DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT # 5

NDA 21-153

AstraZeneca LP
Attention: George A. Kummeth
Global Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Kummeth:

Please refer to your correspondence dated May 9, 2007, requesting changes to FDA's December 31, 2001, Written Request for pediatric studies for esomeprazole magnesium.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on December 31, 2001, and as amended on December 18, 2002, May 7, 2004, December 20, 2005, and March 29, 2007, remain the same.

- In Study 1, your request to add a repeated dose only study has been included.

- In Study 2, your request to add a repeated dose only study has been included.

- In section "Additional Information needed:" your proposal to perform a 26-week carcinogenicity study of omeprazole in p53(+/-) transgenic mice as bridging information for esomeprazole has been accepted.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated December 31, 2001, as amended by this letter and by previous amendments dated December 18, 2002, May 7, 2004, December 20, 2005, and March 29, 2007, must be submitted to the Agency on or before December 31, 2008, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / supplement to an approved NDA 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, via fax (301-827-5911) 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, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC**

STUDIES" in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval), 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice in accordance with section 505A(e)(2).

Under section 505A(j) of the Act, regardless of whether the studies demonstrate that esomeprazole magnesium is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. 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).

Finally, please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

If you have any questions, call Chantal Phillips, Regulatory Project Manager, at 301-796-2259.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III, HFD-103
Center for Drug Evaluation and Research

Attachment

Types of Studies:
As used in this Written Request, a *preterm infant* is an infant who has completed less than 37 complete weeks of gestation. A *term infant* is an infant that has completed 37-42 weeks gestation, and a *post-term infant* is an infant that has completed more than 42 weeks gestation. For preterm infants, *corrected age* is the sum of the gestational age and the age since birth. For example, a preterm infant born after 32 weeks gestation for which 12 weeks have elapsed since birth has a corrected age of 44 weeks. The *neonatal period* is the first 28 days since birth.

STUDY 1: PHARMACOKINETIC (PK), PHARMACODYNAMIC (PD) AND SAFETY STUDY IN NEONATES AND PRE-TERM INFANTS WITH A CORRECTED AGE LESS THAN 44 WEEKS

Inclusion Criteria: To be included in Part A of this study, infants will: (a) be monitored patients admitted to a newborn intensive care unit (NICU) or special care nursery at the time of enrollment in the study, be considered candidates for acid suppressive therapy to treat a presumptive diagnosis of GERD, (c) either be term or post-term infants within the neonatal period, or be preterm infants with a corrected age of less than 44 weeks, and (d) have a body weight of at least 800 grams. Patients of both sexes will be enrolled in this part of the study.

You may do this as a repeated dose study as indicated below.

Repeated dose study: This will be a repeated dose PK, PD, and safety evaluation of esomeprazole magnesium. The dose level(s) and frequency of dosing used in this study will be selected based on a justification from available pharmacokinetic/dynamic data. If more than one dosage regimen is evaluated, patients will be randomly allocated to treatment groups in approximately equal proportions. The duration of exposure should be 5-7 days. At least 12 patients per treatment group will complete this phase of the study if a standard PK approach is used. Alternatively, a population PK approach may be used given difficulties in obtaining adequate samples in small infants with a limited circulating blood volume. Pharmacodynamic assessments of intragastric and/or intraesophageal pH will be performed in at least six patients who require tube placement or pH monitoring for clinical management. These patients may be already enrolled in the study described here, or other patients not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

STUDY 2: PHARMACOKINETIC, PHARMACODYNAMIC AND SAFETY STUDY IN PEDIATRIC PATIENTS 1 TO 11 MONTHS OF AGE

Inclusion Criteria: To be included in this study, infants will (a) be patients considered to be candidates for acid suppressive therapy because of a presumptive diagnosis of GERD, and (b) either be a term or post-term infant beyond the neonatal period but less than 12 months of age, or else be a preterm infant with a corrected age of at least 44 weeks but less than 12 months. Patients of both sexes will be enrolled in this part of the study.

You may do this as a repeated dose study indicated below.

Repeated Dose Study: This will be a repeated dose PK, PD, and safety evaluation of esomeprazole magnesium in pediatric patients. The study will be designed to characterize the change in gastric and/or esophageal pH after repeated doses of esomeprazole magnesium. The dose level(s) and frequency of dosing used in this study will be selected based on a justification from available pharmacokinetic/dynamic data. The duration of exposure should be 5-7 days. If more than one dosage regimen is evaluated, patients will be randomly allocated to treatment groups in approximately equal

proportions. At least 12 patients per treatment group will complete pharmacokinetic assessments if a standard PK approach is used. Alternatively, a population PK approach may be used. Pharmacodynamic assessments of intragastric and/or intraesophageal pH will be performed in at least six patients who require tube placement or pH monitoring for clinical management. These patients may be already enrolled in the study described here, or other patients not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

STUDY 3: EFFICACY AND SAFETY EVALUATION OF PEDIATRIC PATIENTS 1 TO 11 MONTHS OF AGE

Inclusion Criteria: To be included in this study, infants will (a) be patients with a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD, and (b) either be a term or post-term infant beyond the neonatal period but less than 12 months of age, or else be a preterm infant with a corrected age of at least 44 weeks but less than 12 months. Patients of both sexes will be enrolled in this part of the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from this part of the study.

The method by which the clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD is made will be recorded and summarized for each patient. These summaries will include the clinical history and results of laboratory tests used to establish the diagnosis (e.g., pH probe, gastroesophageal endoscopy, radionuclide milk study). Results from such laboratory tests will be provided regardless of whether they supported the final clinical diagnosis or not.

Design: This will either be a multicenter, treatment-withdrawal evaluation or a parallel group placebo controlled study of the efficacy and safety of esomeprazole magnesium.

Treatment Withdrawal Evaluation

Design: This will be a multicenter, treatment withdrawal evaluation of the efficacy and safety of esomeprazole magnesium in which treatment withdrawal is randomized, double-blind and placebo controlled. The dosage(s) of esomeprazole magnesium used in this part of the study will be selected as dosages likely to be therapeutically effective and safe based on data obtained from Study 2, and as suggested by the results of other studies (e.g., literature studies of pediatric patients). The number of patients per treatment group required to complete this part of the study is described in the **Statistical Information** section. Independent data review committees (e.g., for safety, efficacy or both) may be established to review accumulating data to detect early evidence of great benefit or harm of treatment.

Run-in Phase: All patients will receive esomeprazole magnesium in this phase. Treatment in this phase will be of sufficient duration to ensure that gastric acid suppression by esomeprazole magnesium is at steady state. An open-label design is acceptable. The reasons for any patient discontinuations during this phase of the study (e.g., lack of therapeutic response, adverse event) will be captured in detail.

Withdrawal Phase: At the conclusion of the run-in phase, patients will be randomly assigned (in approximately equal proportions) in a double-blind fashion to continue receiving their current dosage of esomeprazole magnesium or to receive matching placebo. Outcome measures will be assessed weekly: at clinic visits that occur at least once every other week, as well as by other appropriate means (e.g., telephone questionnaire) during weeks in which no clinic visits are scheduled. For example, telephone evaluations may be made to assess compliance, adverse events and other clinical outcomes.

Following randomization, patients will be followed closely to allow for prompt discontinuation from randomized study treatment if clinically appropriate. The protocol will define discontinuation criteria for patients who have adverse events or fail therapy during the withdrawal phase. Patients who are removed from randomized study treatment will be given appropriate alternative medical therapies.

Placebo-Controlled Design: Alternatively, a parallel group placebo controlled design may be used. This design will also consider dosing, randomization, stratification, concomitant medications, and other study elements, as mentioned above for the treatment withdrawal design.

STUDY 4: PHARMACOKINETIC, EXPOSURE/RESPONSE, AND SAFETY STUDY IN PEDIATRIC PATIENTS 1 TO 11 YEARS OF AGE

Pharmacokinetic Component:

Part 1 (single dose)

Inclusion criteria: To be included in this study, patients will (a) be 1 to 11 years of age inclusive, (b) have endoscopically proven GERD, and (c) have had endoscopic examination as part of their diagnostic evaluation. Patients of both sexes will be enrolled in the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from the study.

This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of esomeprazole magnesium. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Part 2 (repeated dose)

Inclusion criteria: To be included in this study, patients will (a) be 1 to 11 years of age inclusive and (b) have symptomatic GERD. Patients of both sexes will be enrolled in the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from the study.

This will be a repeated-dose pharmacokinetic and safety study of at least two dose-levels of esomeprazole magnesium. Patients will be randomly allocated to treatment groups in approximately equal proportions. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Exposure/Response Component

Inclusion criteria: To be included in this study, patients will (a) be 1 to 11 years of age inclusive, (b) have endoscopically proven GERD, and (c) have had endoscopic examination as part of their diagnostic evaluation. Patients of both sexes will be enrolled in the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from the study.

This will be a randomized, double blind, dose-ranging study of esomeprazole magnesium. The dosages of esomeprazole magnesium used in this study will be selected as dosages likely to be therapeutically effective and safe, based on data from the pharmacokinetic component of this study as well as from other studies in pediatric patients and adults. Eligible patients will be randomized in approximately equal proportions to one of at least two dose levels of esomeprazole magnesium. After randomization, the overall duration of the trial will be at least eight weeks. Outcome measures will be assessed weekly: at clinic visits that occur at least once every other week, as well as by other appropriate means (e.g., telephone questionnaire) during weeks in which no clinic visits are scheduled.

For example, telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes. At least 40 patients 1 to 5 years of age and 40 patients 6 to 11 years of age will complete at least 8 weeks treatment.

STUDY 5: PHARMACOKINETIC AND SAFETY STUDY IN PEDIATRIC PATIENTS 12 TO 16 YEARS OF AGE

Inclusion criteria: To be included in this study, patients will (a) be 12 to 16 years of age inclusive, and (b) have a clinical diagnosis of suspected GERD, symptomatic GERD or endoscopically proven GERD. Endoscopy is not required for study entry or participation. Patients of both sexes will be enrolled in the single- and repeated-dose components of the study as well as in the eight-week safety component.

Pharmacokinetic Component:

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of esomeprazole magnesium. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeated-dose pharmacokinetic and safety study of at least two dose-levels of esomeprazole magnesium. Patients will be randomly allocated to treatment groups in approximately equal proportions. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Combined: Phase 1 and Phase 2 can be combined into one study
This will be a randomized, single and repeated dose pharmacokinetic, pharmacodynamic, and safety evaluation of at least two doses of lansoprazole. The duration of exposure should be 5-7 days. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 24 patients (i.e., at least 12 per dose group) will complete this study if a standard PK approach is used. Alternatively, a population PK approach may be used given difficulties in obtaining adequate samples in small infants with a limited circulating blood volume. Pharmacodynamic assessments of intragastric and/or intraesophageal pH will be performed after single and repeated doses in at least six patients who require tube placement or pH monitoring for clinical management. These patients may be already enrolled in the study described here, or other patients not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

Eight-week Safety Component:

This will be a multicenter safety study of esomeprazole magnesium. An open-label, non-randomized design is acceptable. Dosages of esomeprazole magnesium used in this study will be selected as dosages likely to be therapeutically effective and safe based on data from the pharmacokinetic component of this study as well as from other studies in pediatric patients and adults. Patients will be treated for at least eight weeks. Outcome measures will be assessed weekly: at clinic visits that occur at least once every other week, as well as by other appropriate means (e.g., telephone questionnaire) during weeks in which no clinic visits are scheduled. For example, telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes. At least 100 patients will complete at least eight weeks of treatment.

INDICATION TO BE STUDIED:

Treatment of gastroesophageal reflux disease (GERD)

OBJECTIVES AND RATIONALE:

Studies 1 and 2:

(a) To characterize the pharmacokinetic/pharmacodynamic profile of repeated doses of esomeprazole magnesium in neonates, pre-term infants, with a corrected age less than 44 weeks, and pediatric patients 1-11 months and to compare these profiles with those in adults and older pediatric patients.

(b) To collect information on the safety of single and repeated doses of esomeprazole magnesium.

Study 3:

(a) To obtain efficacy data for esomeprazole magnesium in pediatric patients 1 to 11 months of age.

(b) To assess the safety of esomeprazole magnesium in pediatric patients 1 to 11 months of age.

Study 4:

(a) To characterize the pharmacokinetic profile of single and repeated doses of esomeprazole magnesium in patients 1 to 11 years of age.

(b) To compare the safety and clinical outcome of pediatric patients 1 to 11 years of age with endoscopically proven GERD across different dosages of esomeprazole magnesium.

(c) To determine the proportion of patients showing endoscopic evidence of healing after completion of therapy across different dosages of esomeprazole magnesium in those pediatric patients 1 to 11 years of age who undergo follow-up endoscopy after treatment.

Study 5:

(a) To characterize the pharmacokinetic profile of single and repeated doses of esomeprazole magnesium in patients 12 to 16 years of age.

(b) To collect information on the safety of single and repeated doses of esomeprazole magnesium in pediatric patients 12 to 16 years of age.

STUDY EVALUATIONS AND ENDPOINTS:

Pharmacokinetics: In the PK studies, appropriate pharmacokinetic parameters will be assessed (e.g., AUC, apparent clearance, T_{max}, $T_{1/2}$, apparent volume of distribution, C_{max}, and others as appropriate). Pharmacokinetic characteristics following repeated dose will be evaluated.

Pharmacodynamics: In the PD studies, appropriate pharmacodynamic parameters will be assessed (e.g., AUC of the gastric H+ concentration over time, intraesophageal pH, gastric pH, percentage of time gastric pH>4, and percentage of time gastric pH>3). Pharmacodynamic assessments will be made just prior to dosing and at appropriate intervals after dosing to encompass the duration of drug effect. For patients receiving repeated doses, pharmacodynamic assessments will be made at baseline (i.e., before therapy) and after the final esomeprazole magnesium dose.

Safety and tolerability: In each study, the evaluation of safety will include a physical examination and clinical laboratory assessment before treatment and, at a minimum, after completion of the pharmacokinetic, pharmacodynamic, or clinical-outcome assessments. Assessment of adverse events will occur throughout each patient's study participation. Patients will be followed until adverse events have been adequately resolved. Withdrawals from the studies because of serious adverse events or

treatment failure will be documented fully, as will the use of any rescue medications. All patients will be followed at least 2 weeks after final administration of test medication.

Other clinical outcomes and endpoints:

Study 3: Supraesophageal and airway complications associated with GERD; GERD signs and symptoms (e.g., vomiting/regurgitation; irritability); growth parameters (including weight and height/length); frequency, severity, and duration of aspiration and wheezing; compliance.

Study 4: Signs and symptoms of pediatric GERD, concomitant antacid consumption, physical well-being.

DRUG INFORMATION:

The studies described above should use an age-appropriate formulation of esomeprazole magnesium. The relative bioavailability of these age-appropriate formulations should be determined and compared with the marketed formulation of esomeprazole magnesium. Full study reports of any relative bioavailability studies must be submitted to the Agency. If age-appropriate formulations cannot be developed, complete documentation of your attempts and a detailed explanation of why the attempts were unsuccessful must be submitted. Under these circumstances other formulations can be used, if they are standardized, palatable, and shown in adults to be of acceptable relative bioavailability (compared with the marketed product).

STATISTICAL INFORMATION:

In each pharmacokinetic study, the pharmacokinetic parameters of esomeprazole magnesium may be summarized using descriptive statistics. In each pharmacodynamic study, the pharmacodynamic analysis will include an assessment of the time course of change of intragastric or intraesophageal pH, along with an assessment of dose effects. Mean ($\pm$SD) and median AUC for hydrogen ion secretion over the evaluation period will be calculated and compared among the doses.

