DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-634
NDA 20-635
NDA 21-721

Ortho-McNeil Pharmaceutical, Inc.
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Ms. Cynthia Chianese
Director, Regulatory Affairs
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869

Dear Ms. Chianese:

Please refer to your correspondence, dated and received on May 22, 2006, requesting a change to FDA's May 19, 2006 Written Request for pediatric studies for levofloxacin.

We have reviewed your proposed change and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supersedes the Written Requests dated December 20, 2001, April 1, 2004, December 19, 2005, and May 19, 2006.

In the design of these studies, consideration is given to the fact that systemic use of levofloxacin has been associated with arthropathy in juvenile animals and developing a quality safety database to better understand the safety profile of this drug in the pediatric population is needed. Obtaining information on the true incidence of rare, serious adverse events in this population, including persistent and disabling arthropathy, as well as gaining additional safety data in pediatric patients with community acquired pneumonia (CAP) including pneumonia due to penicillin-resistant *S. pneumoniae* is needed. In particular, determining if pediatric use of levofloxacin will predispose to musculoskeletal abnormalities following exposure is needed.

Type of Studies:

Study 1: A prospective, randomized, multicenter, comparative, study in the pediatric population 6 months of age to 16 years of age with CAP. The study will compare levofloxacin (orally, intravenously or sequentially) with an established active non-fluoroquinolone antimicrobial control.

Study 2: A study to evaluate the safety, tolerability, and pharmacokinetics of levofloxacin following intravenous administration of single doses to pediatric patients ages 6 months to 12 years.

Study 3: A study to evaluate the safety, tolerability, and pharmacokinetics of levofloxacin following intravenous and oral tablet administration of single doses to older pediatric patients ages 8 to 16 years.

Study 4: A study to evaluate the safety, tolerability, and pharmacokinetics of levofloxacin following administration of single doses of levofloxacin oral suspension to pediatric patients ages 6 months to 16 years.

Study 5: A prospective, multicenter, comparative, active-controlled pediatric study to evaluate long-term musculoskeletal adverse events occurring during the first year following levofloxacin or non-quinolone antimicrobial control drug exposure in pediatric patients. This study may include some patients that were initially treated in Study 1.

Indication to be Studied (Objective):

Study 1: A prospective, randomized, multicenter, comparative, study in the pediatric population 6 months of age to 16 years of age with CAP. The study will compare levofloxacin (orally, intravenously, or sequentially) with an established active non-quinolone antimicrobial control.

The study will address several safety and efficacy concerns of particular importance in children. These include the efficacy in patients with pneumonia and concurrent bacteremia, as well as in pneumonia complicated by empyema. As part of the evaluation of the efficacy of levofloxacin treated pediatric patients with CAP complicated by empyema, the concentration of levofloxacin should be determined in the pleural fluid obtained from the empyema. The concentration of levofloxacin in plasma should also be determined at the same time that the pleural fluid sample was obtained in these patients. An evaluation of the penetration of levofloxacin into pleural fluid relative to plasma should be determined.

Additionally, the pharmacokinetics of levofloxacin at steady state will be determined in a subset of levofloxacin-treated pediatric patients with CAP over the entire range of ages from 6 months to 16 years using a population pharmacokinetic approach with sparse sampling (e.g., approximately 1 to 2 samples per patient at recorded times).

Safety concerns include musculoskeletal adverse events including potential bone and joint toxicity, which should be addressed in the study. Approximately 50% of patients will be less than 5 years of age.

Studies 2, 3, and 4: The primary objective for these studies will be to characterize the plasma pharmacokinetics, safety, and tolerability of single intravenous and oral doses of levofloxacin in pediatric patients.

Study 5: The primary objective of this study will be to evaluate the overall incidence of musculoskeletal adverse events occurring in children after their exposure to either levofloxacin or non-quinolone antimicrobial therapy for an acute bacterial infection in a minimum of 1000 pediatric patients treated with levofloxacin and 700 pediatric patients treated with a non-quinolone antimicrobial and followed up for 1 year. A minimum of 20% of patients will be less than 5 years of age.

The dose, dosage form (IV solution, oral suspension, or oral tablet), route of administration, and time of switch (from IV to oral therapy) should be selected based on the clinical judgment of the treating physician. Follow up of all patients will be for at least one year. Those patients identified with

musculoskeletal adverse events including tendon or joint disorders during this period that are considered to be possibly, probably, or likely related to exposure to levofloxacin or comparator will be asked to undergo evaluation until resolution or yearly for five years if resolution does not occur before.

