DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-272/S-036, S-041
NDA 20-588/S-024, S-028, S-029
NDA 21-444/S-008, S-015

Johnson & Johnson Pharmaceutical Research & Development LLC
Attention: Harindra R. Abeysinghe, Ph.D.
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road, PO Box 200
Titusville, NJ 08560-0200

Dear Dr. Abeysinghe:

Please refer to your supplemental new drug applications dated December 19, 2003, received December 19, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Risperdal® (risperidone) Tablets, Oral Solution, and M-TAB.

We acknowledge receipt of your submissions dated August 10, 2006, September 13, 2006, September 22, 2006, and September 28, 2006, and your secure e-mail transmissions dated September 21, 2006, September 26, 2006, September 29, 2006, October 2, 2006, and October 3, 2006. Your submissions of August 10, 2006 were considered complete, class 2 responses to our July 14, 2006 action letter.

Reference is also made to the following supplemental new drug applications [Changes Being Effected - Labeling]:

NDA	Supplement	Submission Date
20-272	S-041	Submitted February 23, 2005
20-588	S-028 S-029	Submitted February 23, 2005 Submitted February 23, 2005
21-444	S-015	Submitted February 23, 2005

Supplemental new drug applications NDA 20-272/S-036, NDA 20-588/S-024, and NDA 21-444/S-008 provide for the use of Risperdal® in treatment of the irritability associated with autistic disorder.

Supplemental new drug applications NDA 20-272/S-041, NDA 20-588/S-027 and S-028, and NDA 21-444/S-015 provide for revised labeling to strengthen the PRECAUTIONS (Use in Patients with Concomitant Illnesses) section of labeling with new information regarding patients with Dementia with Lewy bodies (DLB) or Parkinson's Disease (PD).

We have completed our review of these applications, as amended. We are superseding all of the above referenced labeling supplements by incorporation into efficacy supplements 20-272 / S-036, 20-588 / S-024, and 21-444 / S-008, respectively. These three efficacy supplements, including final agreed-upon language regarding patients with Dementia with Lewy Bodies (DLB) or Parkinson's Disease

(PD), are approved, effective on the date of this letter, for use as recommended in the attached agreed-upon labeling text [package insert].

The final printed labeling (FPL) must be identical to the enclosed agreed-upon labeling. These revisions are terms of the supplemental NDA approval. Marketing the product before making the revisions, exactly as stated, in the product's labeling may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved Supplemental NDAs 20-272/S-036, 20-588/S-024, and 21-444/S-008.**" Approval of this submission by FDA is not required before the labeling is used.

Pediatric Rule: Partial Waiver
All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. Because your studies have been conducted in children aged 5 to 16 years, we are partially waiving the pediatric study requirements for this application, for children aged 0-2 years [the condition is difficult to diagnose and treat in this age group], 2-4 years, and 17-18 years [efficacy in these age groups can be extrapolated from efficacy demonstrated in the 5-16 year old study population].

Postmarketing Studies: Phase 4 Commitments
We remind you of the following postmarketing commitments [Phase 4 Commitments], agreed upon in your secure electronic communication of September 29, 2006. These commitments are listed below:

Nonclinical Pharmacology and Toxicology: Two Phase 4 Commitments [Juvenile Animal Toxicology Studies: Rat and Dog]
1. Rat Study. You have agreed to perform an additional juvenile rat toxicity study at the requested higher dose of [redacted]. This study will include measurement of levels of Insulin-like Growth Factor (IGF-1).

Protocol Submission:	On or before 30 June 2007.
Final Report Submission:	On or before 31 March 2009.

2. Dog Study. You have agreed to perform a juvenile dog toxicity study to evaluate the effects of risperidone on the development of the organs of reproduction; this study will include a recovery period. This study will also include measurement of levels of Insulin-like Growth Factor (IGF-1) and assessment of long bone growth.

Protocol Submission	On or before 30 June 2007.
Final Report Submission	On or before 31 March 2009.

