The Reference Listed Drug is Methylin (methylphenidate HCL) Oral Suspension, which is an immediate-release formulation with a twice daily dosing requirement. Because of our extensive history with and knowledge of methylphenidate products used to treat ADHD, the Division required a single clinical study to support this application.

The sponsor has demonstrated that NWP06 is safe and effective for the treatment of ADHD in pediatric patients. They have characterized the PK to our satisfaction and we have all the data we need to write a proper label. However, the Chemistry, Manufacturing, and Control (CMC) team has recommended against approval pending the resolution of critical deficiencies detected by the Office of Compliance during inspections of the manufacturing facilities. Until these deficiencies are addressed, we cannot recommend an approval action. There are no outstanding issues precluding approval other than these CMC issues, which are discussed more fully below.

Regulatory History

NWP06 was developed under IND 73-856. The Division had two pre-IND meetings with the sponsor (then Tris Pharma) to provide general advice on development. The IND was placed on Clinical Hold when it was presented to the Division in Nov 2008 secondary to CMC deficiencies. These deficiencies were corrected and the IND was allowed to proceed in Feb 2009. The sponsor conducted a single controlled safety and efficacy study in children and adolescents, as well as several PK studies to support approval. In March 2010 we met in an end-of-phase 3 meeting and

agreed that their study, NWP06-ADD-100 appeared to demonstrate efficacy in children and adolescents with ADHD. This study, along with the safety information gathered in several PK studies, supported filing of the NDA.

The review clock was extended by 3 months due to a major amendment submitted to address various CMC and inspectional deficiencies; one of these deficiencies remains and is precluding approval at this time (see below).

Advisory Committee
There were no issues with this application that required the input of an advisory committee.

Division of Scientific Investigation (DSI) Review
Dr. Orencia and DSI inspected and reviewed the results from both clinical sites that participated in Study NWP06-ADD-100. These were both US sites. Dr. Orencia and DSI concluded that there were no significant issues precluding approval.

Clinical Team Reviews
Drs. Mark Ritter and Robert Levin both agree that the sponsor has demonstrated the efficacy and safety of NWP06 in the treatment of ADHD and that this demonstration forms a sufficient clinical basis for approval. Dr. Levin points out and I agree that the outstanding CMC issues (see below) will preclude approval of this NDA at this time.

Study to Support Approval
NWP06-ADD-100 was an outpatient multicenter randomized, double blind, placebo-controlled, multiple-dose, two-treatment, crossover laboratory classroom study in 45 children ages 6-12 years with a diagnosis of ADHD. The study lasted 7 weeks and included a 4-6 week stabilization/dose-optimization phase followed by a 2-week placebo-controlled laboratory classroom crossover phase.

Appropriately diagnosed children were enrolled and dose-optimization began at 20 mg/day for all patients with titration by 10mg – 20 mg/day per week until an optimal dose was identified. The maximum permitted dose was 60 mg/day.

After optimization, patients were randomized to continue drug or placebo for a week and then these patients were assigned to the reverse treatment group in a typical crossover design. The primary efficacy endpoint was the prospectively designated mean change in SKAMP-Combined score (a generally accepted measure of ADHD symptoms used in many drug trials) at 4 hours post dose. The prospectively designated Key Secondary efficacy endpoint was onset and duration of effect as measured sequentially from 0.75 hours to 12 hours post-dose. Other secondary endpoints included the Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Improvement (CGI-I), and the ADHD Rating Scale (ADHD-RS).

Findings—Efficacy
At hour 4, the SKAMP-Combined mean score for the placebo group was 19.3 and for the drug group was 7.1. LS mean difference was -12.46 ($P<0.0001$). Dr. Ritter outlines in his review that the Key Secondary efficacy findings established that NWP06 demonstrated a statistically significant treatment effect from 0.75 hours through hour 12.

Findings—Safety

There were no new or unexpected findings with this formulation compared to what is expected and labeled for other methylphenidate formulations. Common adverse reactions were decreased appetite, affective lability, insomnia, irritability, headache, dizziness, and gastrointestinal symptoms (stomach pain, diarrhea).

The mean age in this study was 8.8 years with 73% male, 27% with the inattentive subtype of ADHD, 2% with hyperactive subtype, and 71% had the combined subtype which is consistent with what is seen in clinical practice. One third of the patients had a comorbid psychiatric diagnosis, most of these (18%) had comorbid Oppositional Defiant Disorder.

Statistical Findings

Dr. Yeh-Fong confirmed the sponsors findings of efficacy for the primary and key secondary endpoints.

Pharmacology/Toxicology

Dr. Elayan reviewed this submission. She did not identify any issues precluding approval from her perspective. The Pharmacology/Toxicology team has made labeling recommendations which were incorporated into our currently agreed upon draft labeling.

Clinical Pharmacology/Biopharmaceutics

Dr. Huixia Zhang reviewed this submission. She concluded that data from the sponsor's program were adequate to characterize the PK of NWP06 and to support approval.

There had been some concern about the CRO responsible for the PK samples and data collection, because the Office of Scientific Investigations, Office of Compliance (OSI-OC) had issued a deficiency letter on (b) (4) citing multiple areas of concern, including failure to use an adequate analytical method to measure drug concentration, falsified lab records, and other instances of misconduct. As a result, OSI-OC informed the Division that the analysis data from the CRO should be considered unreliable. Since the original problems with unreliable data were identified, the CRO has come into compliance; the sponsor had their samples (n=200) reanalyzed, and Drs. Zhang and Gobburu agree that the reassayed drug concentrations were within 3-17 percent of the original values, and so the original characterization of the PK of this product has been validated and the Office of Clinical Pharmacology (OCP) is satisfied that the data can be relied upon and that no further action is indicated in this regard.

Office of New Drug Quality Assessment (ONDQA)

Dr. Tele reviewed this submission. He has recommended an Complete Response (CR) action secondary to findings by the Office of Compliance (OC) during inspection of the drug substance and drug product manufacturing facilities. Other than the unacceptable inspectional findings by OC, this application was acceptable from a CMC point-of-view.

CMC Quality Issues Precluding Approval

On 5 May 2011, Dr. Tele informed the Division of the findings from the inspection of the drug substance and drug product manufacturing facilities. Dr. Tele received the inspection report findings from Dr. Stock, Consumer Safety Officer in Office of Compliance (OC). These findings included incorrect amounts of materials in released batches (problem with drug product variability in filling) and discolored particulate material in the drug product; this led to an ONDQA

recommendation of WITHOLD. The sponsor was able to resolve most of the CMC issues excepting the variability in filling problem which is the last remaining facilities issue. Unfortunately, addressing this issue will require new equipment to be installed and inspected, and this will not be accomplished by the goal date for this application.

Division of Medication Error Prevention and Analysis (DMEPA)

Dr. Maslov reviewed this submission. She focused her review on the container labels, carton and prescribing information, the dosing device (an oral syringe), and the container closure system. She concluded that there were no issues precluding approval, but made several suggestions to reduce medication errors in reconstituting and administering the product. These suggestions included using different sized bottles for 30-day supplies of the different doses (b) (4) , making it clear that different volumes of diluents are required for the different daily dose strengths of 30-day supply, providing instructions to the pharmacist in the label for reconstitution, and providing Patient Instructions for Use. These recommendations were provided to the sponsor and they have adopted most of them and provided a rationale for their approach acceptable to DMEPA for others. There are no outstanding issues from DMEPA precluding approval.

Labeling/Medication Guide

The product labeling was submitted by the sponsor and has been modeled on approved extended-release methylphenidate formulations. The Division and the review teams edited the label and reached agreement with the sponsor concerning its contents. There were several changes made to bring the label into compliance with current Division standards. One substantial change was made to remove (b) (4) which the sponsor's original draft label had included. (b) (4)

Because there was only one safety/efficacy study submitted as part of this application, we included adverse reactions (ARs) in Section 6 that are common to methylphenidate, as well as a table of ARs seen in the study with this product. With these changes, the agreed upon label adequately characterizes the safety of this product.

At DMEPA's request, we have included specific reconstitution directions in the label, so that the pharmacist can reference this information (the pharmacist will add diluent to prepare the final drug product). In addition, Patient Instructions will be provided with each prescription to give patients and caregivers the information they need to administer the proper dose.

CONCLUSIONS

The safety and efficacy of NWP06 have been established in pediatric patients with ADHD. The only issue precluding approval is the outstanding CMC deficiency discussed above. My recommendation to the Director is to issue a CR letter identifying the CMC/Inspection issue still outstanding and what the sponsor must do to address it. When this last outstanding issue is resolved, this application will meet the standard for approval.

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/s/

MITCHELL V Mathis
08/29/2011

NDA 202100 Cross-Discipline Team Leader Review Memo

Date	May 11, 2011
From	Robert L. Levin, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	202-100
Related IND	73-856
Sponsor	NextWave Pharmaceuticals, Inc.
Submission Date	July 30, 2010
Proprietary / Established name	Qullivant / Methylphenidate extended-release powder for suspension
Dosage forms / strength	Oral powder for suspension Strength (25 mg/5 mL) when reconstituted in water
Proposed Indication	Attention Deficit-Hyperactivity Disorder
Recommended Action:	Complete Response

1. Introduction to the Review

The sponsor has submitted NDA 202-100 to support the marketing authorization of Methylphenidate HCl Extended-Release Powder for Oral Suspension (NWP06) in the treatment of Attention Deficit-Hyperactivity Disorder. The NDA has been 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 (NDA 21-419). Of note, the Division agreed that the sponsor could support the application with a single controlled efficacy trial in pediatric subjects with ADHD, in addition to the required clinical pharmacology data.

The sponsor has demonstrated the efficacy and safety of NWP06 in ADHD and has provided adequate clinical pharmacology data. Thus, from a clinical perspective, I would recommend an Approval action. However, the CMC review team has recommended a Complete Response action, based on critical deficiencies observed by the Office of Compliance during inspection of the manufacturing facilities. The review teams from all other disciplines have recommended an Approval action.

2. Background/Regulatory History/Foreign Regulatory Actions

2.1 Pre-IND and IND Meetings and Submissions

The drug product (NWP06) was developed under IND 73-856. The Division held pre-IND meetings with the initial sponsor, Tris Pharma on 8 May, 2006 and 1 October 2007. The purpose of the meetings was to provide general advice on the CMC, nonclinical, and clinical development plans for NWP06 in the treatment of ADHD.

On 20 November, 2008, Tris Pharma submitted IND 73-856 to support the development of NWP06 for the treatment of ADHD. The initial IND was placed on Clinical Hold on December 22, 2008, because the CMC information was inadequate. On January 22, 2009 Tris Pharma submitted an IND amendment (Sequence 0001) that adequately addressed the CMC deficiencies. The Clinical Hold was removed on February 18, 2009.

On June 3, 2009, the sponsor submitted an IND Amendment (Sequence 0002) to respond to additional (non-hold) issues that were outlined in FDA's December 22, 2008 Clinical Hold letter. On July 16, 2009, an IND Amendment (Sequence 0003) was submitted to respond to the Division's request for the statistical analysis plan (SAP) for clinical efficacy study NWP06-ADD-100. The SAP was modified according to the Division's recommendations prior to unblinding of the clinical database and analysis of the data.

On December 1, 2009, a teleconference was held with medical and clinical pharmacology reviewers from FDA and representatives of Tris Pharma and NextWave Pharmaceuticals. The purpose of the teleconference was to discuss the design of the adult PK study and the PK sampling to be conducted during the efficacy study NWP06-ADD-100. Highlights from the meeting are as follows:

- Tris Pharma agreed to replace Protocol (b) (4) with S09-0238 to utilize Methylin® IR oral solution twice daily as the reference product in the adult relative bioavailability PK study.
- Tris Pharma agreed to conduct a single-dose pediatric PK study in 12 ADHD subjects ages 6 to 17 years.
- Tris Pharma agreed to analyze the trough plasma samples from efficacy study NWP06-ADD-100.
- FDA stated that a multiple-dose PK in pediatric subjects would not be required if accumulation was not observed in adults.
- Tris Pharma committed to submit the adult and pediatric PK protocols as an IND amendment for FDA review and comment. Tris Pharma submitted these protocols to the IND on December 18, 2009 (IND Amendment Sequence 0005) and requested FDA feedback as part of the End of Phase 3 Meeting.

2.2 End of Phase 3 Meeting

On March 22, 2010, representatives of Tris Pharma and NextWave Pharmaceuticals met with FDA representatives at an End-of-Phase 3 meeting. The purpose of the meeting was to review the results of Study NWP06-ADD-100 and to discuss the sponsor's plans for addressing outstanding concerns from the pre-IND meetings and IND submissions before submitting an NDA. The topics discussed included CMC, pharmacology/toxicology, clinical pharmacology, clinical, statistics, and labeling issues.

The clinical pharmacology discussion focused on the proposed designs of Study S09-0238 (a single-dose PK study in healthy adult subjects) and Study NWP06-PPK-101 (a single-dose PK study in pediatric subjects with ADHD). Additionally, we discussed the data to be obtained from the steady-state trough PK samples in Study NWP06-ADD-

100, in order to characterize the accumulation of the drug and the exposure-response relationship was. During the clinical discussion, FDA agreed that Study NWP06-ADD-100, on face, appeared to have demonstrated efficacy and would probably support the filing of an NDA. The statistical analysis plan from this study, modified based upon earlier feedback from FDA, was reviewed and deemed acceptable. Additionally, it was agreed that an Integrated Summary of Safety and an Integrated Summary of Efficacy would not be required for this submission; therefore, no pooling of safety data was performed. All available safety data would be presented individually by study.

2.2 Foreign Regulatory Actions.

There has been no foreign development, marketing, or regulatory action regarding this drug product.

3. Chemistry Manufacture and Controls (CMC) Review – Chhagan Tele, Ph.D.

Chhagan Tele, Ph.D. performed the CMC review for the Division of Psychiatry Products. He has submitted two reviews (filed on March 23 and May 6). Dr. Tele recommends a complete response action, based on the significant findings of the Office of Compliance during inspection of the drug substance and drug product manufacturing facility. These findings are described below. Dr. Tele found all of the other CMC data acceptable.

3.1 Drug Substance

Dr. Tele has concluded that the drug substance data provided are adequate. The sponsor referenced DMF (b) (4) for information on the methylphenidate HCl USP. (The LoA is included in the drug product DMF #23870). A Letter of Authorization to access this DMF was provided for cross-reference. Dr. Tele reviewed DMF (b) (4) and found it adequate. Methylphenidate HCl is manufactured and supplied to the sponsor by the Tris Pharma New Jersey 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.

The sponsor provided adequate batch analysis data on the drug substance used in manufacturing of the drug product in (b) (4). In addition, adequate validated analytical methods were provided in the DMF. Dr. Tele states that the methylphenidate HCl drug substance is stable. This conclusion was supported by the primary stability results conducted for up 36 months. Dr. Tele states that the 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 demonstrated that all stability parameters are well within their respective acceptance criteria after 36 months at 25° C/60% RH. The assay results remained within specification. There is no change in the appearance of the drug substance.

3.2 Drug Product

Dr. Tele has concluded that the drug product data provided are adequate. 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 in water, the product is a light beige to tan viscous suspension containing 25 mg/5mL (5 mg per mL) of methylphenidate hydrochloride. 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. Dr. Tele states that no novel excipients are utilized in the drug product. The product contains no overages. 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 the 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) The commercial batch size is about (b) (4) The Methylphenidate HCl ER Powder for Oral suspension will be manufactured at Tris Pharma, NJ site.

Dr. Tele states that the sponsor provided adequate information in DMF #23870 for the manufacturing, release, and stability of the registration batches of the drug product. The sponsor provided adequate information about the controls of critical steps in the manufacture of registration batches of the QUILLIVANT™ ER Powder for Oral suspension. The sponsor conducted in-process controls for (b) (4) he specifications for the methylphenidate powder included a description and information about (b) (4). For the reconstituted suspension, the information includes a description, identification (HPLC), pH, preservative (HPLC), microbial limits, assay (HPLC), impurity (HPLC), and dissolution (HPLC). The sponsor provided adequate validated analytical.

Dr. Tele stated that the stability data provided are adequate. Updated stability data (18 months long term) from the ongoing stability studies were provided. The holder submitted stability data from 3 batches of Methylphenidate (b) (4) ER Powder (b) (4) 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 25º C/60% RH and 30º C/65% RH and after 6 months of storage at 40º 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 (in amendment 0001 dated 18-AUG-2010) that (b) (4) the contract service provider, will warehouse and distribute the drug product. Methylphenidate (b) (4) ER oral Suspension was demonstrated to be stable at 25° C/60% RH for up to 4 months stored at 25º C/60% RH.

3.3 ONDQA Biopharmaceutics

Angelica Dorantes, Ph.D. performed the biopharmaceutics review. During the review cycle, Dr. Dorantes was concerned that the sponsor had not provided adequate dissolution data for the drug product. Through ONDQA, she provided recommendations to the sponsor. (Refer to the biopharmaceutics review dated 23-MAR-11 by Angelica Dorantes). On 27 April 2011, ONDQA held a teleconference with the DMF holder (Tris Pharma, Inc. to discuss specific recommendations for 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 KH2PO4, pH 4.5 at 37º C).

The 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. Tris Pharma agreed to use the appropriate methods requested by CMC. Table of post-approval stability protocol and commitment (revised dissolution acceptance criteria). The ONDQA and Biopharmaceutics and CMC teams have concluded that the sponsor has responded adequately to the concerns about dissolution methods and specifications.

3.3 Pre-approval Inspection of Facilities and Quality Issues Observed

On May 5, 2011, Dr. Tele informed the Division of the findings from the inspection of the drug substance and drug product manufacturing facilities. Dr. Tele was notified of the findings by Marisa Stock, Consumer Safety Officer in the Office of Compliance (CDER/OC/DMPQ). Dr. Stock outlined the significant inspectional findings in an email dated 05 May 2011 email below. The problems found at Tris Pharma, as reported mid-inspection by NWJ-DO include the following:

- Validation issues: validated times not followed, dissolution failures, 9 batches rejected for one product (unclear on which product), hold times changed in production from validated times
- No justification for sampling plan.
- 2 failed validation batches excluded from validation report (again, unclear on which product)

- Incorrect amounts of materials in released batches
- Black/brown particles observed in products; attributed to excipient but excipient still used in other batches of other products; investigation and corrective action inadequate
- Cleaning validation inadequate
- USP purified water testing only performed at (b) (4) points of use
- Only (b) (4) points of use tested for water system validation

Dr. Stock indicated that the recommendation from the Office of Compliance will be Withhold.

On 10 May 2011, Dr. Tele received the final recommendation from the Office of Compliance regarding the CMC manufacturing facilities inspection. The recommendation is 'Withhold.' Dr. Tele has forwarded the email containing the final District Recommendation of Withhold:

> From: Tele, Chhagan
> Sent: Tuesday, May 10, 2011 4:32 PM
> To: Levin, Robert
> Subject: FW: Withhold DO Recommendation - NWJ NDA 202100/000 CFN: FEI: 3004712471 Profile: POW
>
> -----Original Message-----
> From: ees_admin@fda.gov [mailto:ees_admin@fda.gov]
> Sent: Monday, May 09, 2011 4:01 PM
> To: Olagbaju, Bose*; Tele, Chhagan; Cruz, Concepcion; Smith, Derek *; Salganik, Maria*; Stock, Marisa; Biswas, Sumita; Bouie, Teshara; Oliver, Thomas F; Kyada, Yogesh*
> Subject: Withhold DO Recommendation - NWJ NDA 202100/000 CFN: FEI: 3004712471 Profile: POW
>
> This is a system generated email message to notify you that there is a District Recommendation of 'Withhold' for the above EER.
>
> For general questions about how to use EES in your work, send an email to EESQUESTIONS (EESQUESTIONS@cder.fda.gov). To contact the EES technical staff, send an email to CDER EES Help (EESHELP@fda.hhs.gov). Thank you.

Thus, Dr. Tele has concluded that, from a CMC perspective, ONDQA cannot recommend approval of NDA 202-100, because of the WITHOLD recommendation from the Office of Compliance for the drug substance and drug product sites.

3.4 Unresolved CMC Issues

As discussed above, the Office of Compliance has observed several critical problems at the drug product and drug substance manufacturing site including: 1) incorrect amounts of materials in released batches, and 2) black/brown particles in drug products. In addition, the inspectors found that the manufacturer's investigation of the findings and any corrective actions taken were inadequate.

4. Nonclinical Pharmacology/Toxicology

Ikram Elayan, Ph.D. performed the pharmacology/toxicology review. As of this writing, the formal review has not been filed. However, Dr. Elayan and her team leader, Dr. Fossom have verbally stated that there are no hold issues from their perspective, and there are no unresolved pharmacology/toxicology issues. I agree with the conclusions of the pharmacology/toxicology team.