Age Groups in which Study will be Performed:

Study 1: The following age groups will be studied: ≥ 6 months to < 5 years and ≥ 5 years to < 17 years. Approximately 50% of the study population will consist of patients ≤ 5 years of age.

Study 2: The following age groups of male and female pediatric patients should be studied: 6 months to ≤2 years, >2 years to ≤5 years, and >5 years to 12 years. Patients should be approximately evenly distributed across the age range within each of the age groups.

Study 3: The following age groups of male and female pediatric patients should be studied: 8 to <12 years and ≥12 to 16 years. Patients should be approximately evenly distributed across the age range within each of the age groups.

Study 4: The following age groups of male and female pediatric patients should be studied: 6 months to <2 years, ≥2 years to <5 years, ≥5 years to <10 years, ≥10 years to <12 years, and ≥12 years to 16 years. Patients should be approximately evenly distributed across the age range within each of the age groups.

Study 5: The following age groups of male and female pediatric patients should be studied: ≥ 2 months but < 24 months, ≥ 2 years through < 6 years, ≥ 6 years through < 12 years, and ≥ 12 years through < 17 years. A minimum of 20% of the study population will consist of patients ≤ 5 years of age.

Number of Patients to Be Studied or Power of Study to be Achieved:

Study 1: To determine efficacy of levofloxacin for pediatric patients with CAP, the study will include approximately 480 patients randomized to receive levofloxacin and approximately 160 control patients. Additionally, plasma samples for pharmacokinetic analysis will be obtained from a minimum of 100 levofloxacin treated pediatric patients from Study 1. Pleural fluid and corresponding plasma samples should also be obtained for levofloxacin-treated pediatric patients with CAP complicated by empyema.

Studies 2, 3, and 4: The number of patients enrolled into these studies should be sufficient to allow for adequate characterization of the pharmacokinetics of levofloxacin in pediatric patients in each of the age groups described above. The minimum number of evaluable pediatric patients in each of the age groups (age strata) specified in each study specified is 6, corresponding to a minimum of 18 patients in Study 2, a minimum of 12 patients in Study 3, and a minimum of 30 patients in Study 4.

Study 5: For the purpose of completing the entire study, approximately 1000 levofloxacin-treated patients and approximately 700 non-quinolone antimicrobial-treated patients will be enrolled and complete 1 year of follow-up.

Study Endpoints and Timing of Assessments:

Study 1: This study will evaluate the safety and efficacy of levofloxacin and a non-quinolone control drug in the treatment of pediatric patients with CAP. Patients will be assessed for the development of any adverse event, including any serious adverse event, with particular attention to musculoskeletal events that occur during treatment (day 1-7) and at 10-35 days following levofloxacin or non-quinolone control drug exposure. Clinical evaluations of the musculoskeletal system (including gait/joint examination) should be performed at least once during treatment (day 1-7), at 10-35 days and at 1 year following levofloxacin or non-quinolone control drug exposure; patients may be enrolled into Study 5 to complete the 1 year follow up. Special emphasis should be placed on the evaluation of musculoskeletal adverse event rates using all applicable WHOART "Musculoskeletal and Connective Tissue Disorders" body systems. Gait/joint examinations should be performed by rheumatologists, trained physical therapists experienced in musculoskeletal examinations or clinicians who are trained to perform developmentally appropriate and thorough examination of the musculoskeletal system. Pediatric rheumatologic follow-up should be obtained if any signs or symptoms suggestive of musculoskeletal adverse events develop. Patients who develop joint effusions should have joint fluid evaluations. Patients who develop arthropathy, defined as joint disease diagnosed by a physician experienced in evaluating the musculoskeletal system, should be evaluated with the goal of establishing the cause and extent of the disease.

Efficacy evaluations including clinical and microbiological assessments of children with CAP should also be performed at approximately 1-7 days and 10-35 days following levofloxacin or control drug exposure.