Combined Clinical / Clinical Safety / Clinical Pharmacology Study: Phase 4 Commitment
3. You have agreed to perform a study in autistic children and adolescents to determine the lowest effective dose of risperidone in this indication, and to evaluate the effect of risperidone treatment on fasting glucose, fasting insulin, and insulin resistance in this population. This study will be a 6-week, fixed-dose, parallel-group, placebo-controlled design, to be completed three years after approval of the proposed protocol. The hormone assessment section of this study will also incorporate measurement of growth hormone (GH) and Insulin-like Growth Factor (IGF-1).

Protocol Submission	On or before 30 December 2007.
Final Report Submission	On or before 31 March 2010.

For the above Phase 4 Commitments, submit clinical protocols to your IND(s) for this indication. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to these NDAs. (You may cross-reference to avoid duplicate submissions.)

All submissions, including supplemental New Drug Applications, relating to these Phase 4 Commitments must be prominently labeled **"Postmarketing Study Commitment Protocol", "Postmarketing Study Commitment Final Report", or "Postmarketing Study Commitment Correspondence".**

In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81 (b)(2)(viii), you should include a status summary of each commitment in your annual reports to these NDAs. The status summary should include expected protocol submission, study completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, the number of patients entered into each study.

Advice and Recommendations Regarding Studies to Meet Phase 4 Commitments
We have reviewed the outlines you have provided for the studies you propose to conduct to meet the Phase 4 Commitments listed above. While a full review will be performed when the full protocols are submitted, we have the following advice and recommendations at this point:

1. Juvenile rat toxicity study: we recommend that you increase the number of animals to 15/sex/group for each subset in this study, and that you measure motor activity using the Figure 8 Activity Maze during the treatment phase of the study as well as during the recovery period. The proposed design is otherwise generally acceptable.
2. Juvenile dog toxicity study: we have not considered the proposed doses in the dog study in our evaluation of the proposed protocol design. However, the proposed design is otherwise generally acceptable.
3. Clinical / Clinical Safety / Clinical Pharmacology Study: With respect to the third Phase 4 commitment listed above, we recommend that the initial treatment design include three arms [placebo, 0.125 mg risperidone, 1 mg risperidone] with a six week duration of treatment. Study RIS-CAN-25 included 25 patients per group; for this Phase 4 commitment study, 25 patients per treatment arm would be considered adequate. We also note that although the (b)(4) dose could be administered using the commercially available 1 mg/mL solution, accurate measurement of this dose (b)(4) will be challenging for parents and practitioners; you are

therefore advised to [redacted] (b)(4) support dosing at this level.

With regard to the hormone assessment section of this study, we consider that a 6-week study duration may not be sufficient time to allow for capture of significant data on hormone levels and the effects of any changes in these levels. We therefore recommend that you add a three to six month open-label treatment phase to this study, during which additional data on glucose, fasting insulin, IGF-1, and GH levels, as well as insulin resistance, would be collected.

Advice and Recommendations Regarding Other Suggested Studies

The currently available data do not allow adequate assessment of the effect of risperidone on growth hormone levels, or growth itself, in children and adolescents. Further study of this issue would be valuable, particularly in view of the children and adolescents in clinical trials who had elevated growth hormone levels, and the cases of delayed and precocious puberty reported in the post-marketing setting.

Although not necessary in order to meet your Phase 4 Commitments, we recommend that you conduct a study to assess the effect of long-term risperidone treatment on the growth, development, and sexual maturation of children and adolescents. If conducted, we would recommend rigorous and consistent measurement of IGF-1 and growth hormone levels, and a minimum duration of six months (if height velocity is used as an endpoint for the assessment of growth effects); a longer duration would be preferable. Assessment of other metabolic parameters and adverse events in a long-term study in this population could also be useful.

We would be willing to review and provide comments on a study protocol.

Introductory Promotional Materials

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact Doris J. Bates, Ph.D., Regulatory Project Manager, at (301).796.2260, or contact her via secure electronic mail at doris.bates@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas P. Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment: Final Agreed-Upon Labeling [Package Insert]

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

/s/

Thomas Laughren

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