DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 61,238
NDA 20-498

WRITTEN REQUEST
Amendment # 5

AstraZeneca Pharmaceuticals, LP
Attention: Jennifer Pavillard
Associate Director, Regulatory Affairs
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Pavillard:

Please refer to your correspondence, dated April 27, 2007, to IND 61,238 requesting changes to FDA's April 8, 2005, Written Request (WR) Amendment # 4 for pediatric studies for Casodex (bicalutamide) in the treatment of gonadotropin-independent precocious puberty in boys with testotoxicosis.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. For convenience, the full text of the sections amended follows. Additions to the April 8, 2005, version of the Written Request are noted in **bold** text and deletions are noted by ~~strikethrough.~~ All other terms stated in our Written Request as revised on April 8, 2005, remain the same. For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Study design:

Study 1. This is a randomized, open-label, crossover study in healthy adult volunteers who will receive orally 50 mg bicalutamide in either liquid/dispersible tablet or tablet form in the first treatment period. After a washout period of at least 63 days, the subjects will receive 50 mg bicalutamide in either liquid/dispersible tablet or tablet form, whichever they did not receive during the first treatment period. Serial blood samples will be collected at specified times after each treatment to measure plasma bicalutamide concentrations. This study may be conducted at the same time as, but should not be after, the proposed pediatric clinical safety and efficacy study.

Study 2. This is a randomized, open-label, crossover study in healthy adult volunteers who will receive orally 1 mg anastrozole in either liquid/dispersible tablet or tablet form in the first treatment period. After a washout period of at least 20 days, the subjects will receive 1 mg anastrozole in either liquid/dispersible tablet or tablet form, whichever they did not receive during the first treatment period. Serial blood samples will be collected at specified times after each treatment to measure plasma anastrozole concentrations. This study may be conducted at the same time as, but should not be after, the proposed pediatric clinical safety and efficacy study.

Study 3. A 12-month, open-label, multicenter, observational study of bicalutamide used in combination with anastrozole in boys with testotoxicosis. The study will have at least 12 protocol-defined completers with a full complement of protocol-defined **efficacy and** safety data. **A minimum of 5 patients must be treatment-naïve and the remaining patients may be treatment-experienced to antiandrogen therapy.** ~~All patients must be naïve to antiandrogen therapy.~~ The occurrence of central precocious puberty (CPP) will be monitored and will include a GnRH stimulation test at regular intervals or at any point where the investigator believes CPP has occurred. If CPP develops, treatment with a GnRH agonist must be initiated. During the study, periodic drug level monitoring for both bicalutamide and anastrozole will be performed. To this end, determine plasma levels for both drugs at the following timepoints: predose, trough drug concentrations before the second dose, between days 8 and 14, and at 1 month, 2 months, and 3 months after the first dose. The determination of plasma drug concentrations should allow quick turnaround time for dose adjustment purposes. Every dose adjustment should be followed by trough plasma drug level measurements between days 8 and 14, and at 21 days, 1 month, 2 months, and 3 months after the dose change. Dose adjustment should be based on trough plasma drug concentrations achieved no sooner than three drug half-lives after the previous dose. An assessment of the dose and dosing schedule for both drugs will be performed after evaluating the pharmacokinetic information for the first four patients on treatment. This process will be repeated for additional panels of four patients until an appropriate dose regimen is established.

Age group and number of subjects to be studied:

Studies 1 and 2. Adult volunteers, with 24 volunteers completing each study.

Study 3. Boys – 2 years of age and older, with 12 **protocol-defined completers** ~~evaluable patients~~ who have a full complement of protocol-defined efficacy and safety data at the end of one year of treatment.

Entry criteria:

Studies 1 and 2. Healthy, adult, non-smoking volunteers who do not receive any prescription or over-the-counter medications (except limited use of acetaminophen as an analgesic) or any dietary supplements.

Study 3. Diagnosis of testotoxicosis made by clinical plus biochemical criteria; no evidence of central precocious puberty as demonstrated by GnRH stimulation test. A minimum of six months of pre-study growth information (height and height velocity, ~~and bone age~~) will be available prior to enrollment. In addition, bone age radiographs must be available at screening/baseline for calculation of bone age/chronological age ratio in all patients. If, in addition, six months of pre-study bone age information are available, the baseline rate of bone age maturation should be calculated. Collection of pre-study growth data **must** ~~should~~ meet strict endocrinological standards of accuracy and should be well documented.

Endpoints:

Studies 1 and 2. Bicalutamide and anastrozole pharmacokinetic parameters, such as relative BA, $AUC_{0-\infty}$, AUC_{0-t}, CL/ F, V_d/ F, C_{max}, T_{max}, λ_z, $t_{1/2}$, and their descriptive statistics should be evaluated.