The pharm/tox team has recommended several changes in labeling, which we have incorporated. These include changes in the Special Populations/Pediatrics, Mechanism of Action, and Nonclinical Toxicology sections.

5. Clinical Pharmacology/Biopharmaceutics

Huixia Zhang, Ph.D. performed the Clinical Pharmacology/Biopharmaceutics review. She has concluded that the data from the sponsor's clinical pharmacology studies are adequate to support approval of the application. I agree with her conclusions.

Tris Pharma conducted two pilot pharmacokinetic studies to support development of the formulation:

- **Study S07-0079** was a randomized, single-dose, 3-way crossover relative bioavailability study in 15 healthy adult subjects to evaluate a prototype methylphenidate extended-release powder for oral suspension ((b) (4) NWP06) formulation versus Methylin Oral Solution (18 mg) and Concerta (18 mg).

- **Study S07-0443** was a single-dose, randomized, 2-way crossover relative bioavailability study conducted in 12 healthy adult subjects to evaluate a prototype formulation of NWP06 (72 mg) versus Concerta (72 mg). These studies were sponsored by Tris Pharma, NextWave's development and manufacturing partner.

The sponsor conducted two pivotal clinical pharmacology studies to support the development and registration of this new formulation. These two studies were sponsored by NextWave Pharmaceuticals:

- **Study S09-0238** was a single-dose, randomized, open-label, 3-period, 3-treatment, crossover relative bioavailability study conducted in 28 healthy adult

- **Study NWP06-PPK-101** was a single-dose, open-label, pharmacokinetic study in 14 children and adolescent patients with ADHD to study the intended NWP06 (20 mg or 60 mg) commercial formulation.

Dr. Zhang concluded that the sponsor had adequately characterized the pharmacokinetics of NWP06, evaluating the PK profiles of NWP06 in children and adolescents with ADHD, as well as in healthy adult subjects. Dr. Zhang notes that the pharmacokinetic profile of NWP06 was similar among children, adolescent, and adult subjects. In addition, Dr. Zhang has concluded that the PK of NWP06 and Methylin Oral Solution have significant differences in their shapes of the concentration-time curves, because NWP06 has complex release characteristics. Furthermore, NWP06 was administered once daily, whereas Methylin was administered q 6 hours. Thus, conventional bioequivalence metrics are not appropriate for assessing NWP06, compared to other methylphenidate products. The test-reference ratio for AUC was 0.95 (90% CI: 0.92-0.99); for Cmax, the ratio was 0.69 (90% CI: 0.64 - 0.75).

Dr. Zhang concluded that the administration of food did not significantly affect the pharmacokinetics of NWP06. Food increased the NWP06 AUC by 20%, increased the Cmax by 28%, and shortened Tmax (4 hrs vs. 5 hrs-fasted). Thus, NWP06 can be administered with or without food. In addition, the PK of NWP06 was dose-proportional. Finally, there was no relationship between body weight and a subject's optimized dose at the end of the open-label, dose-optimization phase.

Single-dose Pharmacokinetics of NWP-o6

The single-dose pharmacokinetic parameters of *d*-MPH in children and adolescents with ADHD and in healthy adults following 60 mg oral administration of QUILLIVANT under fed conditions are summarized in the table below.

Table 1. (from Dr. Zhang's review)

Table 1. *d*-MPH PK Parameters (mean ±SD) after 60 mg oral dosing of QUILLIVANT under fed conditions[1]

PK Parameters	Children[2] (n=3)	Adolescent[2] (n=4)	Adult (n=27)
T_{max} (hr)[3]	4.05 (3.98-6.0)	2.0 (1.98-4.0)	4.0 (1.3-7.3)
$T_{1/2}$ (hr)	5.2±0.1	5.0±0.2	5.2±1.0
C_{max} (ng/mL)	34.4±14.0	21.1±5.9	17.0±7.7
AUC_{inf} (hr*ng/mL)	378±175	178±54.2	163.2±80.3
Cl (L/hr/kg)	4.27±0.70	5.06±1.42	5.66±2.15

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

Extended-release Characteristics of NWP-06

NWP-06 is a liquid-based, [redacted] (b) (4) extended-release formulation of methylphenidate that consists of 20% immediate-release and 80% extended-release components. The pharmacokinetic properties are illustrated in the table below.

Table 2 (from Dr. Zhang's review)

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.

Dr. Zhang notes that, because of its half life (~5.7 hr) and once daily dosing regimen, the pharmacokinetics of NWP06 are not expected to change after multiple-dose administration compared to single-dose administration (methylphenidate demonstrates time-independent linear pharmacokinetics). The first dose is almost completely eliminated at the end of a 24-hour period, and no significant accumulation of methylphenidate would be expected.

6. Clinical

Mark Ritter, M.D. performed the clinical review. Dr. Ritter has concluded that the sponsor has demonstrated the efficacy and safety of NWP06 in an adequate and well controlled study. He recommends an approval action. I agree with his conclusions and recommendation.

6.1 Efficacy

6.1.1 Agreement on a Single Efficacy Study

The Division and the sponsor had agreed that one adequate and well controlled study, (along with the required PK data), could support approval of the application, given the extensive, accumulated efficacy data with methylphenidate products. The sponsor could not obtain approval only by meeting standard BE metrics with a reference product, because the varying shapes of the concentration-time curves and the response-time curves for extended-release methylphenidate products demonstrate that such products are not necessarily therapeutically equivalent, even when they are bioequivalent.

6.1.2 Design of Study NWP06-ADD-100

Study NWP06-ADD-100 was a phase 3, outpatient, multicenter (2 U.S. sites), randomized, double blind, placebo-controlled, multiple-dose, two-treatment, two-way crossover laboratory classroom study of NWP06 in 45 children (aged 6-12 years) with a diagnosis ADHD. The total duration of the study was up to 7 weeks. There was a 4 to 6-week, open-label, dose-optimization phase, followed by a 2-week, placebo-controlled laboratory classroom, crossover phase.

Subject Selection Criteria

Subjects were male or females, aged 6-12 years, with a diagnosis of attention deficit-hyperactivity disorder (any subtype) as per DSM-IV criteria using the K-SADS diagnostic instrument. Subjects were required to have a screening or baseline ADHD-RS score $\geq$ the 90th percentile normalized for gender and age in at least one of the following categories: 1) Hyperactive-impulsive, 2) Inattentive, 3) Total score. In addition, they must have had a CGI-S score of $\geq$ 3. Subjects must also have required medication therapy or have achieved suboptimal efficacy with current treatment, or they must have had difficulty tolerating their current medication or were in need of a long-acting liquid stimulant formulation.

The following were exclusion criteria:

- comorbid psychiatric diagnoses other than simple phobias
- clinically significant cognitive impairment defined as an estimated IQ of 80 or less based on clinical judgment or WASI administration
- Evidence of a seizure disorder, cardiac disorder, serious cardiac conditions, glaucoma, Tourette's disorder or tics
- use of psychotropic agents other than stimulants or use of atomoxetine 30 days prior to screening
- significant laboratory deviations from normal at screening
- Positive pregnancy test or drug screen test

Open-label, Dose-optimization Phase

In the dose-optimization phase, subjects underwent individual open-label titration of NWP-06 in order to achieve efficacy. The starting methylphenidate dose for all subjects was 20 mg per once daily in the morning. The dose could be titrated weekly in 10 mg or 20 mg increments until an optimal dose was reached. The maximum permitted dose was 60 mg per day.

Placebo-controlled Crossover Phase

After 4 to 6 weeks of dose optimization, subjects were randomized to one of two double-blind treatment sequences. In Sequence A, subjects were treated with active methylphenidate for one week, with the optimal dose that was established in the open-label, optimization phase, followed by placebo for one week. In Sequence B, the order of

study drug treatments was reversed. At the end of each week, subjects had one day of ADHD assessments in a laboratory classroom. There was a practice laboratory classroom session before the randomized, controlled phase.

6.1.3 Primary and Key Secondary Efficacy Endpoints

The primary efficacy endpoint was the Swanson, Kotin, Agler, M-Flynn, and Pelham rating scale (SKAMP)-Combined score at 4 hours post-dose. The SKAMP is a widely accepted efficacy endpoint that has been used as a primary efficacy endpoint in numerous controlled ADHD trials. The Division and the Sponsor had prospectively agreed on this primary efficacy endpoint.

The key secondary efficacy endpoints were the onset and duration of clinical effect as determined by SKAMP-Combined scores at each post-dose time point. The Division agreed prospectively that the Sponsor could use these key secondary endpoints, provided that the appropriate statistical methods were used. In addition, it is clinically very meaningful to characterize the efficacy of a long-acting stimulant at various time points throughout a single day; an extended-release formulation administered once daily would only be considered useful if it provided consistent effectiveness throughout the majority of the day (i.e., for at least 8 hours).

Other secondary efficacy parameters included the Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Improvement (CGI-I), and the ADHD-RS. All of these endpoints were considered exploratory.

6.1.4 Efficacy Findings

6.1.4.1 Demographics Findings

In Study NWP-06-ADD-100, the mean age was 8.8 years. Approximately 20% of subjects were 6-7 years old, 57% were 8-10 years old, and 23% were 11-12 years old. Approximately 73% of subjects were male, and 27% were female. Approximately 80% of subjects were White, 9% were African American, 7% were Asian, and 5% were Other. Approximately 27% of subjects had the Inattentive subtype, 2% had the Hyperactive-Impulsive subtype, and 71% had the combined subtype. Approximately 30% of subjects had a comorbid psychiatric diagnosis (Oppositional Defiant Disorder: 18%, Elimination Disorder: 9%, Specific Phobia-5%)..

6.1.4.2 Primary Efficacy Findings

Dr. Ritter notes that the sponsor demonstrated efficacy of NWP-06 for the primary endpoint (the SKAMP-Combined score at 4 hours post-dose). The results are illustrated in Table 3 below. At Hour 4, the SKAMP-Combined score was 19.3 for the placebo group and 7.1 in the NWP-06 group; the symptom severity was greater in the placebo group. The LS mean difference was -12.46, which was statistically significant ($p < 0.0001$).

Table 3. Primary Analysis Results for the SKAMP-Combined (SKAMP-C) Score at 4 hours post-dose

STATISTIC	PLACEBO (N=44)	NWP06 (N=44)	DIFFERENCE
ITT population	N=39	N=39	
Mean SKAMP-C Score at 4 hours (SD)	19.3 (8.38)	7.1 (5.64)	-12.2 (7.19)
LS Mean (SE)	19.58 (1.15)	7.12 (1.14)	-12.46 (1.13)*
P-Value			*p <0.0001

6.1.4.3 Key Secondary Efficacy Findings

Dr. Ritter notes that the sponsor demonstrated the early onset of efficacy and maintenance of efficacy of NWP06 throughout the treatment day. NWP-06 had a statistically significant treatment effect compared to placebo, as measured by the SKAMP-Combined scores at every time point (0.75, 2, 4, 8, 10, and 12).

