DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-272

Janssen Research Foundation
Attention: Claude McGowan, Ph.D.
Assistant Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Dr. McGowan:

Reference is made to your Proposed Pediatric Study Request submitted on May 5, 2000, to your New Drug Application for Risperdal (risperidone) tablets.

To obtain needed pediatric information on risperidone, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from trials in pediatric patients with (1) schizophrenia, and with (2) acute mania, as part of bipolar I disorder, as described below.

ADOLESCENT SCHIZOPHRENIA

General Advice for Developing a Drug for Adolescent-Onset Schizophrenia

Schizophrenia is a chronic and debilitating illness that has an estimated lifetime adult prevalence of 0.5 to 1%. According to the DSM IV, the diagnostic criteria for schizophrenia are the same for the pediatric and adult populations, but the symptomatology and prevalence of schizophrenia in these two populations have been recognized to be somewhat different. Within the pediatric age group, a diagnosis of schizophrenia is most commonly made in adolescents, and the symptoms in this age group are generally similar to those in adults (APA Practice Parameters, 1997). Schizophrenia has also been described in children, but it is thought to be uncommon (AACAP Practice Parameters, 2001). Although there are not adequate epidemiological data, one author suggests that 0.1 to 1 % of schizophrenic psychoses will present prior to age 10 (Remschmidt, 1996). In addition, the symptoms in childhood schizophrenia differ from those typically seen in adult schizophrenia and the diagnosis is more difficult to establish in this younger population (Volkmar, 1996).

Given the finding that childhood onset schizophrenia may present with symptoms quite different from those of adult onset schizophrenia, it would be important to systematically study the efficacy of treatment within this pediatric population. The very low incidence of schizophrenia diagnosed prior to the age 13, however, makes it unlikely that it would be possible to conduct a sufficiently large study of this age group within a reasonable time. For this reason, and because there is still controversy about the validity of this diagnosis in children, this written request will be limited to the study of schizophrenia in adolescents aged 13 to 17 years.

In issuing this request, we would like to stress the importance and challenge of accurately diagnosing schizophrenia in the pediatric population. The differential diagnosis may include bipolar disorder, mood disorder with psychosis, personality disorders, other psychotic disorders with organic etiologies,

in addition to many disorders that classically present in childhood, such as the pervasive developmental disorders and developmental language disorders (AACAP Practice parameters, 2001). An indication of the difficulty of diagnosis is an NIMH study reporting that 7 of 31 (23%) children originally diagnosed with treatment-resistant childhood-onset schizophrenia were re-assessed after a 4 week medication free wash-out period and found not to have that disease; revised diagnoses included posttraumatic stress disorder, atypical psychosis, and personality disorder (Kumra, 1999).

Under FDAMA, 1997, adequate assessment of adolescents (data sufficient to support a labeling claim) might be based on a single study in pediatric patients, together with confirmatory evidence from another source, perhaps adult data for that disorder. This approach is explicitly considered in the guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach too requires that the adult data be considered reasonably relevant to the course of the disease and the effects of the drug in the pediatric populations. Although we are aware of only two published placebo controlled studies supporting the efficacy of neuroleptics (haloperidol & loxitane) in the treatment of pediatric schizophrenia (Spencer et al., 1992 & Pool et al., 1976), we believe that a sufficiently strong case has been made for continuity between adult and adolescent schizophrenia to permit a pediatric claim for a drug already approved in adults to be supported by a single, independent, adequate and well-controlled clinical trial in adolescent schizophrenia. In addition, a pediatric schizophrenia program would need to include pharmacokinetic information and safety information in the relevant pediatric age group. For pediatric schizophrenia, we consider the relevant age group to include adolescents aged 13-17 years.

Finally, although we are requiring only certain specific studies, you will be expected to maximize the potential of the studies to demonstrate an effect of the drug in adolescents, if there is one. Toward this end, then, we urge you to perform additional studies (see below) in order to ensure that the required studies meet this goal.

Bibliography

American Academy of Child and Adolescent Psychiatry (2001). Practice Parameter for the Assessment and Treatment of Children and Adolescents With Schizophrenia. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40(7, Supplement), 4S-23S.

American Psychiatric Association (1994), Diagnostic and Statistical Manual of Mental Disorders, 4 th edition (DSM-IV). Washington, DC: American Psychiatric Association.

American Psychiatric Association (1997). Practice guideline for the treatment of patients with schizophrenia. *American Journal of Psychiatry*, 154(4 Suppl): 1-63.