Studies 1, 2, 3, and 4: These studies will determine the relevant pharmacokinetic parameters so that appropriate dosing recommendations for the intravenous and oral administration of levofloxacin for the treatment of target infections (e.g., CAP, complicated urinary tract infections, and pyelonephritis) in the pediatric population, including those patients with varying degrees of renal function (i.e., normal to impaired), may be made. In each of these studies, pharmacokinetic characterization of levofloxacin in pediatric patients may be determined using a traditional (or dense) pharmacokinetic sampling scheme, or alternatively, a population pharmacokinetic approach using a sparse sampling scheme. With the latter population pharmacokinetic approach, approximately 2 to 3 samples per patient staggered at various times throughout the dosing interval should be obtained. [1]

Study 5: The objective of the study is to assess all adverse events, including serious adverse events that occur at 1-7 days and 10-35 days following levofloxacin or non-quinolone control drug exposure and to also assess the development of any musculoskeletal adverse events that occur within 1 year following levofloxacin or non-quinolone control drug exposure. The reversibility of all adverse events should be identified and the severity of adverse events should be characterized. Patients should receive two structured assessments for general, neurological, and musculoskeletal safety, i.e., evaluations of the joints (especially all weight-bearing joints) and gait. These should be conducted 1-7 days after the initiation of therapy and at approximately 10-35 days following exposure. At the end of the first year, a trained interviewer should perform an assessment. All patients that report musculoskeletal adverse

[1] In Study 1, approximately 1 to 2 samples per patient will be obtained, as written under "***Indication to be Studied (Objective*)*:"*** Study 1 on page 2 of this document.

events, in WHOART "Musculoskeletal and Connective Tissue" body systems, will be asked to undergo evaluation until resolution or yearly for 5 years if resolution does not occur before. Definitions pertaining to musculoskeletal adverse events and causality attributions should be developed. Such case definitions should be applied to individual adverse events by an independent Data Safety Monitoring Committee. Pediatric rheumatologic evaluation should be obtained if any signs or symptoms suggestive of arthropathy develop. Patients who develop joint effusions should have joint fluid evaluations. Patients who develop arthropathy, regardless of the degree of severity, should undergo MRI (or other appropriate imaging technique) of the affected joint.

Study Evaluations:

Studies 1, 2, 3, and 4: The pharmacokinetic parameters of levofloxacin will be determined (e.g., Cmax, Tmax, AUC, clearance, and half-life). Sparse plasma samples obtained after dosing to steady state will be used to determine the pharmacokinetics of levofloxacin in the pediatric population with CAP (**Study 1**). Covariates such as age, body weight, and renal function, which may affect the pharmacokinetics of levofloxacin in the pediatric patient population, will also be evaluated across these four studies.

Study 5: Evaluation of pediatric patients will be made at baseline, approximately 10-35 days and 1 year following treatment. All patients that report having a musculoskeletal adverse event will be asked to undergo evaluation until resolution or yearly for 5 years if resolution does not occur before. Attempts should be made by the investigator to obtain the reason for the loss to follow-up if a patient does not undergo the yearly evaluation.

Drug Information:

Study 1:

Dosage Forms*:*	I.V. solution, oral tablet, or oral suspension
Regimen:	The levofloxacin dosage regimen should be determined by pharmacokinetic studies; comparator dosage regimens are those currently approved for pediatric patients.
Route of Administration*:*	Intravenous or Oral

Study 2:

Dosage Form:	I.V. solution
Regimen:	7 mg/kg single dose to a maximum dose of 500 mg
Route of Administration:	Intravenous

Study 3:

Dosage Forms:	I.V. solution and oral tablet
Regimen:	7 mg/kg single dose to a maximum dose of 500 mg
Route of administration:	Intravenous and Oral

Study 4:

Dosage Form:	Oral suspension
Regimen:	7 mg/kg single dose to a maximum dose of 500 mg
Route of Administration:	Oral

Study 5:

Dosage Forms*:*	I.V. solution, oral tablet, or oral suspension
Regimen:	The levofloxacin dosage regimen should be determined by pharmacokinetic studies
Route of Administration*:*	Intravenous or Oral

Drug-Specific Safety Concerns:

Studies 1, 2, 3, 4, and 5: The development of arthropathy, arthritis, or neurologic events is the major safety concern.

Studies 1 and 5: In addition to the above, any reported adverse events under the WHOART "Musculoskeletal and Connective Tissue Disorders" body systems.

