

## Clinical Pharmacology Review Amendment

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

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### **Background:**

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

[REDACTED] (b) (4)

[REDACTED] (b) (4), the sponsor submitted the sample reanalysis report for study S09-0238 and study NWP06-PPK-101 to provide evidence for the reliability of the original bioanalytical data and PK results.

### **Recommendation:**

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

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

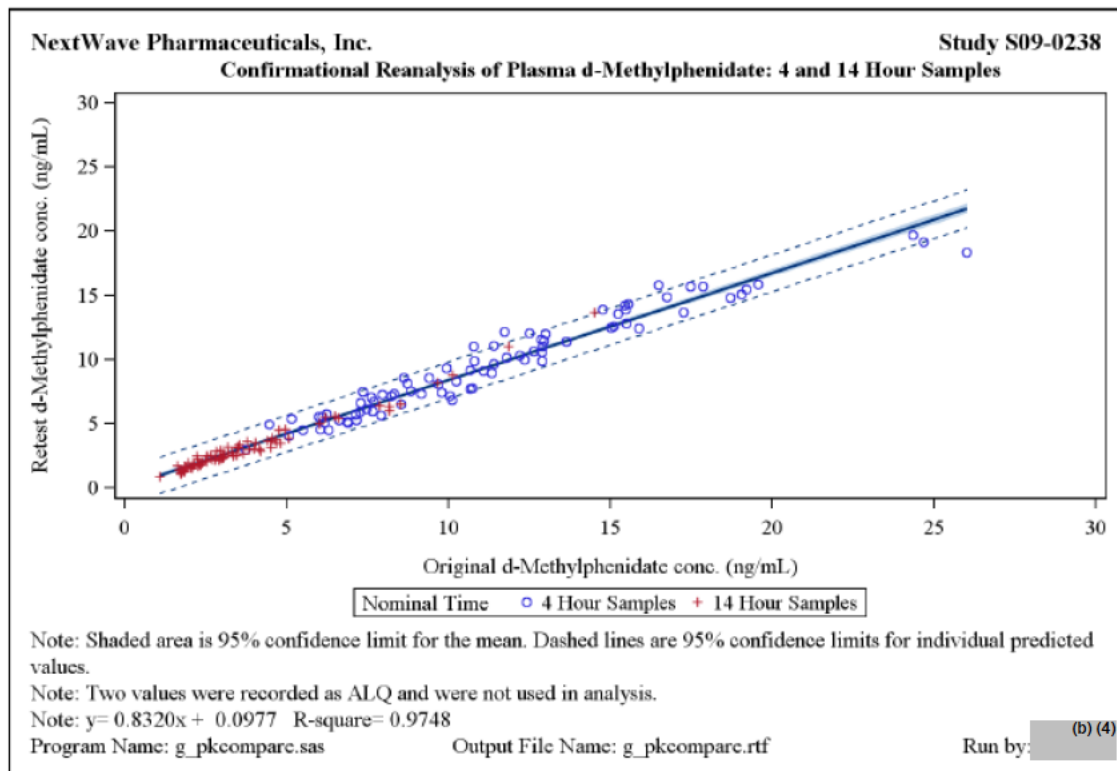
analysis. For study NWP06-PPK-101, the retested concentrations for 27 out of the 29 samples were within 20% of the original values. For study S09-0238, the retested concentrations for 98 out of the 166 samples were within 20% of the original values.

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

### **Reanalysis Result:**

#### **Study S09-0238**

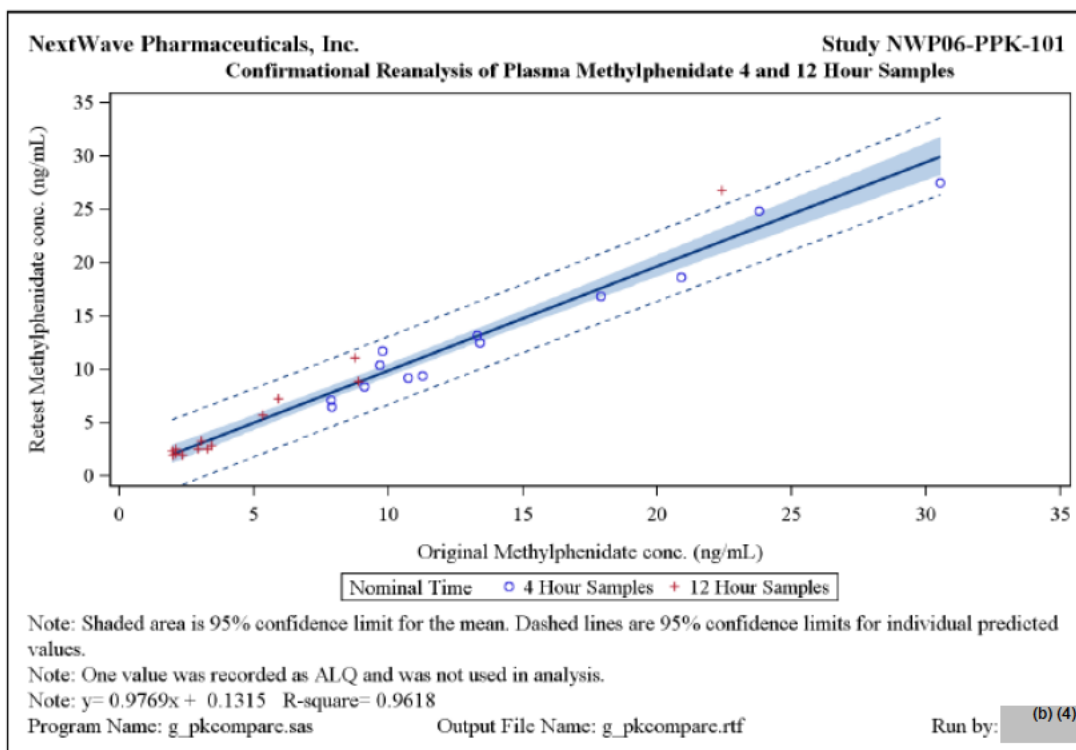
A total of 166 samples from study S09-0238 were reassayed for d-methylphenidate concentration. The samples selected were 4 hr and 14 hr postdose from all three study periods (Quillivant fasting, Quillivant fed, and Methylin IR solution (RLD) fasting) in all subjects. Linear regression analysis of the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



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

### **Study NWP06-PPK-101**

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



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

### **Issue identified**

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

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

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

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

**Cross Study Comparison:**

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

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

**SIGNATURES**

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

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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HUIXIA ZHANG  
08/29/2011

JOGARAO V GOBBURU  
08/29/2011