Kumra, S, Briguglio C, Lenane M, et al. (1999), Including Children and Adolescents with Schizophrenia in Medication-Free Research. *American Journal of Psychiatry,* 156:7: 1065-1068.

Pool D, Bloom W, Mielke DH et al. (1976), A controlled evaluation of loxitane in seventy-five adolescent schizophrenia patients. *Current Therapeutic Research Clinical and Experimental* 19:99-104.

Remschmidt H, Schulz E, Herpertz-Dahlmann B (1996), Schizophrenic Psychoses in Childhood and Adolescence *CNS Drugs* Aug: 6(2):100-112.

Spencer EK, Jafantaris V., Pardron-Gayol MV, et al. (1992), Haloperidol in schizophrenic children: early findings from a study in progress *Psychopharmacol Bull* 28:183-186.

Volkmar F (1996), Childhood and Adolescent Psychosis: a Review of the Past 10 Years *Journal of the American Academy of Child and Adolescent Psychiatry* 35(7):843-851.

Specific Study Requirements for Development Program in Adolescent Schizophrenia

Types of Studies

Pediatric Pharmacokinetic Study

Pediatric Efficacy and Safety Study

Pediatric Safety Study

Objective/Rationale

The overall goal of the development program would be to establish the safety and efficacy of the study drug in the treatment of adolescent schizophrenia, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

Study Design

Pediatric Pharmacokinetic Study

- You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population kinetic approaches applied to the controlled efficacy trial or to other safety trials. However, pharmacokinetic data obtained in a controlled trial that fails to identify a drug effect due to inadequate design, as described under "Pediatric Efficacy and Safety Study," will not be considered to have met the requirements of this request. For this reason, we strongly recommend that you perform preliminary tolerability studies (in which kinetic data can be obtained) to fully explore the range of tolerated doses, before conducting the definitive pharmacokinetic study and before conducting the definitive efficacy and safety study. Adequate pharmacokinetic data from studies in a single indication would be sufficient to meet this requirement. You should be aware that a guidance document on population pharmacokinetic studies is available under [www.fda.gov/cder/guidance/1852fnl.pdf].

Pediatric Efficacy and Safety Study

- For the controlled efficacy study, you must conduct a randomized, double-blind, parallel group, placebo-controlled acute trial, with a recommended duration of at least 6 to 8 weeks. The trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms are not adequately controlled to a specific extent at some point on assigned treatment or who worsen. At least 50% of patients assigned to active drug must complete to the nominal endpoint of this trial in order for it to be considered a completed trial. The trial must maximize the opportunity to detect a treatment effect of the drug, if there is one in this population. Specifically, if you perform a flexible dose ranging study that fails to detect an effect of the drug, this will not be considered to have met the requirements of this request. Therefore, we strongly recommend that the trial be a fixed dose study that includes fixed doses that fully explore the tolerated dose range in this population. A relapse prevention trial should follow the acute treatment trial, in which responders to acute treatment would be randomized to study drug or placebo, with follow-up observation for relapse for a period of 6 months or more with assessment of time to relapse and

treatment of relapsed patients. As for the acute study, this trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms worsen to a clinically significant extent on assigned treatment. Both the acute and the relapse prevention trials should be limited to patients capable of giving assent to participate in the trial. In addition, given the concerns about placebo assignment to pediatric patients with schizophrenia, this study must have a Data Safety Monitoring Board to oversee its conduct in order to ensure that it is conducted safely.

Pediatric Safety Study

- Safety data must be collected in the controlled efficacy trial. In addition, longer-term safety data, for a minimum duration of 6 months exposure to the drug, must be collected. The longer-term safety data could come from open studies, e.g., a longer-term open extension of the controlled efficacy trial populations, from separate longer-term open safety studies, or from controlled studies, e.g., a longer-term safety and efficacy trial. Adequate longer-term safety data from studies in a single indication would be sufficient to meet this requirement. The long-term safety data must be at or above the dose or doses identified as effective in an adequately designed trial, as described above. If an adequately designed and conducted effectiveness trial fails to detect a drug effect, you must still collect long-term safety data, at doses at least as high as the doses currently used in treating patients off-label with this drug.

Age Group in Which Study(ies) will be Performed –All Studies

Adolescents (ages 13 to 17 years) must be included in the sample, and there must be a reasonable gender and age distribution within this sample.

Number of Patients to be Studied

Pediatric Pharmacokinetic Study

- A sufficient number of patients to adequately characterize the pharmacokinetics of the study drug and its major active metabolite in the above age group.