Table 4. Least Square Mean SKAMP Combined scores at all time points

TIME POST DOSE (HR)	LS MEAN SKAMP-C SCORE (SE) PLACEBO	LS MEAN SKAMP-C SCORE (SE) NWP06	DIFFERENCE (SE)	P-VALUE
0.75	16.16 (1.00)	9.84 (1.00)	-6.32 (1.09)	<0.0001
2	17.28 (1.01)	7.31 (1.01)	-9.98 (1.02)	<0.0001
4	19.58 (1.14)	7.12 (1.14)	-12.46 (1.13)	<0.0001
8	20.41 (9.33)	10.8 (8.23)	-9.33 (1.28)	<0.0001
10	18.29 (1.37)	14.50 (1.37)	-3.79 (1.11)	0.0016
12	20.26 (1.58)	15.49 (1.58)	-4.77 (1.40)	0.0016

6.2 Safety

6.2.1 General Safety Considerations

The sponsor conducted adequate safety assessments and submitted adequate safety data for assessing the safety profile of treatment with. The types and frequency of safety assessments were adequate. The safety assessments included the following: adverse events monitoring, vital signs, ECG (at baseline only), pregnancy testing, and clinical laboratory testing (only at baseline).

There was adequate exposure to NWP06 in the safety database to support the application. In the four NWP06 PK studies, there were 70 subjects exposed to single doses of NWP06 (14 pediatric and 56 adult subjects). In the pediatric subgroup, 7 were treated with 20 mg, and 7 were treated with 60 mg. In the clinical efficacy study (NWP06-ADD-100), there were 44 pediatric subjects treated with multiple-doses of NWP06 ranging from 20 mg per day to 60 mg per day.

In study NWP06-ADD-100, the mean duration of exposure in the open-label phase was 29 days. The mean durations for the 20, 30, 40, 50, and 60 mg doses were 9, 14, 10, 10, and 10 days, respectively. The mean duration of exposure in the controlled phase was 7 days. For the uncontrolled and controlled phases combined, the mean daily dose of NWP06 was 32.8 mg.

6.2.2 Major Safety Findings

There were no new or unexpected findings compared to what one would expect with methylphenidate treatment. There were no deaths or serious adverse events in the study. Two subjects were discontinued from the controlled phase of the study due to adverse events. A 6 year old male subject developed aggressive behavior and tantrums, and an 8 year old male subject developed affect lability. These subjects had been treated with NWP06 at the time of the events. Both of these adverse reactions are known to occur with methylphenidate treatment, and both of them are prominently labeled.

Common adverse events reported during the open-label, dose-optimization phase of Study NWP06-ADD-100 included: appetite decreased, upper abdominal pain, vomiting, diarrhea, affect lability, insomnia, irritability, logorrhea, aggression, headache, dizziness, fatigue, and flushing. In the controlled phase, the most common (reported for $\geq$2% of NWP06 subjects at a rate greater than placebo) adverse reactions were affect lability, excoriation, insomnia, decreased appetite, vomiting, motion sickness, and tic. These adverse reactions are consistent with the adverse reactions commonly reported with methylphenidate treatment in other studies.

7. Statistical Findings

Yeh-Fong Chen, Ph.D. performed the statistical review. Essentially, Dr. Chen confirmed the sponsor's primary efficacy and key efficacy findings, and she concluded that the study demonstrated the efficacy of NWP-06 in the treatment of ADHD in children (ages 6-12 years).

7.1 Analysis for the Primary Efficacy Endpoint

The primary efficacy endpoint was the SKAMP-Combined score at 4 hours post-dose. The primary efficacy analysis was conducted on the ITT population. Treatment comparisons for the SKAMP-Combined score at 4 hours post-dose on the classroom test days were assessed using an analysis of variance (ANOVA) model. The ANOVA model included: sequence (Placebo/NWP06 or NWP06/Placebo), period (First test laboratory classroom day (Visit 7) or Second test laboratory classroom day (Visit 8), and treatment (NWP06 or Placebo) as fixed effects.

The sponsor's analysis results for the SKAMP-Combined Scale score at 4 hours post-dose are summarized in the table below:

Table 3. Sponsor's Analysis Results for SKAMP-Combined Scale at 4 Hours Post-Dose.

Time-point	Statistics	Treatment		NWP06 - Placebo (N=44)
		Placebo (N=44)	NWP06 (N=44)	
SKAMP Combined Scale				
4 Hours Post-Dose	N	39	39	39
	Mean (SD)	19.2 (8.38)	7.1 (5.64)	-12.2 (7.19)
	LS Mean (SE)	19.58 (1.14)	7.12 (1.14)	-12.46 (1.13)
	95% C.I.	(17.31, 21.86)	(4.85, 9.39)	(-14.75, -10.17)
	P-value			<0.0001
	Effect Size			2.519

Source: Sponsor's Table 11.3 of CSR.

Dr. Chen notes that, based on the primary analysis, the sponsor concluded that at 4 hours post-dose, subjects treated with NWP06 had a statistically significantly lower SKAMP-Combined score (7.12) compared with subjects treated with placebo (19.58). The treatment difference LS mean was -12.46; $p < 0.0001$).

7.2 Analysis for the Key Secondary Endpoints

The key secondary efficacy parameters were the onset and duration of clinical effect as determined by SKAMP-Combined scores at each post-dose time point by using a closed testing procedure. If the primary efficacy endpoint were statistically significant, the key secondary variables of onset and duration of efficacy would be tested using a closed testing procedure, based on the same ANOVA model as for the primary efficacy variable. The closed testing procedure would begin at the 0.75 hours post-dose time point and proceed to the 2, 4, 8, 10 and 12 hours post-dose time points.

The analysis results demonstrated statistically significant differences between NWP-06 and placebo at all time points assessed (0.75, 2, 4, 8, 10, and 12 hours post-dose). Thus, the onset of efficacy was determined to be 0.75 hours post-dose. Efficacy was maintained throughout the 11.25-hour post-dose assessment period. (Refer to Table 4 above).

7.3 Treatment-by-Period Effect (Sequence Effect)

The statistics review team observed that the efficacy data in Study NWP06-ADD-100 were very different between periods 1 and 2 of the study. There was a statistically significant treatment-by-period interaction (sequence effect). As a result, it would not be appropriate to pool the efficacy data for the primary or key secondary analyses. The reviewers recommended using data only from Period 1 (Visit 7) for the analysis. The reason for this sequence effect is currently unclear; however, similar sequence effects have been observed in other stimulant crossover, laboratory classroom studies.

Based on data from Period 1 (Visit 7), Dr. Chen found that the differences between the drug and placebo groups were statistically significant at all time points. To evaluate the robustness of the efficacy findings, Dr. Chen also performed the permutation test. The

permutation test results demonstrated that the differences between drug and placebo were statistically significant at all time points based on the first period data.

8. Division of Medication Error Prevention and Analysis

Yelena Maslov, Pharm.D. performed the Division of Medication Error Prevention and Analysis review. The review focused on evaluation of the container labels, carton and prescribing information labeling, the dosing device (oral syringe), and the container closure system (glass bottles, closure caps, oral syringe and syringe adapter). Dr. Maslov concluded that there are no DMEPA issues that would prevent approval of the NDA. However, DMEPA has made a number of requests and recommendations for the sponsor, in order to minimize the risk of medication errors with the product.

8.1 Labels, Labeling, and Packaging Risk Assessment

Dr. Maslov found that the container caps and syringe adapter were suitable for dosing and administration of the product. The container closure is child resistant. The syringe adapter fits well on all bottle sizes. The glass bottle containers are appropriate in color and size. The bottles have transparent, amber color which protects the drug product powder from light, and it allows practitioners and consumers to see the product in powder or liquid form through the glass. However, Dr. Maslov identified several concerns about the bottle containers:

• The bottles use (b) (4) which may contribute to wrong strength selection errors.

• There are six different volumes of diluent needed for the different strengths of the product, which may result in the wrong amount of diluent used for reconstitution

The evaluation of the proposed container labels, carton, and prescribing information labeling identified several areas of concern, which could increase the risk of medication errors:

• The prescribing information labeling lacks adequate information regarding reconstitution of Methylphenidate HCl Extended-release Powder for Oral Suspension (for pharmacists).

• The prescribing information labeling does not contain information in the patients' instructions for use regarding measuring the dose using the oral syringe.

• The labeling does not have Patient Instructions for Use that patients will use to administer Methylphenidate HCl Extended-release Powder for Oral Suspension

• Some of the important information on the container labels and carton labeling such as the product's net quantity once reconstituted, reconstitution statement, and storage information are not prominent, which may lead to the information being overlooked.

Dr. Maslov's evaluation of the dosing device (oral syringe) and its design found that the device is adequate for the use with the product. The syringe contains clearly expressed 1 milliliter graduation marks, which in this case is suitable for a dosing device to help with accurate dosing of this product. Additionally, the volume of the oral syringe (12 mL) is appropriate, because the highest dose of 60 mg corresponds to the volume of 12 mL. However, Dr. Maslov identified the following area of needed improvement in order to minimize the potential for medication errors:

• The oral syringe contains the manufacturer's name instead of the product's name and strength.

8.2 Conclusions and Recommendations

Dr. Maslov notes that the proposed dosage form of powder for suspension of Methylphenidate HCl Extended-release may lead to a number of medication errors related to the reconstitution and administration of the product. Therefore, in order to minimize the potential for these errors, the labels and labeling should contain prominent and clear information regarding reconstitution instructions, the name and the amount of diluent required, the strength of the product when reconstituted expressed in milligrams per milliliter, and the total drug content expressed in milligrams and milliliters. Additionally, the sponsor should include clear patient's instructions for use explaining how to correctly administer the product. The DMEPA evaluation of the proposed container labels, carton, prescribing information, and oral syringe labeling highlighted areas of needed improvements in order to minimize the potential for medication errors. **Section 5.1 Comments to the Division** of the DMEPA review contains specific recommendations regarding prescribing information labeling. **Section 5.2 Comments to the Applicant** of the DMEPA review contains specific recommendations for the container labels, the carton labeling, and dosing device. DMEPA requested that the recommendations in Section 5.2 be communicated to the Applicant prior to approval.

