DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-121

McNeil Consumer & Specialty Pharmaceuticals
Attention: Susan Cousounis
Assistant Director, Regulatory Development
7050 Camp Hill Road
Fort Washington, PA 19034

Dear Ms. Cousounis:

Reference is made to your Proposed Pediatric Study Request submitted on April 7, 2003.

To obtain needed pediatric information on Concerta® (methylphenidate HCl) Extended-release Tablets, 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 Attention Deficit Hyperactive Disorder (ADHD), as described below.

ADOLESCENT ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

General Advice for Developing a Drug for Adolescent ADHD

Attention deficit hyperactivity disorder (ADHD) has been recognized as a common pediatric disorder. Although there is recent recognition of ADHD as a disease of adulthood as well, drug development and the published literature for this indication has focused primarily on the pediatric population where treatment of this disorder is most prevalent.

Under FDAMA, 1997, adequate assessment of adolescents with ADHD (data sufficient to support a labeling claim) might be based on a single study in adolescent patients with this disorder, together with confirmatory evidence from another source, in particular, data from children with this 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 would require that the child data be considered reasonably relevant to the course of the disease and the effects of the drug in the adolescent population. We believe that there is a very strong argument for continuity between childhood and adolescent ADHD, such that an adolescent claim for a drug already approved for ADHD in children could be supported by a single, independent, adequate and well-controlled clinical trial in adolescent ADHD. In addition, an adolescent ADHD program would need to include pharmacokinetic information and safety information in the relevant adolescent age group. For adolescent ADHD, we consider the relevant age group to include patients aged 13-17.

At this point in time, we are not requesting that you assess the preschool population, even though there is now fairly wide agreement that ADHD is a recognizable entity in this younger population. One difficulty is a lack of validated diagnostic and assessment methods for this younger population. In general, the methodology for conducting studies in the preschool age group has not been well-established, and this would serve as a barrier to the conduct of such trials.

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.

Specific Study Requirements for Development Program in Adolescent ADHD

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 ADHD, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the adolescent 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," may 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. 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 to 4 weeks. 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. In addition, we recommend that you consider a relapse prevention trial to 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, with assessment of time to relapse and treatment of relapsed patients.

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. 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 typically used in treating patients with this drug.

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

Adolescents (ages 13 to 17 years) must be included in these studies, and there must be a reasonable gender (at least 25% female) and age distribution within these studies.

Number of Patients to be Studied

Pediatric Pharmacokinetic Study

- A sufficient number of patients (with a minimum of 12 patients for a traditional pharmacokinetic study) to adequately characterize the pharmacokinetics of dextro- and levo-methylphenidate 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 clinical trials that were the basis for this drug's approval in children. It will probably be necessary to conduct a multicentered study to ensure a sufficient population.

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 typically used in treating patients 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 ADHD. Given the difficulty in making the diagnosis for screening purposes, it is recommended that a clinical interview of adolescents 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 dextro- and levo-methylphenidate. For each of dextro- and levo-methylphenidate, the data collected must provide adequate estimates of important pharmacokinetic parameters, e.g., AUC, half-life, Cmax, Tmax, and apparent volume of distribution and oral clearance (this parameter for parent only) in pediatric patients in the relevant age range. If you are planning to obtain pediatric pharamacokinetic information from the efficacy and safety trial using a population approach with sparse sampling, the sampling strategy needs to cover all doses within the therapeutic dose range and a full range of sampling times subsequent to dosing in order to fully characterize the pharmacokinetics of this drug in the adolescent population. 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

- An instrument specific to ADHD and sensitive to the effects of drug treatment of ADHD in the target population must be used. The choice of the primary assessment instrument and the primary outcome will need to be justified. Specifically, if you choose instruments and outcomes used in child studies, you will need to justify that these measures are appropriate for use in the adolescent population. Alternatively, you may perform preliminary trials to identify sensitive rating instruments 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, for ADHD, this would be change from baseline to endpoint on some measure of ADHD.

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 (using a stadiometer), clinical laboratory measures (chemistry, hematology, and urinalysis), ECGs, and monitoring for adverse events. Tanner staging should be obtained for all subjects. In addition, there is concern that drugs in this class may have even longer-term effects on growth and development. Thus, you must commit to obtaining at least 2 year follow-up data on a cohort of patients who are treated chronically. This could include patients continued from the controlled trial and also patients recruited specifically for longer-term follow-up. The outcomes of interest would be height and weight, obtained at roughly 4 month intervals. While the actual follow-up data from this 2 year, open label study would not be

required as part of your response to the Written Request, you must commit to obtaining such follow-up and provide a detailed plan in your response for such follow-up.

Statistical Information

Pediatric Pharmacokinetic Study

- Descriptive analysis of the pharmacokinetic parameters. The data analysis plan must address the effect of covariates such as age, body weight, and gender on pharmacokinetic parameters such as apparent volume of distribution and half-life. The pharmacokinetic parameters derived from the adolescent population should be compared to historical values from adults and children ages 6 to 12.

Pediatric Efficacy Study

- This trial must have a detailed statistical plan. The trial must 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 child 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 must be included. Growth curve data, i.e., height and weight, may be used to assess growth in open label studies by using z-scores. The z-score is the number of standard deviations a patient is from his/her gender/age standardized mean. Each subject's z-score should be determined at the beginning and again at the end of the observation period. If the mean change in the z-score is negative, then the group did not grow as expected based on normal population data. These calculations should be done for both height and weight.

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 13 to 17), your marketed solid dosage formulation should be adequate for these studies.

Drug Concerns

Specific concerns related to administration of any stimulants to pediatric patients, including Concerta®, are effects on appetite and possible effects on growth and development.

Labeling That May Result from the Studies

The adolescent ADHD 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 not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.

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. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

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 STUDY" 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 STUDIES" 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 STUDIES" 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, please contact Ms. Anna Marie H. Weikel, R.Ph., Senior Regulatory Health Project Manager, at (301) 594-5535.

Sincerely yours,

{See appended electronic signature page}

Rachel Behrman, M.D.
Deputy 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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