Pediatric Efficacy and Safety Study

- The study must have a sufficient number of patients to provide 85% power to show a difference between drug and placebo equivalent to the median drug-placebo difference seen in the adult trials that were the basis for this drug's approval in adults. It will probably be necessary to conduct a multicentered study to ensure a sufficient population accurately diagnosed with schizophrenia.

Pediatric Safety Study

- A sufficient number of pediatric patients to adequately characterize the safety of the study drug at or above the dose or doses identified as effective in an adequately designed trial, or if this trial fails to detect a drug effect, at doses at least as high as the doses currently used in treating patients off-label with this drug. At least 100 patients exposed to drug for at least 6 months would be a minimum requirement for long-term safety.

Entry Criteria

The protocol must include a valid and reliable diagnostic method for recruiting and enrolling adolescents meeting DSM-IV criteria for schizophrenia. Given the difficulty in making the diagnosis for screening purposes, it is recommended that a clinical interview of children and their parents or caregivers be conducted by an adequately trained clinician (e.g. child psychiatrist) to assure accurate diagnosis. It is also recommended that the diagnosis be confirmed using a reliable and valid semi-structured interview.

Patient Evaluations and Study Endpoints

Pediatric Pharmacokinetic Study

- Pharmacokinetic assessments must be made with respect to the study drug and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite measured, the data collected must provide adequate estimates of important pharmacokinetic parameters, e.g., AUC, half-life, C_{max} , T_{max}, and apparent oral clearance (this parameter for parent only) in pediatric patients in the relevant age range. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available at [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacology (Draft)].

Pediatric Efficacy and Safety Study

- A scale specific to schizophrenia and sensitive to the effects of drug treatment of schizophrenia in the target population should be used. The choice of the primary assessment instrument and the primary outcome will need to be justified. Specifically, if you choose scales and outcomes used in adult studies, you will need to justify that these measures are appropriate for use in the pediatric population. Alternatively, you may perform preliminary trials to identify sensitive rating scales in this population. Justification of primary endpoint selection will be of particular concern if the definitive effectiveness trial fails to distinguish drug from placebo. It may also be useful to add a global measure, e.g., the Clinical Global Impression (CGI). It is essential to identify a primary outcome (or outcomes if more than one is considered important) for the controlled efficacy trial; ordinarily this would be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trial.

Pediatric Safety Study

- Routine safety assessments must be collected at baseline and appropriate follow-up times, i.e., vital signs (pulse rate and blood pressure), weight, height, clinical laboratory measures (chemistry, including serum prolactin, hematology, and urinalysis), ECGs, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias, using appropriate rating instruments). Although not a part of this Written Request, we remind you that it may be important to determine the effect of the study drug on the growth and development of pediatric patients, and we encourage you to consider longer-term studies of a year or more to address this question if the acute studies demonstrate efficacy in schizophrenia.

Statistical Information

Pediatric Pharmacokinetic Study

- Descriptive analysis of the pharmacokinetic parameters.

Pediatric Efficacy and Safety Study

- This trial must have a detailed statistical plan. The trial should be designed with at least 85% statistical power to show a difference between drug and placebo equivalent to the median drug-placebo difference seen in the adult trials that were the basis for this drug's approval, at conventional levels (alpha=0.05, 2-tailed) of statistical significance.

Pediatric Safety Study

- Descriptive analysis of the safety data.

PEDIATRIC BIPOLAR DISORDER

General Advice for Developing a Drug for Mania in Pediatric Bipolar Disorder

According to the DSM IV, the diagnostic criteria for mania are the same for the pediatric and adult population. However, the lower end of the age range for bipolar disorder is not clear. Bipolar disorder below the age of 10 years is considered both uncommon and difficult to diagnose. On the other hand, bipolar disorder in the 10 to 17 year-old population is thought to be relatively common and phenomenologically similar to bipolar disorder seen in adults. Thus, the study of bipolar disorder in 10 to 17 year-olds should be feasible and should yield useful information.

Under FDAMA, 1997, adequate assessment of pediatric patients (data sufficient to support a labeling claim) might be based on a single study in pediatric patients, together with confirmatory evidence from another source, perhaps adult data for that disorder. This approach is explicitly considered in the guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach too requires that the adult data be considered reasonably relevant to the course of the disease and the effects of the drug in the pediatric populations. We believe that a sufficiently strong case has been made for continuity between adult and pediatric bipolar disorder, down to the age of 10, to permit a pediatric claim for a drug already approved in adults for mania to be supported by a single, independent, adequate and well-controlled clinical trial in pediatric mania (ages 10 to 17) in association with bipolar disorder. Of course, Risperdal is not yet approved for mania in adults. You are, however, clearly interested in developing Risperdal for adult mania, and therefore, we consider it essential that you include a pediatric mania safety and efficacy study in your pediatric program. In addition, a pediatric mania program would need to include pharmacokinetic information and safety information in the relevant pediatric age group. For pediatric mania, we consider the relevant age group to include patients aged 10-17 years.