Study 3. Primary endpoint: change in growth rate after 12 months of treatment relative to the growth rate during the ≥ 6-month pre-study period **for treatment-naïve patients**.

*Additional assessments **for treatment-naïve patients** in Study 3:*

- Change in growth rate (centimeters and standard deviation score) after 6 months of treatment relative to the growth rate during the ≥ 6-month pre-study period
- Bone age/chronological age ratio after 6 and 12 months of treatment relative to the bone age/chronological age ratio at baseline
- Change in rate of bone age maturation after 6 and 12 months of treatment relative to the rate of bone age maturation during the ≥ 6-month pre-study period for patients with baseline rate of bone age maturation information available (rate of bone age maturation will be defined as interval change in bone age/interval change in chronological age)
- Comparison of on-study data with historical data from the referenced study (Lescheck et al.) at the end of one year of treatment for growth rate, bone age maturation (if pre-study data are available), and percentage of patients showing improvement in aggressive behavior and acne lesions
- Number and percent of patients who achieve and/or maintain growth rates between the 5th and the 95th percentile
- Change in predicted adult height (PAH) at the end of the study compared to baseline PAH
- Incidence of patients with breast pain and gynecomastia at the beginning and the end of the trial
- Evolution of signs and symptoms of virilization while on study medication (virilization signs and symptoms to be followed are: testicular volume, Tanner staging, number of acne lesions, and aggressive behavior)
- Descriptive statistics of the plasma bicalutamide and anastrozole concentrations.

For non-naïve patients the same assessments as described for treatment-naïve patients will be conducted.

Drug information:

Studies 1 and 2.

Dose:	50 mg bicalutamide or 1 mg anastrozole
Dosage form:	liquid or dispersible tablet (to-be-developed for both test medications), or marketed tablet (for both marketed test medications)
Route of administration:	oral

Regimen:	each subject will receive the liquid or dispersible tablet or marketed tablet for both test medications
Formulation:	pediatric liquid or dispersible tablet (to-be-developed for both test medications), or marketed tablet (for both marketed test medications)

Study 3.

Dosage form:	liquid or dispersible tablet (to-be-developed)
Route of administration:	oral
Regimen:	bicalutamide will be started at a daily dose of 0.5 to 1 mg/kg and will be titrated to a plasma level in a range of 5 to 15 µg/mL; anastrozole will be started at a daily dose of 0.5 mg and will be titrated with the goal of maintaining normal serum estrogen levels
Formulation:	age appropriate

Use an age-appropriate formulation in the studies described above. Any unapproved formulation will need to be supported by a study of relative bioavailability; these studies may be conducted in adults. A formulation you develop for use in children should meet standards for marketing approval. If you cannot develop a potentially marketable formulation, you will need to document the attempt to do so, and the Agency will consider another formulation that is standardized and palatable. Full study reports of any relative bioavailability studies should be submitted to the Agency as part of the response to this Written Request.

[redacted]

~~Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.~~

~~Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.~~

~~If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.~~

~~Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.~~

Statistical information:

For treatment-naïve patients:

- Change in growth rate after 12 months of treatment relative to growth at baseline will be analyzed using a one-sample T-test. A 95% 2-sided confidence interval also will be calculated for the mean change in growth rate. All other endpoints will be summarized using descriptive statistics. Mean changes and individual changes will be presented.

- Change in growth rate and, if pre-study data are available, change in rate of bone maturation after 12 months of treatment will be compared with the data generated in the referenced study (Lescheck, et al.).

For non-naïve patients, the efficacy data will be summarized descriptively.

~~Conduct two sets of analyses: an all-treated analysis, consisting of patients who are treated and have on-treatment data, and a protocol-valid analysis for all patients who adhere to the protocol.~~

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before **June 30, 2008** ~~March 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 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.

Reports of the studies that meet the terms of the Written Request as revised on April 8, 2005 as amended by this letter, must be submitted to the Agency on or before June 30, 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) 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 **IND 61,238**. 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 bicalutamide 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.

When you submit your new drug application in response to this written request, you should include a population pharmacokinetic analysis of the plasma bicalutamide and anastrozole concentrations.

If you have any questions, call Jennifer Johnson, Regulatory Project Manager, Division of Metabolism and Endocrinology Products, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Acting Director
Office of Drug Evaluation II
Center for Drug Evaluation Research

Enclosure: Complete copy of Written Request as amended

IND 61,238 WRITTEN REQUEST
NDA 20-498

AstraZeneca Pharmaceuticals, LP
Attention: Jennifer Pavillard
Associate Director, Regulatory Affairs
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Pavillard:

Reference is made to your Proposed Pediatric Study Request submitted on December 13, 2002, to Pre-IND 61,238 for Casodex (bicalutamide) tablets.