On April 18, 2011, the Division sent a letter to the sponsor containing the requests and recommendations outlined by the DMEPA team.

9. Advisory Committee Meeting

We did not convene an advisory committee meeting, because the review issues were clear. There were no controversial issues.

10. Financial Disclosure

There are no unresolved issues regarding financial disclosures.

11. Labeling

We have completed a labeling review and sent our version of labeling to the sponsor on May 10, 2011.

12. DSI Inspections

Anthony Orencia, M.D. performed the DSI review. The Division selected for DSI inspection the two clinical sites that participated in Study NWP-06-ADD-100.

Site 1. Ann Childress, M.D., Center for Psychiatry and Behavioral Medicine, Inc. 7351 Prairie Falcon Road, Suite 150, Las Vegas, NV 89128

Site 2. Sharon B. Wigal, M.D., Child Development Center, 19722 MacArthur Boulevard University of California Irvine, CA 92612-2418

For both sites, the inspector evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected. Dr. Orencia concluded that, at both sites, the study appeared to have been conducted adequately. There were no significant issues identified during the inspection. The data in support of clinical efficacy and safety from the 2 clinical sites appear acceptable for this specific indication.

13 Conclusions and Recommendations

The sponsor has demonstrated the efficacy and safety of NWP06 in the treatment of ADHD in an adequate and well controlled study. It would be sufficient to base approval of NWP06 on the results of a single pivotal trial, because there are extensive, accumulated efficacy and safety data for methylphenidate treatment in ADHD.

I agree with the conclusions and recommendations of the reviewers from all disciplines. Except for the CMC inspectional findings, there are no unresolved issues that would prevent a recommendation for approval. However, the findings of the Office of Compliance regarding inspection of the manufacturing facilities indicate that there are critical, unresolved problems that would preclude a recommendation for an approval action. Therefore, I recommend a Complete Response action. The sponsor must resolve the CMC issues identified by the Office of Compliance.

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/s/

ROBERT L LEVIN
05/11/2011

CLINICAL REVIEW

Application Type	NDA
Application Number	202-100
Priority or Standard	Standard
Submission Date	30 July 2010
Received Date	30 July 2010
PDUFA Goal Date	30 May 2011
Division/Office	ODE1/DPP
Reviewer Name	Mark Ritter, M.D. RPh.
Review Completion Date	1 April 2011
Established Name	Methylphenidate ER Powder
Trade Name	(Currently undetermined)
Therapeutic Class	Stimulant
Applicant	Next Wave Pharmaceuticals
Formulation	Oral Powder for Suspension
Dosing Regimen	Once Daily
Indication	Attention Deficit Hyperactivity Disorder
Intended Population	Children and Adolescents

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

This reviewer concludes that the formulation that has been submitted with this NDA is acceptable for approval, provided that risk management plans are adopted and prospectively analyzed (i.e. reconstitution error rates are calculated with every post-marketing surveillance utilization report, with a minimum of at least one annual report of reconstitution error rates) to reduce the risk of reconstitution errors with this formulation.

In addition, it is recommended that the external labeling of this product clearly mark both the exact amount of water with which it is to be reconstituted, as well as an appropriate mark on the product's label on the bottle which provides a visual check for pharmacy staff and patients to ensure that the appropriate amount of water was used to reconstitute the product, thus providing appropriate final volume and concentration strength of product. The label should also note that reconstitution should only be performed by a pharmacist. The patient MedGuide should also clearly instruct patients to not use product if final volume does not fall within the range of the mark on the bottle.

1.2 Risk Benefit Assessment

NWP06 is an extended release oral stimulant preparation in liquid form that was developed for patients who have difficulty tolerating or cannot tolerate ingestion of an extended release table or capsule. The benefits of stimulant administration have been well characterized for nearly 50 years, while adverse events are generally well tolerated. Current class-product labeling for stimulant products clearly elucidate specific long term administration adverse events of growth suppression and potential cardiovascular risks in patients with underlying cardiovascular risks with use.

Should appropriate risk management strategies to reduce reconstitution errors be adopted, this reviewer feels that the benefit of having an easy to administer oral liquid extended-release stimulant product outweighs the safety risks associated with stimulant use and this product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Division of Medication Error Prevention and Analysis (DMEPA) were consulted on the concerns over reconstitution errors with this product. At this time the consult has not been completed however recommendations from this consult are recommended to be adopted as part of the risk-management plans for this product.

1.4 Recommendations for Postmarket Requirements and Commitments

(b) (4)

(b) (4)

2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Methylphenidate is pharmacologically classified as a stimulant. Although the exact mechanism of *in vivo* pharmacological action is not known in humans, dexmethylphenidate and methylphenidate are thought to block the reuptake of released monoamines into the presynaptic neuron, thus increasing the synaptic concentration of these monoamines in the synapse. It has been postulated that increased monoamine activity, particularly in the frontal cortex of the brain, enhances attention, focus and alertness similar to what has been observed in the 'flight or fight' response in mammalian species.

2.2 Tables of Currently Available Treatments for Proposed Indications

Methylphenidate was approved in 1956 for the indication of ADHD. Since the time of approval, other stimulant and non-stimulant compounds have been used to treat ADHD as shown below:

Table 1: Available Products Used to Treat ADHD

Product	Maximum daily dose
Stimulants	
Methylphenidate	60mg
Dexmethylphenidate	30mg
Amphetamine salts	60mg

Lisdexamphetamine	70mg
Non Stimulant	
Atomoxetine	100mg
Guanfacine	4mg

2.3 Availability of Proposed Active Ingredients in the United States

Methylphenidate is available in a wide variety of oral and (recently approved) dermal patch formulations with different dosing strengths. The various formulations are designed to impart different pharmacokinetic properties to extend the release of methylphenidate and deliver ADHD symptom relief through various times throughout the day.

There is currently one oral methylphenidate solution, Methylin 5mg/ml solution that is currently available in the United States. Although this is the reference drug for this 505 (b) (2) application, Methylin is an immediate release preparation of methylphenidate. With this submission, the sponsor is seeking approval for the first extended release oral suspension of methylphenidate.
Of note, the sponsor has formulated the (b) (4)

2.4 Important Safety Issues With Consideration to Related Drugs

The Agency has recently added cardiovascular warning language to the approved labeling for all stimulant medication products, including Focalin XR, and atomoxetine regarding patients with pre-existing cardiac abnormalities. The basis for these additional warnings stemmed from an analysis of post-marketing safety reports of sudden deaths that were seen in patients with pre-existing cardiac defects taking stimulant medications when compared to the background incidence of sudden death.

In addition, the American Heart Association[1] has recently made a class 2A recommendation to obtain ECG recordings prior to initiation to stimulant therapy. At this time, the Agency has not indicated whether additional regulatory action is or is not indicted with the stimulant class of medications.

[1] Vetter VL et al "Cardiovascular Monitoring of children and adolescents with heart disease receiving stimulant drugs: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing" *Circulation* 2008 May 6;117(18):2407-23

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On 8 May 2006, the sponsor and the Agency met via teleconference as a pre-IND meeting to discuss various questions for development of IND 73,856 Methylphenidate (b) (4) Extended release Oral Suspension (b) (4) The sponsor had planned to demonstrate bioequivalence between the proposed product and Methylin solution. The sponsor agreed to submit at least 6 months of stability data with a 505 (b) (2) application submission.

On 1 October 2007, the sponsor and the Agency met via teleconference for another pre-IND meeting to discuss a change in the reference product from Methylin to Concerta, (b) (4) The sponsor also proposed to conduct a single bioequivalence study (b) (4) The Agency recommended a fixed-dose study design for the clinical efficacy study required for approval of an NDA.

On 20 November 2008, the sponsor submitted IND 73,856 for Methylphenidate (b) (4) ER for Oral Suspension (25mg/5ml). (b) (4) .The reference product was extended-release Metadate CD. During the review of the IND, additional data was requested by the CMC reviewer. Since the sponsor did not have the requisite stability data by the end of 30 days, the IND was placed on clinical hold. The sponsor submitted the requisite stability data, and the IND was allowed to proceed on 18 Feb 2009. The phase 3 clinical efficacy study (NWP06-ADD-100) began in April 2009 and was completed on 1 Aug 2009.

Two IND amendments were submitted:

- On 3 June 2009, an amendment was submitted to address non-clinical hold issues from the IND initial review.
- On 16 July 2009, an amendment to the statistical analysis plan was submitted. This included the modifications requested by the Agency.

An end of Phase 3 meeting was held on 22 March 2010 to discuss filing of a 505 b (2) NDA application and address any outstanding issues. The sponsor planned to submit two PK studies, one using Methylin as a reference product. The sponsor also planned to submit the clinical efficacy study (NWP06-ADD-001) and a PK study (S07-0443) to demonstrate the BE of a 72mg single dose of product to single dose Concerta 72mg. The sponsor planned to provide stability data for the powder product including information as to whether (b) (4) Issues were also raised by the Agency on the packaging system and syringe markings. We would likely consult CDRH if a commercial syringe was to be developed and submitted with the NDA. In addition, we discussed various issues regarding labeling of the final product. The Division conveyed the following conclusions and recommendations:

- The indications section would read “for the treatment of ADHD,” along with then a statement that the claim was based on a study in 6-12 year olds.
- Under the dosage and administration section, the required language must reflect only the actual dosing and administration used in the pivotal trial. The duration of the clinical effect would be described only in the clinical studies section.
- A dosing recommendation of (b) (4)-20mg would be considered if a minimum effective dose was not established in the clinical efficacy study. The sponsor must provide a detailed rationale in the NDA submission.
- Safety labeling must include all relevant safety data for other methylphenidate products, as well as safety data regarding (b) (4) and other relevant excipient components

The sponsor also planned to request a partial waiver for studies in children less than 6 and for children 13-17.

On 21 July 2010, the sponsor submitted NDA 202-100 for Methylphenidate (b) (4) ER powder for oral suspension.

2.6 Other Relevant Background Information

No other pertinent background information regarding this submission is available for this product.

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

This reviewer finds no issues with the submission quality and integrity of the data contained within the submission.

3.2 Compliance with Good Clinical Practices

The studies that have been conducted under this submission appear to have been conducted with adherence with good clinical Practices.

3.3 Financial Disclosures

According to the FDA Form 3454 submitted with this NDA, none of the clinical investigators who participated in the clinical program had any financial arrangements that interfered with the outcome of the study; had a financial interest in the sponsor; or received other significant payments IAW 21 CFR 54.2 (a), (b) and (f) respectively.

