DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-272

DEC 29 [illegible]

Janssen Research Foundation
Attention: Ruth Wasserman
Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

Dear Ms. Wasserman:

Reference is made to your New Drug Application (NDA) dated April 15, 1992, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for RISPERDAL® (risperidone) 1 mg, 2 mg, 3 mg, 4 mg, and 5 mg Tablets.

We also acknowledge receipt of your additional communications dated:

May 1, 1992	June 4, 1992	June 22, 1992
June 26, 1992	June 30, 1992	July 7, 1992
July 9, 1992	July 14, 1992	July 16, 1992
September 30, 1992	October 27, 1992	October 28, 1992
October 30, 1992	November 9, 1992	November 20, 1992
November 24, 1992	December 7, 1992	December 9, 1992
December 21, 1992	December 22, 1992	December 23, 1992
February 1, 1993	February 2, 1993	February 10(2), 1993
March 5, 1993	March 9, 1993	March 11, 1993
March 15, 1993	March 25(2), 1993	March 29(2), 1993
March 30(2), 1993	March 31, 1993	April 1, 1993
April 2(2), 1993	April 8, 1993	April 13, 1993
May 4(2), 1993	May 12, 1993	May 14, 1993
May 17(2), 1993	May 24, 1993	June 3, 1993
June 18, 1993	July 1, 1993	July 6, 1993
July 9, 1993	August 10, 1993	August 20, 1993
August 23, 1993	August 25, 1993	August 27, 1993
September 24, 1993	October 13, 1993	October 28, 1993

We have completed our review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final text of labeling attached to this letter. Accordingly, the application, with these labeling revisions, is approved, effective as of the date of this letter.

Labeling

Accompanying this letter (ATTACHMENT 1) is the verbatim text of the labeling under which RISPERDAL® may be marketed.

Temp6

Biopharmaceutics

Dissolution Specifications

(a) The following "interim" dissolution specification for all strengths of Risperdal® tablets are required:

Method: USP Apparatus II (Paddle) at 50 rpm
Media: 500 mL of 0.1 N HCl
NLT 80% drug released in 45 minutes

(b) Within three months of the date of this approvable action, you are requested to submit dissolution data on 12 individual tablets, for each strength of Risperdal® tablets manufactured at both the sites (Beerse, Belgium and Gurabo, Puerto Rico) according to the dissolution method specified below:

USP apparatus (Paddle method) at rpm in mL of simulated gastric fluid (without pepsin and a pH of 1.2) at 37±0.5°C.

You have apparently conducted some dissolution using this method and based on limited data, it appears that simulated gastric fluid may reduce the variability and accelerate drug release for all the tablet strengths as compared to the current medium which is 0.1 N HCl. This may allow for setting of a more appropriate dissolution specification.

Bio-Waiver

The tablet cores for each of the five dosage strengths proposed for marketing are proportionally identical for all excipients. There are minor differences in the film coating for each of the tablet strengths representing the different color additives. Therefore, a waiver of in vivo bioequivalence study for the 2 mg, 3 mg, and 5 mg strength tablets manufactured at Beerse, Belgium and also in vivo bioequivalence study between the two manufacturing sites (Beerse, Belgium and Gurabo, Puerto Rico) for all the tablet strengths (1, 2, 3, 4, and 5 mg) are granted, based on the linear kinetics of the drug and on in vitro dissolution profiles submitted in this application for this immediate release product.

Post-Marketing Studies

Although you have provided clear evidence of the effectiveness and safety of RISPERDAL®, a number of important questions related to its optimal use remain to be answered. We note your agreement to carry out the following studies after approval:

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Clinical

Long-Term Effectiveness Studies:

Although the evidence submitted unequivocally documents the short-term efficacy of RISPERDAL® in the management of the manifestations of psychosis, there is no evidence bearing directly on the effectiveness of this drug in the maintenance treatment of remitted/partially remitted psychotic patients. Because it is likely that Risperdal will be widely used for these purposes, it is critical that appropriate clinical studies be undertaken to evaluate its safety and effectiveness in long-term use.

We note your submitted protocol for a study of relapse prevention and staff of the Division of Neuropharmacological Drug Products expect to discuss this and any other proposals with you.

Pharmacokinetic Interaction Study:

Although in vitro studies suggest that risperidone is not a potent inhibitor of cytochrome P450IID6, only in vivo studies would be capable of confirming whether or not risperidone or its active metabolite have a clinically important effect on the pharmacokinetics of other drugs metabolized by this isozyme. Consequently, an in vivo study is needed to explore the potential for such interaction. It is possible that a detailed submission of literature study N97249, which reported no effect of risperidone 6 mg on the metabolic ratio of dextromethorphan, will be sufficient.

Pharmacology

A lack of understanding of the mechanism underlying the high rate of perinatal mortality observed in rat pups impairs the ability of prescribers to make an informed judgement in the use of this drug product. Studies to clarify this matter are therefore needed.

The segment III reproduction studies and a multigenerational study in rats revealed an increase in pup mortality during the first four days of lactation for pups born to dams receiving risperidone at doses ranging from 0.16 to 5 mg/kg/day. Because it cannot be determined if this effect on survival is related to effects of the drug on the developing fetus in utero or is secondary to maternal neglect, we have labeled risperidone pregnancy category C. We recommend that you conduct a cross-fostering experiment in order to determine whether the deaths occurred as a result of fetal abnormalities or if they occurred because of other problems during lactation. If this experiment clearly establishes that the adverse effect on pup mortality is occurring as a result of maternal neglect rather than an effect of drug on the fetus, the labeling may be changed from pregnancy category C to pregnancy category B.

We suggest a study comparing a control group and the high dose group (5 mg/kg/day) treated from gestation day 15 through postnatal day 21. Each group should contain 20 pregnant dams. Half of the dams in each group should be removed from the cage after giving birth and placed with a litter from the other treatment group for nursing. All groups should continue nursing through day 21 postpartum.

MANUFACTURING AND CONTROLS

The validation of the analytical methods has not been completed for this application. We would appreciate your full cooperation in resolving any problems that may arise.

Promotional Material

Please submit, in triplicate, the advertising copy that you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Neuropharmacological Drug Products and two copies to the Division of Marketing, Advertising and Communications, HFD-240, Room 17B-17. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

At the present time, we would consider any advertisement or promotional labeling for RISPERDAL® false, misleading, or lacking fair balance under sections 502(a) and 502(n) of the Act if there is presentation of data that conveys the impression that risperidone is superior to haloperidol or any other marketed antipsychotic drug product with regard to safety or effectiveness.

Please submit 12 copies of the FPL as soon as it is available. Seven of the copies should be individually mounted on heavy-weight paper or similar material. The submission should be designated for administrative purposes as "FPL for approved NDA 20-272". Approval of the submission by FDA is not required before the labeling may be used. Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required. We remind you that you must comply with the requirements for an approved NDA as set forth under 21 CFR 314.80 and 314.81

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENT