DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022063

WRITTEN REQUEST – AMENDMENT 2

Shire Development, LLC
Attention: Chayla Freeman, MS, JD
Associate Director, Global Regulatory Affairs
300 Shire Way
Lexington, MA 02421

Dear Ms. Freeman:

Please refer to your correspondence dated January 4, 2019, requesting changes to FDA's July 14, 2017 Written Request for pediatric studies for Mydayis (mixed salts of a single entity amphetamine product).

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 July 14, 2017, and as amended on September 12, 2018, remain the same. (Text added is underlined. Text deleted is strikethrough.)

BACKGROUND:

These studies investigate the potential use of MYDAYIS [mixed salts of a single entity amphetamine product (hereafter, "amphetamine")] in preschool children (ages 4 to 5 years) for the treatment of attention deficit hyperactivity disorder (ADHD). The Agency initially required you to evaluate ~~Additionally,~~ the efficacy and safety of a lower, (b) (4) dose of amphetamine ~~will be evaluated~~ in 6 to 12 year-old patients with ADHD; however, preliminary efficacy data from MYDAYIS 6.25 mg, the (b) (4) dose, indicate a lack of efficacy. Therefore, the Agency has deemed that evaluation of long-term safety with the lower dose is unnecessary.

Study 3: Pediatric Open-Label Safety Study in patients age 4 to 12 years (at the time of entry into Study 1 or 2 or at the time of enrollment if directly enrolled into Study 3) with ADHD

- *Objective study:* The primary objective of Study 3 is to evaluate the ~~12 month,~~ long-term safety of this formulation of amphetamine in the treatment of attention deficit hyperactivity disorder.

- *Study endpoints:*

Safety Endpoints: The safety study must include the identical safety assessments required in the controlled study, including adverse events, tolerability, vital signs, laboratory parameters, and growth parameters. All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- You must collect adequate longer-term safety data~~, with minimum drug exposure of 12 months~~. The longer-term safety data could come from an open-label study, e.g., a longer-term open-label extension study from the controlled efficacy trials, or from a separate longer-term open safety study(ies). No minimum number of patients completing longer-term safety study are being required, because preliminary data indicate lack of efficacy in 4 to 12 year olds.

Format and types of reports to be submitted
You must submit full study reports ~~(which have not been previously submitted to the Agency)~~ for Study 1 and Study 2 by March 15, 2019. ~~at the time of your NDA supplement submission, and a 6-month interim report for Study 3 to include 6-month data on no fewer than 50 subjects and 12-month data on approximately 20 subjects within 120 days of your NDA supplement submission that address the issues outlined in this request, with full analysis, assessment, and interpretation.~~ Any safety data collected from Study 3 will be submitted in an abbreviated report within 120 days of your NDA supplement submission (June 28, 2019). In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino, or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Timeframe for submitting reports of the study(ies)
Reports of the above studies 1 and 2 must be submitted to the Agency on or before March 15, 2019.

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 July 14, 2017, as amended by this letter and by previous amendment dated September 12, 2018, must be submitted to the Agency on or before March 1, 2019, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a 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 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:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

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.

If you have any questions, contact Latrice Wilson, PharmD, Regulatory Project Manager, at latrice.wilson@fda.hhs.gov or 240-402-5317.

Sincerely,

{See appended electronic signature page}

Ellis Unger, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022063

WRITTEN REQUEST

Shire Development, LLC
Attention: Chayla Freeman, MS, JD
Global Regulatory Affairs Lead
300 Shire Way
Lexington, MA 02421

Dear Ms. Freeman:

Reference is made to your March 17, 2017, Proposed Pediatric Study Request for MYDAYIS (mixed salts of a single entity amphetamine product).

BACKGROUND:

These studies investigate the potential use of MYDAYIS [mixed salts of a single entity amphetamine product (hereafter, "amphetamine")] in preschool children (ages 4 to 5 years) for the treatment of attention deficit hyperactivity disorder (ADHD). The Agency initially required you to evaluate the efficacy and safety of a lower, (b) (4) dose of amphetamine in 6 to 12 year-old patients with ADHD; however, preliminary efficacy data from MYDAYIS 6.25 mg, the (b) (4) dose, indicate a lack of efficacy. Therefore, the Agency has deemed that evaluation of long-term safety with the lower dose is unnecessary.

ADHD is not recognizable or diagnosed in neonates.

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN THE PRESCHOOL POPULATION

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder in children and adolescents. It is characterized by a pattern of developmentally inappropriate and maladaptive inattentiveness, impulsivity, and hyperactivity resulting in clinically significant impairment in family, social, academic, and occupational functioning. ADHD symptoms often manifest several years prior to entry into elementary school. The estimated prevalence of ADHD in the preschool population (ages 3 to 5 years) is 3 to 5%, which is similar to the prevalence of ADHD throughout childhood and adolescence (also 3 to 5%). Preschool-age children with ADHD demonstrate significant impairments in family, social, and pre-academic function. They may be aggressive towards others and may sustain injuries secondary to impulsivity. Data suggest that only a small proportion of preschool-age children with ADHD respond adequately

to behavioral therapy. The diagnosis of ADHD is likely to be stable and to lead to a wide range of long-term negative consequences.

Controlled data regarding pharmacotherapy for ADHD in the preschool population is needed to guide treatment decisions. Reliable diagnostic tools and age-appropriate assessments of ADHD symptom severity are available for use in clinical trials. There are very few adequate and well-controlled studies of pharmacotherapy in preschool-age children with ADHD. The lack of controlled safety and efficacy data combined with the substantial prevalence of stimulant prescribing in preschool-age children with ADHD suggests that controlled efficacy and safety studies of stimulants in this population are needed as such studies would inform clinicians regarding the safety, efficacy, pharmacokinetics, and appropriate dose selection for stimulant treatment in this population.

Clinicians currently prescribe stimulants such as amphetamine for the treatment of ADHD in preschool-age children. Drug utilization data in the preschool population provides evidence that immediate- (IR) and extended-release (ER) amphetamine products are being prescribed concurrently; this is particularly relevant to MYDAYIS given its intended duration of effect. An adequate and well-controlled trial of MYDAYIS in pediatric patients (6 to 17) with ADHD revealed higher than expected rates of adverse events in 6 to 12 year-olds, including insomnia (28% of patients in the MYDAYIS treatment group compared to 2% in the placebo group) and decreased appetite (43% on MYDAYIS compared to 8% on placebo) at the 12.5 mg or 25 mg dose. Lower doses have not been evaluated; however, it is reasonable to suspect a lower dose may have a more favorable risk/benefit profile. Although we agree that the efficacy findings in school-age children (ages 6 to 17 years) can be applied to preschool children (ages 4 to 5 years), the safety findings cannot be extrapolated to the latter age group.

To obtain needed pediatric information for MYDAYIS, 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), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

GENERAL ADVICE FOR DEVELOPING A DRUG FOR ADHD IN THE PEDIATRIC POPULATION

A demonstration of the efficacy and safety of amphetamine for the treatment of ADHD in 6 to 12 year-old children would require at least one adequate and well-controlled clinical trial of a lower dose than currently approved in this population. The efficacy and safety study must be a randomized, double-blind and placebo-controlled trial. A placebo control is necessary for providing fully interpretable efficacy and safety results. There are no significant ethical concerns regarding pediatric patients treated with placebo in the ADHD clinical trials because of the nature of this disorder; subjects could be immediately discontinued from the studies and directed to standard treatments if they have an inadequate response.

Your ADHD program in this pediatric population must include collection of adequate short-term and longer-term safety data and pharmacokinetic data in the relevant age group (ages 4 to 12 years).

- *Nonclinical study*:
  Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*
  Study 1: Pediatric Efficacy and Safety Study in patients ages 6 to 12 with ADHD
  Study 2: Pediatric Safety, Tolerability, and Pharmacokinetic (PK) Study in patients ages 4 to 5 years
  Study 3: Pediatric Open-Label Safety Study in patients age 4 to 12 years (at the time of entry into Study 1 or 2 or at the time of enrollment if directly enrolled into Study 3) with ADHD

- *Overall objectives of studies:*

The overall goal of the development program is to establish the safety and efficacy of amphetamine for the treatment of ADHD in 4 to 12 year-old patients.

The efficacy and safety study results in children ages 6 to 12 years should be submitted to your IND. Efficacy in patients ages 4 to 5 years may be extrapolated from data in older children and safety will be determined by the studies outlined in the Written Request.

The PK study (Study 2) must be completed in a manner to assess the safety, tolerability, and PK profile of amphetamine.

Study 1: Pediatric Efficacy and Safety Study for patients age 6 to 12 years with attention deficit hyperactivity disorder

- *Objective of study:* The primary objective of Study 1 is to evaluate the efficacy and safety of amphetamine in the treatment of attention deficit hyperactivity disorder by evaluating a safe and effective dose (i.e., a dose lower than 12.5mg). The study design should include a dose to be agreed upon with the Agency.

- *Patients to be studied:*
  - *Age group in which study will be performed*: Pediatric patients 6 to 12 years-old with ADHD.

- *Inclusion and Exclusion Criteria*
  - Screening procedures and inclusion and exclusion criteria in the protocol must be agreed upon by the Agency.