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls (CMC)

Please refer to the Chemistry Review for further details

The CMC review of this application was perfomed by Chhagan Tele, PhD and completed on 25 March 2011. The recommendations made by Dr Tele in this review are that the application cannot be approved at this time pending results for three CMC issues (from Dr Tele's review) that are as yet unresolved:

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.

The division met on 28 March 2011 to review the recommendations based in the CMC review, as well as a review of a teleconference between CMC and the sponsor on 21 March 2011. During the meeting it was revealed that the CMC issues raised were to be addressed by the sponsor by the 10 April 2011 and therefore should be fully satisfied by the PDUFA deadline. If, however, the sponsor does not fulfill the CMC requirements by the PDUFA deadline, CMC has recommended that these issues should be addressed as a phase IV post-marketing commitment at the time of action for this application.

Upon review of the initial IND application from 20 November 2008, the sponsor noted that during formulation development, the originally proposed [redacted] (b) (4)

Due to concerns that powder reconstitution errors will likely occur and lead to variability of product concentration (either lower or higher concentrations than 25mg/5ml, depending on amount of water incorrectly added to powder) at time of dispensing for this powder preparation, this reviewer requested [redacted] (b) (4)

(b) (4) On 14 February 2011, the sponsor submitted the following data:

(b) (4)

(b) (4)

(b) (4)

This reviewer concludes that the formulation that has been submitted with this NDA is acceptable, provided that risk management plans are adopted and prospectively analyzed (i.e. reconstitution error rates are calculated with every post-marketing surveillance utilization report, with a minimum of at least one annual report of reconstitution error rates) to reduce the risk of reconstitution errors with this formulation. (b) (4)

4.2 Clinical Microbiology

Not applicable for this submission.

4.3 Preclinical Pharmacology/Toxicology

The sponsor has referenced Methylin oral solution as the reference product for this 505 (b) (2) submission. Please refer to the Methylin labeling and reviews on file for NDA 21-419 Methylin.

There were no issues of concern noted by the assigned pharmacology/toxicology reviewer Ikram Elayan, PhD.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Although the exact mechanism of *in vivo* pharmacological action is not known in humans, dexmethylphenidate and methylphenidate are thought to block the

reuptake of released monoamines into the presynaptic neuron, thus increasing the synaptic concentration of these monoamines. It has been postulated that increased monoamine activity, particularly in the frontal cortex of the brain, enhances attention, focus and alertness, similar to what has been observed in the 'flight or fight' response in mammalian species.

4.4.2 Pharmacodynamics

Please refer to the pharmacodynamic section of the Methylin solution label and reviews completed by the Office of Clinical Pharmacology and toxicology/pharmacology for a review of the pharmacodynamics.

The sponsor intends to reference the pharmacodynamics section of the NWP06 label using labeling from the reference listed drug Methylin solution.

4.4.3 Pharmacokinetics

Please refer to the review completed by the Office of Clinical Pharmacology (OCP) for an extensive review of the pharmacokinetics.

The division of psychiatry products attended a meeting with the primary reviewers in OCP for this application. These reviewers were Huizia Zhang, PhD, Hui Zheng, PhD., Yaning Wang, PhD. and team leader Jogarao Gobburu, PhD. A brief review of the findings from the OCP review revealed similar PK parameters for children and adolescents with ADHD. Due to a different shape of the concentration-time curves between the reference listed product Methylin Oral solution immediate release and NWP06, conventional bioequivalence metrics were not appropriate for this product. Also, NWP06 can be taken with or without food.

To summarize the pertinent findings from their reviewer, OCP has concluded the following:

OCP Recommendation:

Decision	Acceptable to OCP?	Comment
Overall	Yes	Pending labeling
Evidence of effectiveness	Yes	One positive registration trial in 6-12 years; efficacy bridged from Concerta for >13 years.
Duration of clinical response	Yes	Statistically significant difference observed between treatment and placebo from 45 min to 12 hrs post-dose
Proposed dose for patients 6-17 years	No	(b) (4)

		d [redacted] (b) (4), we recommend 20 mg starting dose.
Proposed dose for adult patients	Yes	[redacted] (b) (4)
Labeling	No	Pending satisfactory agreement with sponsor

This reviewer concurs with the recommendations proposed by OCP.

5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials

Phase 3 Studies	
NWP06-ADD-001 Dose-optimization/fixed dose	A seven week, outpatient, multicenter, double-blind, parallel-group, placebo controlled, randomized (1:1 drug: placebo), two-way, two-period (1 week each) cross-over laboratory classroom study of 45 pediatric patients (ages 6-12 years of age) with a current clinical diagnosis of attention deficit hyperactivity disorder (according to DSM-IV criteria using the K-SADS instrument) dose optimized (up to 60mg/day) according to clinical symptomatology for the first four to six weeks with double-blind dosing for 1 week with cross-over for the second week.
Phase 1 Studies	
S09-0238 Single dose Food Effect	An outpatient, single site, open-labeled, single dose, three period (1 day), three treatment (60mg dose of NWP06 fed vs. 60mg dose NWP06 fasting vs. Methylin 30mg and 6 hours later under fasting conditions) food effect study of 30 adults aged 18 years or older.
NWP06-PPK-101	An inpatient (12 hours) , single site, open-label, single dose, two treatment (NWP06 20mg orally, NWP06 60mg orally) pharmacokinetic study of 14 children aged 6-12 and 13-17 years old (1:1) receiving either a single dose of 20mg NWP06 (4 aged 6 to 12; 3 aged 13 to 17) or 60mg NWP06 (3 aged 6-12; 4 aged 13-17)

Only safety data collected from the single dose pharmacokinetic studies will be reviewed as no clinical efficacy data was collected in either study.

5.2 Review Strategy

After ensuring all appropriate regulatory information and documentation was submitted IAW 21 CFR 314 and 505 (b) (2), the review of this NDA focused solely on the single clinical efficacy study for safety and efficacy of this product for the clinical indication being sought.

5.3 Discussion of Individual Studies/Clinical Trials

Please refer to the table above.

6 REVIEW OF EFFICACY

Efficacy Summary

Efficacy was established in a single phase 3, randomized, double-blind, placebo controlled, multicenter, two-way crossover laboratory classroom study in 45 children aged 6-12 years of age who had a diagnosis of ADHD. Subjects entered an open-label, dose-optimization phase during which their dose of methlyphenidate was optimized (up to 60mg/day), prior to initiation of two weeks of double-blind, placebo-controlled treatment. The primary efficacy endpoint was the SKAMP-combined score at 4 hours post-dose between Methylphenidate treatment vs. placebo. The key secondary efficacy endpoint was the onset and duration of clinical effect as determined by scores on the SKAMP-combined scores at all time points, compared to placebo treatment. The changes from pre-dose SKAMP-combined scores were obtained, but they were secondary analyses. The primary efficacy analysis was changed (b) (4) to scores at 4 hours post-dose based on FDA comments on the statistical analysis plan (SAP) on 29 Sep 2009.

The primary efficacy analysis clearly demonstrated statistically significant reduction of SKAMP-Combined scores (i.e. improved symptomatology) at hour 4 in Methylphenidate-treated subjects as compared to placebo treatment

Table 2: Change in SKAMP Combined (SKAMP-C)score at 4 hours post dose (ITT population)

	PLACEBO N=39	METHYLPHENIDATE N=39	TREATMENT DIFFERENCE	P-VALUE
Mean SKAMP-Combined score at hour 4 (SD)	19.3 (8.38)	7.1 (5.64)	-12.2 (7.19)	
LS Mean (SE)	19.58 (1.14)	7.12 (1.14)	-12.46 (1.13)	<0.0001

6.1 Studies Pertinent to Claim 1

6.1.1 Rationale for Selection of Studies for Review

As this application is a 505 (b) (2) application, a single clinical efficacy study was required for approval for this NDA. Thus only one clinical efficacy study was conducted to support this NDA.

6.1.2 Study Summaries

Study 1

Methods/Study Design/Analysis Plan

Study NWP06-ADD-100 was conducted in 2009-2010 to establish efficacy of NWP06 in the treatment of ADHD using a laboratory classroom setting.

The study design consisted of two distinct phases:

- Phase 1: a pre-dose screening (up to 4 weeks) to determine whether inclusion/exclusion criteria were met and to washout any previous ADHD medication use.
- Phase 2: a four-week, open-label dose optimization (flexible dose) design followed by a two week randomized, two period, double-blind, placebo controlled cross-over treatment of dose-optimized study medication or placebo (one week each). Laboratory classroom testing was performed at the end of week 4(end of open-label phase), week 5, and week 6.

INCLUSION CRITERIA
Forty (40) patients who were male or female aged 6-12 years of age with a DSM-IV diagnosis of ADHD (any type) as determined by a psychiatrist, psychologist, developmental pediatrician or pediatrician via review of K-SADS administration.

Patients were required to have an ADHD-RS score at screening OR baseline equal to or greater than the 90th percentile normalized for gender and age in at least one of the following categories:

- Hyperactive-impulsive
- Inattentive
- Total score

AND a CGI-S score of 3 or greater.

Patients must also require medication therapy or have received suboptimal efficacy, or have problems with safety and/or tolerability of current medication regimen or in need of a long acting liquid formulation.

EXCLUSION CRITERIA

The following patients were not eligible for participation in the trial:

- DSM-IV diagnoses other than ADHD or simple phobias
- Clinically significant cognitive impairment defined as an estimated IQ of 80 or less based on clinical judgment or WASI administration
- Evidence of a seizure disorder, cardiac disorder, serious cardiac conditions, glaucoma, Tourette's disorder or tics
- Any psychotropic agents other than stimulants if inclusion criteria for stimulants is met or use of atomoxetine 30 days prior to screening
- Significant laboratory deviations from normal at screening
- Positive drug test or pregnancy

DOSING

During phase 1, all subjects received an initial morning dose of 20mg of NWP06 suspension (reconstituted as 25mg/5ml). Doses were then titrated on a weekly basis by 10-20 mg based on clinical response and tolerability to a maximum dose of 60mg/day by week 4.

Once the optimized dose was determined at the end of week 4, subjects then entered the double-blind, randomized, cross-over phase of the study.

EFFICACY ENDPOINT

The primary efficacy endpoint for this study (b) (4) , using the laboratory classroom setting and serial administrations of the SKAMP-Combined rating scale. Based on FDA comments on the statistical analysis plan on 29 Sep 2009, the sponsor changed the endpoint from (b) (4) to "SKAMP-combined score at 4 hours". (b) (4)

In addition, two key secondary efficacy variables that were measured were modified from:

(b) (4)

To:

1. Onset of efficacy of action was determined at 0.75 hrs post dose if the difference between the two treatments was statistically significant (p<=0.05) at that time point.
2. If the difference between the two treatments was statistically significant (p<= 0.05) at the 0.75 hour time point, the duration of efficacy was claimed at the last time point at which the difference was still statistically significant.

STATISTICAL ANALYSIS PLAN
The original statistical analysis plan proposed the following analyses to be conducted:

(b) (4)

However, previous internal Agency discussions identified potential issues with using (b) (4) In order to correct for this effect, the FDA provided comments on the SAP to the sponsor on 29 Sep 2009 which were adopted by the sponsor. The sponsor proposed the following analysis strategy:

- The primary efficacy analysis will be based on the SKAMP-Combined scores at 4 hours post dose, (b) (4)
- Secondary efficacy analyses will be based on observed scores at each time point, (b) (4)
- The onset of effect was assessed at the 0.75 hr time point. If the difference between the two treatments was not statistically significant, no

onset claim would be made. If the difference was significant, then onset would be claimed at 0.75h time point. The duration of efficacy will be determined as the last consecutive time point at which the difference between the two treatments was statistically significant

- ANOVA will be used with subject within sequence as a repeated effect.

Results

Demographics and Baseline Characteristics

In general, the patients who participated in this trial were aged 8.8 years of age, male (73%) and white (78%).

The majority of children had the combined subtype of ADHD (71%), and 27% had the inattentive subtype. Most children had a diagnosis of ADHD without a history of co morbid psychiatric disorders (69%). However, in patients who had a co morbid psychiatric diagnosis, oppositional defiant disorder was the most prevalent (18%)

Table 3: Demographics and Baseline characteristic of the Safety population (N=45)

CHARACTERISTIC	VALUE (SD)
Age (y)	8.8 (1.69)
Male	73%
White	78%
ADHD-Combined type	71%
ADHD-inattentive	27%
No psychiatric co morbidity	69%
Co-morbid ODD	18%

Patient Disposition
A total of 45 patients were randomized to treatment in the study. Six (6) patients discontinued from the study during the open-label phase of the protocol prior to double-blind treatment, as illustrated in the table below:

Table 4: Disposition of Patients who Prematurely Discontinued the Trial

REASON FOR DISONTINUATION	N
Withdrawal of Consent/Assent	2
Adverse Event	2
Lack of efficacy	1
Lost to follow-up	1
Total	**6**

Adverse events that led to discontinuation were affect lability (in one patient 18 days after study medication administration) and aggression/temper tantrum (in another patient on day 9 of study medication administration). In both cases, the adverse events resolved within one day and no long-term clinical sequelae were reported. Both adverse events are consistent with known adverse events associated with stimulant medication, and these are prominently labeled as adverse events in the RLD label.

Concomitant Medication Use

Most patients (84% 31/45) took at least one concomitant medication during the study. Topical dermatological preparations were the most commonly administered concomitant medications (60%), followed by antihistamines (20%) and analgesics (20%). In view of the pharmacological actions of these concomitant medications, it is unlikely that the use of these medications substantially affected the results of the efficacy analysis or safety/tolerability of the study medication.

Table 5: Concomitant medication use (N=45)

MEDICATION	PROPORTION
Topical antipruritics	60%
Systemic antihistamines	20%
Analgesics	20%
Multivitamins	13%
Anti-inflammatory	7%
Inhales B2 agonists	4%
Vitamin C	4%
Beta lactam antibiotics	4%
Expectorants	2%
Oral cold preparations	2%
Psycho Stimulants	2%
Stomatological preparations	2%
Viral vaccines	2%
Scabacides	2%
Posterior Pituitary Hormones	2%

Important Protocol Violations

Ten patients (22%) had documented treatment deviations. In addition, 3 patients (7%) did not have PK samples collected. The sponsor did not specify which "treatment deviations" occurred or how severe the effect of these deviations may have had on clinical efficacy results.

Because of the large treatment effect observed, it is unlikely that the unspecified treatment deviations would have changed the efficacy or safety results of this study.

Dosing
The overall mean length of exposure to NWP06 was 41 days: 28.8 days in the open label phase and 13.8 days in the double blind portion of the study.

The mean daily dose of NWP06 during the study was 32.8mg.

Efficacy Results

Primary Efficacy

The results of the primary efficacy analysis demonstrated a statistically significant change in SKAMP scores at the 4 hour time point in the NWP06 treated subjects compared to placebo treatment:

Table 6: Change in SKAMP Combined (SKAMP-C)score at 4 hours post dose (ITT population)

STATISTIC	PLACEBO (N=44)	NWP06 (N=44)	DIFFERENCE
ITT population	N=39	N=39	
Mean SKAMP-C Score at 4 hours (SD)	19.3 (8.38)	7.1 (5.64)	-12.2 (7.19)
LS Mean (SE)	19.58 (1.15)	7.12 (1.14)	-12.46 (1.13)*

*p <0.0001

(b) (4)

Conclusions

Efficacy at the 4 hour pot-dose time point was clearly established when compared to placebo.

6.1.3 Crosscutting Issues

Subgroup Analyses

The sponsor performed additional analyses by site, final dose (20mg, 30/40mg, and 50/60mg), age, gender, ADHD type, and ADHD baseline severity. In addition, efficacy by treatment sequence was evaluated by the Agency.

Site Analysis
Both sites demonstrated a statistically significant treatment decrease in SKAMP-C scores as compared to placebo

Table 8: Change in SKAMP-C Score at 4 hours post dose by site (ITT population)

STATISTIC	PLACEBO (N=44)	NWP06 (N=44)	DIFFERENCE
Site One N=26			
Mean SKAMP-C Score at 4 hours (SD)	20.3 (7.56)	7.0 (4.77)	-13.2 (7.35)
LS Mean (SE)	20.48 (1.21)	7.02 (1.21)	-13.45 (1.35) *
Site Two N=13			
Mean SKAMP-C Score at 4 hours (SD)	17.3 (9.84)	7.2 (7.30)	-10.2 (6.67)
LS Mean (SE)	17.63 (2.54)	7.5 (2.54)	-10.13 (1.99)**

* $p<0.0001$; **$p=0.0003$

Age
Consistent with the primary efficacy results, a decrease in SKAMP-C scores were observed in each age group at the 4 hour time point.

In patients aged 6-7, efficacy was not established past the hour 8 time point. In subjects aged 11-12, efficacy was not demonstrated past the 10 hour time point. However, because there were a small number of subjects in each of these age groups and there were wide variations seen in results, it is difficult to interpret these findings. Additional studies are recommended to be conducted to confirm this finding.

Table 9: Change in SKAMP-C Score at 4 hours post dose by age (ITT population)

STATISTIC	PLACEBO (N=44)	NWP06 (N=44)	DIFFERENCE
Age 6-7 N=7			
Mean SKAMP-C Score at 4 hours (SD)	24.7 (10.36)	8.9 (9.67)	-15.9 (7.10)
LS Mean (SE)	25.38 (3.45)	9.71 (3.45)	-15.67 (2.91)*
Age 8-10 N=23			
Mean SKAMP-C Score at 4 hours (SD)	18.7 (6.78)	5.5 (3.36)	-13.3 (7.03)
LS Mean (SE)	19.02 (1.08)	5.30 (1.08)	-13.73 (1.30)**
Age 11-12 N=9			
Mean SKAMP-C Score at 4 hours (SD)	16.4 (9.53)	9.8 (5.63)	-6.7 (4.74)
LS Mean (SE)	16.58 (2.79)	9.83 (2.79)	-6.75 (1.68)***

*** p=0.003; **p <0.0001' ***p=0.0050**

Gender

A statistically significant reduction in SKAMP-C scores was seen at the 4 hour time point for both sexes. With the exception of females not demonstrating a statistically significant effect past hour 10, there were significant decreases in scores at all other time points.

Table 10: Change in SKAMP-C Score at 4 hours post dose by gender (ITT population)

STATISTIC	PLACEBO (N=44)	NWP06 (N=44)	DIFFERENCE
Male N=28			
Mean SKAMP-C Score at 4 hours (SD)	19.3 (8.62)	8.5 (5.99)	-10.9 (6.36)
LS Mean (SE)	19.92 (1.40)	8.69 (1.40)	-11.24 (1.20)*
Female N=11			
Mean SKAMP-C Score at 4 hours (SD)	19.2 (8.13)	3.5 (2.21)	-15.6 (8.33)
LS Mean (SE)	19.05 (1.87)	3.57 (1.87)	-15.48 (2.60)**

* p<0.0001; **p=0.0002

ADHD subtype

A treatment effect was observed in patients with either the inattentive or combined ADHD subtype.

In the inattentive subgroup, no statistically significant change in SKAMP-C scores was seen past 10 hours post dose.

Table 11: Change in SKAMP-C Score at 4 hours post dose by ADHD-Subtype (ITT population)

STATISTIC	PLACEBO (N=44)	NWP06 (N=44)	DIFFERENCE
Inattentive N=11			
Mean SKAMP-C Score at 4 hours (SD)	16.5 (7.12)	7.4 (4.20)	-6.1 (4.48)
LS Mean (SE)	13.30 (1.80)	7.25 (1.80)	-6.05 (1.42)*
Combined N=27			
Mean SKAMP-C Score at 4 hours (SD)	21.4 (7.86)	7.0 (6.28)	-14.3 (6.61)
LS Mean (SE)	22.12 (1.29)	7.24 (1.29)	-14.88 (1.18)**

*** p=0.0021; **p <0.0001**

ADHD-Severity at baseline

Regardless of baseline ADHD severity on the SKAMP-C combined score (at or below median severity; above median severity), NWP06 treatment resulted in a decrease in SKAMP-C scores. Even in patients with less severe symptoms, a greater than 50% reduction in SKAMP-C scores was still observed at 4 hours post dose with onset at 0.75hr.

Table 12: Change in SKAMP-C Score at 4 hours post dose by ADHD-Severity at baseline (ITT population)

STATISTIC	PLACEBO (N=44)	NWP06 (N=44)	DIFFERENCE
Equal/Below Median N=20			
Mean SKAMP-C Score at 4 hours (SD)	14.8 (7.15)	5.8 (3.75)	-9.0 (6.77)
LS Mean (SE)	14.58 (1.37)	5.54 (1.37)	-9.13 (1.63)*
Above Median N=19			
Mean SKAMP-C Score at 4 hours (SD)	24.1 (6.88)	8.5 (6.95)	-15.6 (6.12)
LS Mean (SE)	23.88 (1.52)	8.43 (1.52)	-15.45 (1.32)**

*** p<0.0001; **p <0.0001**

Dose Response

Potential dose-response relationships cannot be determined from this dose-optimization study, because subjects were not randomized to fixed-dose treatment arms.

