Clinical Pharmacology Review Amendment

NDA:	202100
Proposed Brand Name:	(b) (4)
Generic Name:	Methylphenidate HCl
Dosage Form:	Extended-Release Powder for Oral Suspension
Dosage Strength:	25 mg/5 mL
Indication:	Attention Deficit Hyperactive Disorder (ADHD)
Sponsor:	NextWave Pharmaceuticals Inc.
Submission type:	505(b)(2)
Submission dates:	July 29, 2010; Aug 24, 2011
OCP Reviewers:	Huixia Zhang, PhD, Jogarao Gobburu, PhD,

Background:

In the current submission, the Sponsor has submitted the results (b) (4) 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) (b) (4). PK samples from (b) (4) study NWP06-PPK-101 were analyzed by (b) (4) during the time period of (b) (4).

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

In response to the Agency's letter issued on Aug. 2nd, 2011, the sponsor submitted the sample reanalysis report for (b) (4) study NWP06-PPK-101 to provide evidence for the reliability of the original (b) (4) 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 (b) (4) PK results, based on the following:

1. The (b) (4) (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. (b) (4) .

3. The clinical response in the (b) (4) 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 (b) (4) 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.

(b) (4)

Reanalysis Result:

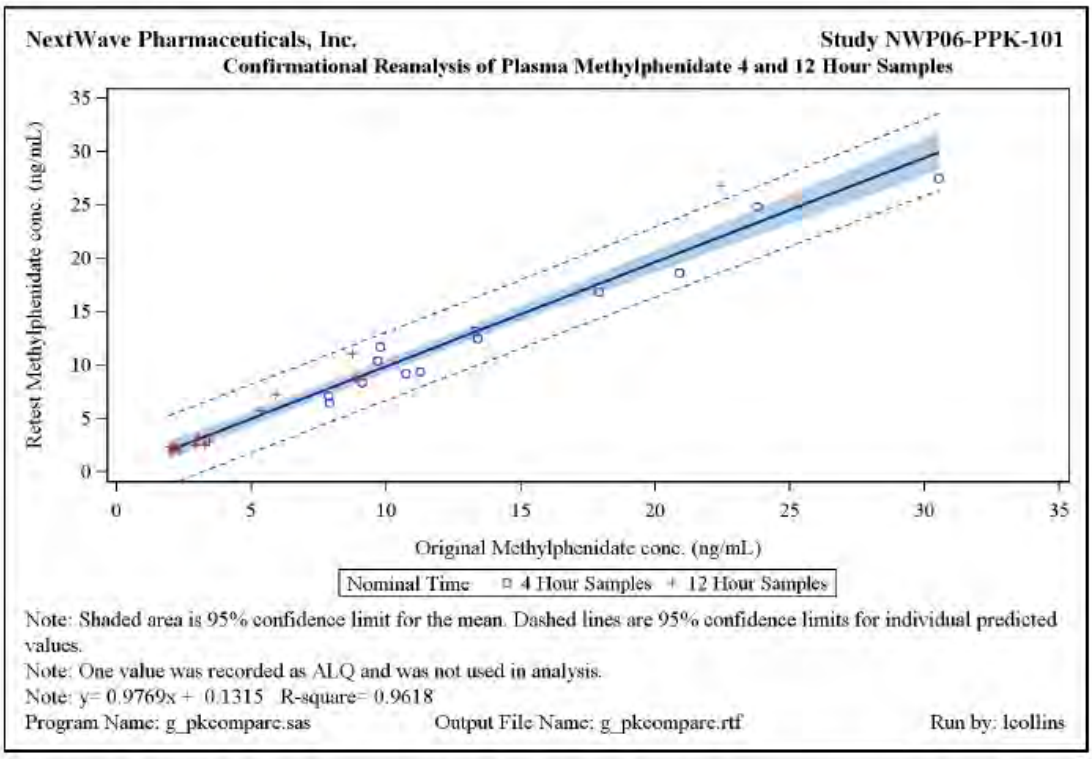
(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

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

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

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

Cross Study Comparison:

PK parameters for Methylin IR oral solution (b) (4) 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). (b) (4)

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.
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Cc: NDA 202100, DCP1 (Mehta, Uppoor, Gobburu, Zhang)

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/s/

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08/29/2011

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08/29/2011