Finally, although we are requiring only certain specific studies, you will be expected to maximize the potential of the studies to demonstrate an effect of the drug in this population, if there is one. Toward

this end, then, we urge you to perform additional studies (see below) in order to ensure that the required studies meet this goal.

Bibliography

American Psychiatric Association (1994), Diagnostic and Statistical Manual of Mental Disorders, 4 th edition (DSM-IV). Washington, DC: American Psychiatric Association.

Specific Study Requirements for Development Program in Pediatric Mania in Association with Bipolar Disorder

Types of Studies

Pediatric Pharmacokinetic Study

Pediatric Efficacy and Safety Study

Pediatric Safety Study

Objective/Rationale

The overall goal of the development program would be to establish the safety and efficacy of the study drug in the treatment of pediatric mania in association with bipolar disorder, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

Study Design

Pediatric Pharmacokinetic Study

- You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population kinetic approaches applied to the controlled efficacy trial or to other safety trials. However, pharmacokinetic data obtained in a controlled trial that fails to identify a drug effect due to inadequate design, as described under "Pediatric Efficacy and Safety Study," will not be considered to have met the requirements of this request. For this reason, we strongly recommend that you perform preliminary tolerability studies (in which kinetic data can be obtained) to fully explore the range of tolerated doses, before conducting the definitive pharmacokinetic study and before conducting the definitive efficacy and safety study. Adequate pharmacokinetic data from studies in a single indication would be sufficient to meet this requirement. You should be aware that a guidance document on population pharmacokinetic studies is available under [www.fda.gov/cder/guidance/1852fnl.pdf].

Pediatric Efficacy and Safety Study

- For the controlled efficacy study, you must conduct a randomized, double-blind, parallel group, placebo-controlled acute trial, with a recommended duration of at least 3 weeks. The trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms are not adequately controlled to a specific extent at some point on assigned treatment or who worsen. At least 50% of patients assigned to active drug must complete to the nominal endpoint of this trial in order for it to be considered a completed trial. We strongly recommend that the trial be a fixed

dose study including at least two fixed doses of the study drug. Given the lack of a robust evidence base for the use of lithium in pediatric mania, there is uncertainty about the optimal therapeutic approach in this population. Thus, this could be a monotherapy trial, or an add-on trial, e.g., adding study drug or placebo to patients already taking lithium. In addition, you may consider a relapse prevention trial to follow from the acute treatment trial, in which responders to acute treatment would be randomized to study drug or placebo, with follow-up observation for relapse for a period of 6 months or more with assessment of time to relapse and treatment of relapsed patients. As for the acute study, this trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms worsen to a clinically significant extent on assigned treatment. Both the acute and the relapse prevention trials should be limited to patients capable of giving assent to participate in the trial. In addition, given the concerns about placebo assignment to pediatric patients with mania, this study must have a Data Safety Monitoring Board to oversee its conduct in order to ensure that it is conducted safely.

In any event, as noted above, the trial must maximize the opportunity to detect a treatment effect of the drug, if there is one in this population. Specifically, if you perform a flexible dose ranging study that fails to detect an effect of the drug, this will not be considered to have met the requirements of this request. Therefore, we strongly recommend that the trial be a fixed dose study that includes fixed doses that fully explore the tolerated dose range in this population.

Pediatric Safety Study

- Safety data must be collected in the controlled efficacy trial. You may consider collecting longer-term safety data. The longer-term safety data could come from open studies, e.g., a longer-term open extension from the controlled efficacy trial and/or in separate longer-term open safety studies, or from controlled studies, e.g., a longer-term safety and efficacy trial. Adequate longer-term safety data from studies in a single indication would be sufficient to meet this requirement. The long-term safety data must be at or above the dose or doses identified as effective in an adequately designed trial, as described above. If an adequately designed and conducted effectiveness trial fails to detect a drug effect, you must still collect long-term safety data, at doses at least as high as the doses currently used in treating patients off-label with this drug.

Age Group in Which Study(ies) will be Performed –All Studies

Pediatric patients (ages 10 to 17 years) must be included in the sample, and there must be a reasonable gender and age distribution.