Key Secondary Variables

With regard to the key secondary endpoint of onset and duration of effect, NWP06 treatment demonstrated a statistically significant effect on mean SKAMP-C scores at every time point measured, compared to placebo treatment:

Table 13: Least Square Mean Change in SKAMP Combined (SKAMP-C)score at all time points measured post dose (ITT population)

TIME POST DOSE (HR)	LS MEAN SKAMP-C SCORE (SE) PLACEBO	LS MEAN SKAMP-C SCORE (SE) NWP06	DIFFERENCE (SE)	P-VALUE
0.75	16.16 (1.00)	9.84 (1.00)	-6.32 (1.09)	<0.0001
2	17.28 (1.01)	7.31 (1.01)	-9.98 (1.02)	<0.0001
4	19.58 (1.14)	7.12 (1.14)	-12.46 (1.13)	<0.0001
8	20.41 (9.33)	10.8 (8.23)	-9.33 (1.28)	<0.0001
10	18.29 (1.37)	14.50 (1.37)	-3.79 (1.11)	0.0016
12	20.26 (1.58)	15.49 (1.58)	-4.77 (1.40)	0.0016

Key Secondary efficacy analyses were similar in the per-protocol population, with all time points showing statistically significant decreases in SKAMP-C scores at all time points tested in the NWP06 group vs. placebo.

Long-Term Efficacy

Long-term efficacy was not evaluated as part of this NDA application.

Pediatric Development

This product has been developed for pediatric use.

6.1.4 Efficacy Conclusions Regarding Claim 1

Efficacy has been established for this product.

7 REVIEW OF SAFETY

Safety Summary

NWP06 was well tolerated by most patients. Adverse events that occurred in the trial are consistent with known adverse events associated with methylphenidate administration and are labeled appropriately in the label for the RLD.

No deaths or serious adverse events occurred during this trial. Two patients were withdrawn because of severe adverse events: aggression/temper tantrum and affect lability. These adverse events were associated with methylphenidate treatment. These are known adverse events which are prominently labeled in the RLD label. Both patients fully recovered.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data that was obtained from the one clinical efficacy study was reviewed.

7.1.2 Categorization of Adverse Events

Adverse events were categorized using the most current version of MedDRA.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling of data was performed because only one clinical study was conducted.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

For study NWP06-ADD-100, the overall mean length of exposure to the study medication was 28.8 $\pm$4.60 days in the open-label optimization phase and 13.8 $\pm$0.45 days in the double blind phase. The average daily dose of NWP06 was 32.8 $\pm$7.82 mg.

Please refer to section 6.1.2 for a review of the patient demographics for study NWP06-ADD-100.

7.2.2 Explorations for Dose Response

Dose-response relationships for adverse events cannot be determined, because subjects were not randomized to fixed doses.

7.2.3 Special Animal and/or In Vitro Testing

The sponsor has cross-referenced to preclinical data in the Methylin oral solution application as part of this 505 (b) 2 application.

7.2.4 Routine Clinical Testing

Routine clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable for this submission.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during the clinical development program of this NDA.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events (SAEs) that occurred during the clinical trial.

7.3.3 Dropouts and/or Discontinuations

There were two (2) patients who were discontinued from the study secondary to adverse events that occurred during the open-label phase (dose optimization) trial:

Subject 02-006: an 8 yo male who was discontinued at day 18 for adverse event of affect lability

Subject 02-016: a 6 yo male who was discontinued on day 9 for adverse event of temper tantrum/aggression

As these adverse events occurred prior to the double-blind treatment phase, these discontinuations had no impact on the efficacy results. In addition, both adverse events have been commonly associated with use of stimulants and are currently labeled in the class labeling for stimulant medications.

7.3.4 Significant Adverse Events

There were no significant or unusual adverse events that occurred in this trial.

7.3.5 Submission Specific Primary Safety Concerns

There were no submission-specific primary safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events that occurred during the double-blind, placebo controlled study are consistent with the labeling of the reference listed product. Due to the dose optimization study design, dose-response relationships for adverse events cannot be evaluated in this study

Table 14: Adverse Events occurring during the double blind cross-over phase (safety population) N=45

Adverse event	Placebo	NWP06
Affect lability	4%	7%
Upper abdominal pain	2%	2%
Aggression	2%	-
Initial insomnia	-	2%
Stereotypy	2%	-
Tic	-	2%
Vomiting	-	2%
Motion Sickness	-	2%
Eye pain	-	2%
Decreased Appetite	-	2%

7.4.2 Laboratory Findings

Clinical laboratory testing was performed only at baseline in this study. Therefore clinical laboratory changes over time with study medication use cannot be determined in this study.

Current stimulant labeling does not indicate clinically significant laboratory changes with use over time. Based on review of stimulant class labeling and literature review examining laboratory changes with stimulant use, this reviewer feels that no additional testing is indicated.

7.4.3 Vital Signs

There were small mean changes from baseline to week 2 in systolic and diastolic blood pressure. These changes are consistent with the known effects of stimulant administration and are labeled appropriately in the proposed label for NWP06.

7.4.4 Electrocardiograms (ECG's)

ECGs were performed only at baseline in this study. Therefore ECG changes over time with study medication use cannot be determined in this study.

Current stimulant labeling does not indicate clinically significant ECG changes with use over time. Based on review of stimulant class labeling and literature review to examine ECG changes with stimulant use, this reviewer feels no additional testing is indicated.

7.4.5 Special Safety Studies/Clinical Trials

No additional safety studies or special safety studies were conducted with this NDA.

7.4.6 Immunogenicity

Immunogenicity studies were not performed as part of this NDA application under 505 B (2).

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency of adverse reactions cannot be determined form this study, because patients were dose-optimized prior to double-blind treatment. No fixed dose clinical efficacy assessment was performed.

7.5.2 Time Dependency for Adverse Events

Based on the short term adverse event data that was collected in the double-blind study, adverse events did not appear to be related to duration of treatment exposure. However a full analysis of time dependent adverse events could not

be performed as there were no long-term controlled data that was collected during the clinical development program.

7.5.3 Drug-Demographic Interactions

There were no explorations done to examine drug-demographic interactions in the clinical development program. Also, as the number of subjects enrolled in the clinical study was small, such an analysis would have limited power to detect any interactions if such interactions existed.

7.5.4 Drug-Disease Interactions

No additional studies were performed in patients with clinically significant medical illnesses.

7.5.5 Drug-Drug Interactions

There were no explorations done to examine drug-drug interactions in the clinical development program.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The sponsor has referenced Methylin oral solution as the reference product for this 505 (b) (2) submission. Please refer to the Methylin labeling and reviews on file for NDA 21-419 Methylin.

7.6.2 Human Reproduction and Pregnancy Data

The sponsor has referenced Methylin oral solution as the reference product for this 505 (b) (2) submission. Please refer to the Methylin labeling and reviews on file for NDA 21-419 Methylin.

7.6.3 Pediatrics and Assessment of Effects on Growth

Please refer to the product labeling for Methylin solution for details on inhibition of growth in pediatric patients who use stimulant medications. Section 5.4 of the proposed label includes the mandatory class labeling describing the effects of long term growth suppression and stimulant administration:

> Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or nonmedication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and nonmedication-treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and

2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.

Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth; however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Please refer to the Methylin Product labeling for details. During the clinical development program for NWP06, there were no intentional or unintentional cases of overdose in patients who received NWP06.

7.7 Additional Submissions/Safety Issues

Phase 1 Pharmacokinetic Study Safety Review

Study S09-02348
This review will focus on adverse events that occurred with the single dose of 60mg NWP06 that was given as part of this two-treatment food effects study.

No deaths or SAEs were reported in this study. The adverse events recorded are consistent with the current labeling of the reference listed product. There were no discontinuations due to adverse events.

Table 15: Adverse Events occurring after single dose administration of 60mg NWP06

Adverse event	Fed Conditions N=29	Fasting Conditions N=29
Headache	17%	11%
Dizziness	7%	7%
Palpitations	7&	4%
Nervousness	3%	4%
Blurred vision	3%	4%
Hot Flush	3%	-

Study NWP06-PPK-101

No deaths or SAEs were reported in this study. There were no discontinuations due to adverse events. Three (3) patients experienced an adverse event during this trial:

- Patient 002 (6-12 yo group 60mg) experienced a transient mild episode of presyncope during a screening blood draw.

- Patient 011 (6-12 yo group 20mg) experienced a mild episode of presyncope during a PK blood draw.
- Patient 003 (6-12 yo group 60mg) experienced vomiting 2 hours after receiving the study medication.

Additional Safety Concerns

This reviewer has submitted a consult to the Division of Medication Errors Prevention and Analysis (DMEPA) due to concerns over potential reconstitution errors that may occur with powder reconstitution at the level of dispensing. Since the final reconstituted suspension will have a concentration of 5mg/ml, any errors with under-reconstitution would lead to potentially clinically significant overdosage and suboptimal dosing with over-reconstitution. This is of particular concern because dosing with stimulant medications requires precise dosing; the therapeutic window is quite narrow, compared to reconstituted antibiotic suspensions, for example, where the therapeutic window is much larger and thus generally safer in cases of over or under dosing.

While this reviewer supports the approval of an extended release methylphenidate suspension, since some patients cannot tolerate swallowing tablets or capsules, this reviewer strongly feels that significant errors and adverse events will occur due to under or over reconstitution of an extended release preparation. (b) (4)

(b) (4)

This reviewer concludes that the formulation that has been submitted with this NDA is acceptable for approval, provided that risk management plans are adopted and prospectively analyzed (as described previously) to reduce the risk of reconstitution errors with this formulation. (b) (4)

8 POSTMARKET EXPERIENCE

Not applicable at this time as this product has not yet been approved in the United States.

9 APPENDICES

9.1 Literature Review/References

No literature reviews were performed or reviewed as part of this NDA review, because the safety and efficacy of methylphenidate has been well-established.

9.2 Labeling Recommendations

A separate review of the label will be performed and is not included in this review.

9.3 Advisory Committee Meeting

An advisory committee meeting was not scheduled for this NDA.

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

/s/

MARK A RITTER
04/01/2011

ROBERT L LEVIN
04/07/2011
I recommend approval of the NDA. See memo to file.