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

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/s/

MARK A RITTER
08/20/2012

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