Number of Patients to be Studied

Pediatric Pharmacokinetic Study

- A sufficient number of patients to adequately characterize the pharmacokinetics of the study drug and its major active metabolite in the above age group.

Pediatric Efficacy and Safety Study

- The study must have a sufficient number of patients to provide 85% power to show a difference between drug and placebo equivalent to the median drug-placebo difference seen in adult trials

with this disorder. It will probably be necessary to conduct a multicentered study to ensure a sufficient population accurately diagnosed with mania.

Pediatric Safety Study

- A sufficient number of pediatric patients to adequately characterize the safety of the study drug at or above the dose or doses identified as effective in an adequately designed trial, or if this trial fails to detect a drug effect, at doses at least as high as the doses currently used in treating patients off-label with this drug. At least 100 patients exposed to drug for at least 6 months would be a minimum requirement for long-term safety.

Entry Criteria

The protocols must include a valid and reliable diagnostic method for recruiting and enrolling pediatric patients meeting DSM-IV criteria for mania. Given the difficulty in making the diagnosis for screening purposes, it is recommended that a clinical interview of children and their parents or caregivers be conducted by an adequately trained clinician (e.g. child psychiatrist) to assure accurate diagnosis. It is also recommended that the diagnosis be confirmed using a reliable and valid semi-structured interview.

Patient Evaluations and Study Endpoints

Pediatric Pharmacokinetic Study

- Pharmacokinetic assessments must be made with respect to the study drug and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite measured, the data collected must provide adequate estimates of important pharmacokinetic parameters, e.g., AUC, half-life, C_{max}, T_{max}, and apparent oral clearance (this parameter for parent only) in pediatric patients in the relevant age range. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available at [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacology (Draft)].

Pediatric Efficacy and Safety Study

- A scale specific to mania and sensitive to the effects of drug treatment of mania in the target population should be used. The choice of the primary assessment instrument and the primary outcome will need to be justified. Specifically, if you choose scales and outcomes used in adult studies, you will need to justify that these measures are appropriate for use in the pediatric population. Alternatively, you may perform preliminary trials to identify sensitive rating scales in this population. Justification of primary endpoint selection will be of particular concern if the definitive effectiveness trial fails to distinguish drug from placebo. It may also be useful to add a global measure, e.g., the Clinical Global Impression (CGI). It is essential to identify a primary outcome (or outcomes if more than one is considered important) for the controlled efficacy trial; ordinarily this would be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trial.

Pediatric Safety Study

- Routine safety assessments must be collected at baseline and appropriate follow-up times, i.e., vital signs (pulse rate and blood pressure), weight, height, clinical laboratory measures (chemistry, including serum prolactin, hematology, and urinalysis), ECGs, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias, using appropriate rating instruments). Although not a part of this Written Request, we remind you that it may be important to determine the effect of the study drug on the growth and development of pediatric patients, and we encourage you to consider longer-term studies of a year or more to address this question if the acute studies demonstrate efficacy in bipolar disorder.

Statistical Information

Pediatric Pharmacokinetic Study

- Descriptive analysis of the pharmacokinetic parameters.

Pediatric Efficacy and Safety Study

- This trial must have a detailed statistical plan. The trial should be designed with at least 85% statistical power to show a difference between drug and placebo equivalent to the median drug-placebo difference seen in adult trials for mania, at conventional levels (alpha=0.05, 2-tailed) of statistical significance.

Pediatric Safety Study

- Descriptive analysis of the safety data.

GENERAL REQUIREMENTS AND COMMENTS

Drug Information

Use age appropriate formulations in the studies described above. Since the pediatric patient population consists of pediatric patients (ages 10 to 17), your marketed solid dosage formulation should be adequate for these studies.

Drug Concerns

No specific concerns related to administration to schizophrenic or manic pediatric patients were identified while studying risperidone in adults, nor have specific concerns been identified during the postmarketing experience.

Labeling That May Result from the Studies

The pediatric schizophrenia and mania efficacy, safety, and pharmacokinetic studies described in this request could result in the addition to labeling of information pertinent to these studies.

Format of Reports to be Submitted

Full study reports or analyses, not previously submitted to the Agency, addressing the issues outlined in this request, with full analysis, assessment, and interpretation.

Timeframe for Submitting Reports of the Study(ies)

Reports of the above studies must be submitted to the Agency within 5 years from the date of this letter to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUD**Y" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIE**S" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIE**S" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, contact Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely yours,

{See appended electronic signature page}

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

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

/s/

Rachel Behrman

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