To obtain needed pediatric information on bicalutamide, 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 the following studies:

Type of studies:

Study 1. A relative bioavailability (BA) study between a pediatric bicalutamide oral liquid or dispersible tablet formulation (to be developed) and the marketed 50-mg bicalutamide oral tablet.

Study 2. A relative BA study between a pediatric anastrozole oral liquid or dispersible tablet formulation (to be developed) and the marketed 1-mg anastrozole oral tablet.

Study 3. An efficacy study of bicalutamide and anastrozole.

Objectives/ rationale:

Study 1. To investigate the relative BA of bicalutamide between a pediatric liquid or dispersible tablet formulation and the marketed tablet in adults.

Study 2. To investigate the relative BA of anastrozole between a pediatric liquid or dispersible tablet formulation and the marketed tablet in adults.

Study 3. To assess the efficacy and safety of bicalutamide when used in combination with anastrozole for the treatment of precocious puberty in boys with testotoxicosis.

Indication to be studied:

Treatment of gonadotropin-independent precocious puberty in boys with testotoxicosis.

Study design:

Study 1. This is a randomized, open-label, crossover study in healthy adult volunteers who will receive orally 50 mg bicalutamide in either liquid/dispersible tablet or tablet form in the first treatment period. After a washout period of at least 63 days, the subjects will receive 50 mg bicalutamide in either liquid/dispersible tablet or tablet form, whichever they did not receive during the first treatment period. Serial blood samples will be collected at specified times after each treatment to measure plasma bicalutamide concentrations. This study may be conducted at the same time as, but should not be after, the proposed pediatric clinical safety and efficacy study.

Study 2. This is a randomized, open-label, crossover study in healthy adult volunteers who will receive orally 1 mg anastrozole in either liquid/dispersible tablet or tablet form in the first treatment period. After a washout period of at least 20 days, the subjects will receive 1 mg anastrozole in either liquid/dispersible tablet or tablet form, whichever they did not receive during the first treatment period. Serial blood samples will be collected at specified times after each treatment to measure plasma anastrozole concentrations. This study may be conducted at the same time as, but should not be after, the proposed pediatric clinical safety and efficacy study.

Study 3. A 12-month, open-label, multicenter, observational study of bicalutamide used in combination with anastrozole in boys with testotoxicosis. The study will have at least 12 protocol-defined completers with a full complement of protocol-defined efficacy and safety data. A minimum of 5 patients must be treatment-naïve and the remaining patients may be treatment-experienced to antiandrogen therapy. The occurrence of central precocious puberty (CPP) will be monitored and will include a GnRH stimulation test at regular intervals or at any point where the investigator believes CPP has occurred. If CPP develops, treatment with a GnRH agonist must be initiated. During the study, periodic drug level monitoring for both bicalutamide and anastrozole will be performed. To this end, determine plasma levels for both drugs at the following timepoints: predose, trough drug concentrations before the second dose, between days 8 and 14, and at 1 month, 2 months, and 3 months after the first dose. The determination of plasma drug concentrations should allow quick turnaround time for dose adjustment purposes. Every dose adjustment should be followed by trough plasma drug level measurements between days 8 and 14, and at 21 days, 1 month, 2 months, and 3 months after the dose change. Dose adjustment should be based on trough plasma drug concentrations achieved no sooner than three drug half-lives after the previous dose. An assessment of the dose and dosing schedule for both drugs will be performed after evaluating the pharmacokinetic information for the first four patients on treatment. This process will be repeated for additional panels of four patients until an appropriate dose regimen is established.

Age group and number of subjects to be studied:

Studies 1 and 2. Adult volunteers, with 24 volunteers completing each study.

Study 3. Boys – 2 years of age and older, with 12 protocol-defined completers who have a full complement of protocol-defined efficacy and safety data at the end of one year of treatment.

Entry criteria:

Studies 1 and 2. Healthy, adult, non-smoking volunteers who do not receive any prescription or over-the-counter medications (except limited use of acetaminophen as an analgesic) or any dietary supplements.

Study 3. Diagnosis of testotoxicosis made by clinical plus biochemical criteria; no evidence of central precocious puberty as demonstrated by GnRH stimulation test. A minimum of six months of pre-study growth information (height and height velocity, will be available prior to enrollment. In addition, bone age radiographs must be available at screening/baseline for calculation of bone age/chronological age ratio in all patients. If, in addition, six months of pre-study bone age information are available, the baseline rate of bone age maturation should be calculated. Collection of pre-study growth data must meet strict endocrinological standards of accuracy and should be well documented.

Endpoints:

Studies 1 and 2. Bicalutamide and anastrozole pharmacokinetic parameters, such as relative BA, $AUC_{0-\infty}$, AUC_{0-t}, CL/F, V_d/F, C_{max}, T_{max}, λ_z, $t_{1/2}$, and their descriptive statistics should be evaluated.

Study 3. Primary endpoint: change in growth rate after 12 months of treatment relative to the growth rate during the ≥ 6-month pre-study period for treatment-naïve patients.

Additional assessments for treatment-naïve patients:

Study 3.

- Change in growth rate (centimeters and standard deviation score) after 6 months of treatment relative to the growth rate during the ≥ 6-month pre-study period
- Bone age/chronological age ratio after 6 and 12 months of treatment relative to the bone age/chronological age ratio at baseline
- Change in rate of bone age maturation after 6 and 12 months of treatment relative to the rate of bone age maturation during the ≥ 6-month pre-study period for patients with baseline rate of bone age maturation information available (rate of bone age maturation will be defined as interval change in bone age/interval change in chronological age)
- Comparison of on-study data with historical data from the referenced study (Lescheck et al.) at the end of one year of treatment for growth rate, bone age maturation (if pre-study data are available), and percentage of patients showing improvement in aggressive behavior and acne lesions
- Number and percent of patients who achieve and/or maintain growth rates between the 5th and the 95th percentile
- Change in predicted adult height (PAH) at the end of the study compared to baseline PAH
- Incidence of patients with breast pain and gynecomastia at the beginning and the end of the trial

- Evolution of signs and symptoms of virilization while on study medication (virilization signs and symptoms to be followed are: testicular volume, Tanner staging, number of acne lesions, and aggressive behavior)
- Descriptive statistics of the plasma bicalutamide and anastrozole concentrations.

For non-naïve patients the same assessments described for treatment-naïve patients will be conducted.

Drug information:

Studies 1 and 2.

Dose:	50 mg bicalutamide or 1 mg anastrozole
Dosage form:	liquid or dispersible tablet (to-be-developed for both test medications), or marketed tablet (for both marketed test medications)
Route of administration:	oral
Regimen:	each subject will receive the liquid or dispersible tablet or marketed tablet for both test medications
Formulation:	pediatric liquid or dispersible tablet (to-be-developed for both test medications), or marketed tablet (for both marketed test medications)

Study 3.

Dosage form:	liquid or dispersible tablet (to-be-developed)
Route of administration:	oral
Regimen:	bicalutamide will be started at a daily dose of 0.5 to 1 mg/kg and will be titrated to a plasma level in a range of 5 to 15 µg/mL; anastrozole will be started at a daily dose of 0.5 mg and will be titrated with the goal of maintaining normal serum estrogen levels
Formulation:	age appropriate

Use an age-appropriate formulation in the studies described above. Any unapproved formulation will need to be supported by a study of relative bioavailability; these studies may be conducted in adults. A formulation you develop for use in children should meet standards for marketing approval. If you cannot develop a potentially marketable formulation, you will need to document the attempt to do so, and the Agency will consider another formulation that is standardized and palatable. Full study reports of any relative bioavailability studies should be submitted to the Agency as part of the response to this Written Request.

Drug-specific safety concerns:

The safety profile of bicalutamide/anastrozole combination in children is not known. To this end, a 3- month juvenile rat toxicity study (males only) of bicalutamide/anastrozole combination will be completed and the results will be presented to the agency for review prior to initiating the clinical study.

During the clinical study, bicalutamide-specific adverse events should be monitored, particularly, hepatic adverse events (e.g., elevated transaminases, jaundice, diarrhea, nausea, vomiting, asthenia). Anastrozole-specific adverse events identified in the drug label should also be monitored.

Statistical information:

For treatment-naïve patients:

- Change in growth rate after 12 months of treatment relative to growth at baseline will be analyzed using a one-sample T-test. A 95% 2-sided confidence interval also will be calculated for the mean change in growth rate. All other endpoints will be summarized using descriptive statistics. Mean changes and individual changes will be presented.

- Change in growth rate and, if pre-study data are available, change in rate of bone maturation after 12 months of treatment will be compared with the data generated in the referenced study (Lescheck, et al.).

For non-naïve patients, the efficacy data will be summarized descriptively.

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:

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. 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.

Although not required at the time of pediatric exclusivity determination, we request that you monitor the study participants until final height is reached in all patients. To this end, submit the information in annual reports. Patients should be monitored with respect to above listed endpoints/assessments every 6 to 12 months.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before June 30, 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 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.

Reports of the studies that meet the terms of the Written Request dated April 8, 2005, as amended by this letter must be submitted to the Agency on or before June 30, 2008, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit protocols for the above studies to **IND 61,238** 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. Please 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 a new drug application (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 (301-594-0183) 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 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 **IND 61,238.** 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.

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1. the type of response to the Written Request (i.e., complete or partial response);
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If you have any questions, please call Jennifer Johnson, Regulatory Project Manager, Division of Metabolism and Endocrinology Products, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Acting Director
Office of Drug Evaluation II
Center for Drug Evaluation Research

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

/s/

Curtis Rosebraugh
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