In Study 3, treatment regimens will be compared with regard to clinical outcomes using appropriate statistical methods. A sufficient number of patients will complete the study to ensure at least 80% statistical power to detect a clinically meaningful treatment effect at conventional statistical significance (i.e., two-sided $p \leq 0.05$). Additionally, treatment regimens will be compared with regard to change in growth parameters, symptoms, and other responses.

In Study 4, treatment regimens will be compared with regard to change in symptoms and other responses.

Additional Information Needed:
Perform a thorough review of the medical literature on the use of esomeprazole magnesium in pediatric patients and provide a critical analysis and summary.

In addition, you should address the use of esomeprazole magnesium for the maintenance of healed erosive esophagitis in pediatric patients. This can be done by: (1) reviewing, assessing, and submitting the available published information on the use of esomeprazole magnesium in these patient populations and considering whether for the pediatric population or any portion of the pediatric population the disease and drug effects in those pediatric patients are similar as in adults; or (2) completing a prospectively designed, randomized, controlled clinical trial in these indications.

The Agency is concerned that pediatric patients may show progression of cellular changes beyond the proliferative changes in enterochromaffin-like (ECL) cells observed in adults who have used esomeprazole magnesium. Experimentally, proton pump inhibitors have been shown to be genotoxic (mutagenic, clastogenic) and carcinogenic. The experimental carcinogenicity was expressed not only by development of carcinoids, but by the neoplastic growth of other gastrointestinal and systemic tumors in animals.

To address this concern, the following studies must be performed with esomeprazole magnesium:

- A 4-week repeated dose toxicity study in neonatal rats and
- A 90-day repeated dose toxicity study in neonatal dogs

In these nonclinical studies, gastric ECL cell morphology must be specifically evaluated and toxicokinetic measurements must be made. Special attention should be paid to the developmental parameters in these neonates. The study designs must also include three-month recovery groups. These nonclinical studies must be performed before clinical pediatric studies in patients less than 1 year of age are conducted. These nonclinical studies may be performed concurrently with clinical pediatric studies in patients 1 year of age and older.

To further assess the carcinogenicity potential of esomeprazole magnesium and its safety for human use, perform a minimum 26-week carcinogenicity study in heterozygous p53 (+/-) transgenic mice. The dose selection for this study should be based on a 4-week dose ranging study in C57BL/6 mice. The high dose for the carcinogenicity study should be the maximum tolerated dose (MTD) determined on toxicity-based endpoints. This study in transgenic mice may be performed concurrently with clinical pediatric studies of esomeprazole magnesium. Conversely, performing a 26-week carcinogenicity study of omeprazole in p53 (+-) transgenic mice as bridging information for esomeprazole is acceptable.

In addition, provide a critical summary of clinical data (e.g., from the medical literature) that helps to determine whether pediatric patients are at any increased risk with respect to proliferative changes in gastric ECL cells.

Complete study reports for these nonclinical studies and the summary of clinical data must be submitted to FDA on or before the date specified below in the section titled "**Timeframe for Submitting Reports of the Studies**."

Labeling that may result from the studies:
Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted:
Please submit full study reports – addressing the issues outlined in this request with full analysis, assessment, and interpretation – that have not been submitted to the Agency. 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 must 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 must be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for submitting study reports:
Reports of the above **cited** studies must be submitted to the Agency on or before December 31, 2008. 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**s** of the stud**ies** in response to this Written Request.

Response to Written Request:
As per the Best Pharmaceuticals for Children Act (BPCA), 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. 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 New Drug Application (NDA) or 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.

In accordance with section 9 of the BPCA, *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 within 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. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.
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/.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval), 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice in accordance with section 505A(e)(2).

Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that ACTIVE MOIETY is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

5. the type of response to the Written Request (i.e. complete or partial response);
6. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
7. the action taken (i.e. approval, approvable, not approvable); or
8. the exclusivity determination (i.e. granted or denied).

Finally, please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.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.

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/s/

Julie Beitz

10/10/2008 11:41:10 AM