Statistical Information and Power of the Study:

Study 1: The study will enroll approximately 480 levofloxacin-treated patients and 160 comparator-treated patients. This sample size is based on the confidence interval approach for establishing non-inferiority and the following assumptions: a 3:1 randomization, a 90% cure rate for both treatment arms, 78% clinical evaluability rate, a 95% confidence interval, and a 10% non-inferiority margin.

Studies 2, 3, and 4: For pharmacokinetic analyses, see the section ***Number of Patients to be Studied***.

Study 5: The study will enroll approximately 1000 levofloxacin-treated patients and approximately 700 non-quinolone antimicrobial-treated patients who complete follow-up through 1 year. This sample size is based on providing 95% confidence that the serious adverse event rate is no greater than 1 in 333 (0.3%) in patients if no serious adverse event is observed among 1000 levofloxacin-exposed patients.

Statistical Analyses of Data to be Performed:

Study 1: Adverse event rates for both treatment arms will be calculated for all adverse events. Comparative statistical analyses will be used for clinical and bacteriological assessments.

Studies 2, 3 and 4: Pharmacokinetic analyses will be performed to determine pharmacokinetic parameters in the pediatric population that will allow for adequate pediatric dosing recommendations. Descriptive statistics of the pharmacokinetic parameters of levofloxacin will be provided. Additionally, age should be treated as a continuous variable and as a categorical variable in these pharmacokinetic analyses.

Study 5: Adverse events rates will be calculated for all events. Ninety-five percent confidence intervals should be calculated for the rates of all musculoskeletal adverse events and serious adverse events occurring through the evaluations at approximately 10-35 days following levofloxacin or non-quinolone control drug exposure. Ninety-five percent confidence intervals should be calculated for the rates of all musculoskeletal adverse events occurring after the visit at approximately 10-35 days through the one year follow-up visit. Rates and confidence intervals will be generated separately for levofloxacin-treated and non-quinolone antimicrobial-treated pediatric patients. Lifetime tables should be provided to present cumulative incidence rates for events occurring at these time points in the levofloxacin and non-quinolone comparator groups, for all patients as well as stratified by pubescence stage (where prepubescence is defined as girls < 9years, boys <11years, pubescence is defined as girls 9-14 years, boys 11-15 years, and postpubescence is defined as girls >14 years and boys >15 years).

Labeling that may Result from the Studies: These studies will provide safety information including the incidence of musculoskeletal adverse events for levofloxacin in pediatric patients. Information regarding the proper dose for safe and efficacious use in pediatric patients with serious infections will also be provided. Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of Reports to be Submitted: Full study reports of requested Studies 1, 2, 3, 4, and 5 not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. As an alternative, you may submit an abbreviated study report along with all data in electronic form, with a case report form annotated with the names of the SAS variables used for each blank on the form. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity, one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for Submitting Reports of the Studies: Reports of each of the studies must be submitted to the Agency on or before August 1, 2010. 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 report of the study 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.

Animal Study: Post-Dosing Arthrotoxicity Susceptibility Study

An animal study designed to evaluate the potential for levofloxacin to cause latent arthrotoxicity in the juvenile dog model should be performed. Juvenile dogs should be dosed for a period of 7 to 14 days at three discrete dose levels (high, middle, and low) of levofloxacin. A no-treatment control group should be included. The study design should include the sacrifice of 3 dogs from both sexes per dose level at 24 hours following the final dose and at 6 to 9 months of age. Gross pathology, histopathology, and electron microscopic analysis of chondrocytes should evaluate all weight-bearing joints and growth plates (where present) from each dog.

A full study report of the requested animal study, including full analysis, assessment, and interpretation, will be submitted in the usual format. Reports of the study must be submitted to the Agency on or before August 1, 2010. 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 report of the study in response to this Written Request.
Reports of the studies that meet the terms of the Written Request dated December 20, 2001, as amended April 1, 2004, and by this letter must be submitted to the Agency on or before August 1, 2010, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

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. 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.

Submit reports of the studies as supplements to the approved NDAs with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, send a copy of the cover letter of your submission, by 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.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur with 180 days of supplement submission, will

apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, 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.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

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, call Rebecca D. Saville, Pharm.D., Regulatory Project Manager, at 301-796-1600.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D., M.P.H.
Director
Office of Antimicrobial Products
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/

Edward Cox
6/16/2006 09:29:30 AM
for Mark J. Goldberger, MD MPH