DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 31,931

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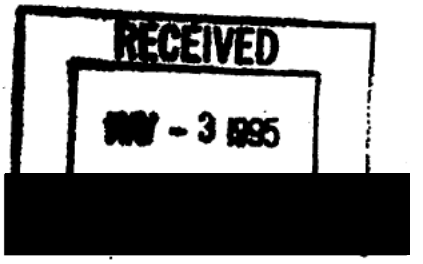

Janssen Research Foundation
Attention: [redacted]
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560-0200

Dear [redacted]:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug and Cosmetic Act for Risperdal (risperidone).

Reference is also made to your amendment (N-090) of February 10, 1995, and to protocol RIS-USA-63 entitled, "A Randomized, Double-Blind, Placebo-Controlled Study of Fixed Doses of Risperidone for Treatment of Behavioral Disturbances in Subjects with Dementia."

Your submission contains, among other documents, a cover letter in which you "invite ...[The Division's]... concurrence that this study [RIS-USA-63], should the results indicate efficacy, will serve as an adequate and well controlled assessment of the behavioral disturbances associated with dementia for the purpose of label revision."

While we have no safety objections to the conduct of your proposed study, we cannot provide assurance regarding your plans for label revision based on this study. Risperdal was developed as an antipsychotic drug in patients with schizophrenia and is currently approved only for the "management of the manifestations of psychotic disorders." If your interest had been in targeting another psychotic population, e.g., a subgroup of demented patients with associated psychotic symptoms, the labeling could be easily enhanced by simply describing the results of such a study, if positive, in the Clinical Trials subsection of Clinical Pharmacology. This would not really be an expansion of the basic claim for Risperdal, but rather, an extension of the population base supporting the claim. Such information would be potentially useful to clinicians and would improve labeling.

Alternatively, you appear to be exploring Risperdal's potential value for a much broader and more diffuse clinical target, namely "behavioral disturbances in demented patients." While this broad label would certainly include psychotic phenomena, e.g., delusional thinking, suspiciousness, and hallucinations, it would also encompass a range of other clinical findings, e.g., anxiety, depression, agitation, aggressiveness, verbal outbursts, wandering, etc., that would not necessarily be considered psychotic manifestations. Your entry criteria for this study would certainly not limit your sample to demented patients with associated psychotic symptoms. In addition, the BEHAVE-AD, your primary

outcome measure, includes a number of behavioral signs and symptoms that are not readily classified as manifestations of psychosis. Some of these findings, e.g., aggressiveness or verbal outbursts, might even be construed by some as appropriate responses to the deplorable conditions under which some demented patients are housed, thus raising an ethical question regarding the use of antipsychotic medications for inappropriate behavioral control. Nevertheless, the major concern we want to focus on is how any results from the study you are proposing might be incorporated into labeling in a way that is useful to clinicians and is not misleading.

The term "behavioral disturbances in demented patients" is so broad that it might be misinterpreted by clinicians to mean that a drug shown effective for such a target would be effective for all the various signs and symptoms that fall under such an umbrella, e.g., anxiety, depression, phobic fears, panic attacks, diurnal rhythm disturbances, etc. We would consider such a claim misleading in that sense, and consequently, we would not consider this broad claim, either as a new claim under Indications, or as an implied claim that would derive from permitting the description of your proposed study under Clinical Trials. Rather, we would suggest that you attempt to parcel out the various distinct clinical targets that are subsumed under the broad heading of "behavioral disturbances" and study these separately. Since risperidone is already approved for psychosis, an obvious initial target would be the subgroup referred to above, i.e., demented patients with associated psychotic symptoms.

There is a further difficulty. Even if agreement can be reached concerning the nature of the target signs and/or symptoms that will be treated, the linkage of those phenomena to dementia will remain problematic. The issue here involves the general problem of 'pseudospecificity' of labeling claims that occurs whenever a treatment for a symptom or sign that is common to several conditions is evaluated in only one of them. In such instances, it is impossible to discern when a beneficial treatment effect is found whether or not it is in any way linked to the diagnosis of the patients treated.

For example, assume that you were able to show by ordinary standards that risperidone does reduce agitation in a sample of patients with dementia. That finding, however, is not proof that the effect of risperidone is in any way specific to dementia. In fact, the only reason that a seeming link would exist in this situation between the demonstrated effect and dementia would arise from your decision to study risperidone in a sample of demented patients. Accordingly, such a result would not be sufficient to justify a dementia related claim.

You may, of course, our explanations of the issues affecting our views notwithstanding, still wish to pursue a claim for Risperdal in dementia. If so, you should understand that we are in no way opposed to such an effort; indeed, we would welcome one. In that case, however, you would have to demonstrate that the effects of Risperdal (and we would have to develop an explicit enumeration of the behaviors targeted) are in some way predicted by the diagnosis of dementia. Put another way, to gain a claim for

appropriate target behaviors associated with dementia, you would have to show that these behaviors are suppressed in dementia patients and not in patients with other conditions or diseases where they are also seen. The task, we acknowledge, is not easily accomplished, but without such evidence, you will not be able to assert a unique dementia related claim for an antipsychotic product.

Incidentally, the same general advice applies to any attempt to gain a specific disease related claim for a product that exerts a pharmacological action currently held to be more or less independent of the disease state in which it occurs, for example, disease specific claims for anxiolytics or analgesics.

In conclusion, the trial you propose cannot provide results that would, on their own, serve as a basis for expansion of the claimed indications for the use of Risperdal, nor would they be sufficient to serve as a basis for any other substantive modification of current product labeling. However, the results of the proposed study may well provide information critical to the planning and development of either 1) a program for further systematic evaluation of risperidone's use or uses in the management of one or more undesirable/untoward behaviors (e.g., agitation, seeming purposeless motor activity, etc.) that occur in a number of clinical conditions, including, but not limited to, dementia or 2) a program to define better the doses and regimens required to manage the psychotic manifestations exhibited by demented patients.

Should you have any further questions, please contact Steven D. Hardeman, R.Ph., Regulatory Management Officer, at (301) 594-2777.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research