- Patients must have a DSM-5-defined diagnosis of ADHD, assessed using a clinically-validated and age-appropriate instrument for diagnosing psychiatric illnesses in children and confirmed with a structured clinical interview of patients and caregivers conducted by a clinician with appropriate clinical training and expertise in diagnosing psychiatric disorders in children.

- *Number of patients to be studied:*

  - The gender distribution of participants in this study must reflect the distribution of those affected with this condition.
  - The trial must have at least 85% power to demonstrate efficacy in patients 6 to 12 years old. The study population must have 50% of subjects in a 6 to 8 year-old group and 50% of subjects in a 9 to 12 year-old group for age subgroup safety comparison.
  - A minimum of 50 patients must be included in the study.

- *Study endpoints:*

  Efficacy Endpoints:
  A scale specific to ADHD and sensitive to the effects of drug treatment for 6 to 12 year-old patients with ADHD must be used. You must provide justification for your choice of primary efficacy measure, with Agency review and agreement prior to initiating the study.

  Safety Endpoints:
  Safety and tolerability endpoints include the occurrence of treatment-emergent adverse events (TEAEs), evaluation of blood pressure, pulse, weight, BMI, clinical laboratory evaluations, and ECG results. The study must include specific age-appropriate assessments of suicidal ideation and suicidal behavior. In addition, the study must include specific assessments of sleep using a validated clinical rating scale agreed upon by the Agency, such as the Post Sleep Questionaire.

- *Statistical Information:*
  - Clinical Study 1 must have a detailed statistical analysis plan (SAP). The preliminary SAP must be submitted for review and you must obtain agreement on the final plans prior to initiation of Study 1. The study must be designed with at least 85% statistical power to demonstrate efficacy at a Type I error rate of 5% (two-sided). You must obtain agreement from the Division on the treatment effect (postulated magnitude of treatment effect along with its standard deviation) used for sample size calculation prior to initiating the study.
  - To ensure your study is adequately powered, you must obtain an estimate of variability from an interim analysis and follow a pre-specified rule to adjust the sample size to achieve the specified target power. Such interim analysis must be performed when the studies are close to completion (for example, when >75% of initially randomized patients have completed/discontinued). You may estimate the

variability based on a blinded and pooled analysis of all groups. If you want to perform an interim efficacy assessment at any time, you must propose an appropriate alpha adjustment method.

- With respect to the primary efficacy analysis, the protocol will describe the estimand of primary interest. If the estimand of interest is the treatment effect in all patients randomized regardless of adherence, you should include provisions to limit missing data through study design and education of investigators and patients, and pre-specify analysis methods to account for missing data for the primary and key secondary efficacy analyses. We recommend designs that encourage continued collection of efficacy data even after study treatment discontinuation, following the recommendation from the NAS report on missing data in clinical trials. If you believe the treatment effect in all patients randomized regardless of adherence is not the most clinically important estimand, the protocol should specify which estimand is of most clinical importance and why. Statistical methods to quantify this estimand should be specified in the protocol.

Patients from Study 1 may be enrolled directly in Study 3 upon completion of Study 1.

Study 2: Safety, Tolerability, and Pharmacokinetic Study
The safety, tolerability, and pharmacokinetic study can be considered as the initial phase of the long-term safety study (Study 3). Patients who complete participation in this study should be given the option to be enrolled in the long-term safety study (Study 3). The safety data collected in this study can be considered part of the long-term safety study results (Study 3).

- *Objective of study:* The primary objective of Study 2 is to evaluate the safety, tolerability, and pharmacokinetics of amphetamine in 4 to 5 year-old patients with ADHD.

- *Patients to be Studied:*
  - *Age group in which study will be performed*: Pediatric patients 4 to 5 years-old with ADHD

  - *Number of patients to be studied:*
    - A sufficient number of patients must be studied to characterize adequately the appropriate dose, tolerability, and pharmacokinetics of the study drug and its major active metabolite(s) in the relevant age group.
    - The gender distribution of participants in this study must reflect the distribution of those affected with this condition.
    - For pharmacokinetic evaluation, the study must be prospectively powered to target a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for parent and major (active) metabolites in the entire age range.

- *Study endpoints:*

Pharmacokinetic Endpoints: Pharmacokinetic assessments must be made with respect to the study drug and any metabolites that make substantial contributions to its efficacy and/or toxicity. You may use sparse pharmacokinetic sampling. You must measure and collect data to characterize the shape of pharmacokinetic profile and exposure levels at the time of interest (i.e., exposures around typical dinner and bed times for pediatric patients 4 to 5 years of age, and around t_{max}), and to develop adequate estimates of important pharmacokinetic parameters, including t_{max}, C_{max}, $AUC_{0-\infty}$, AUC_{last}, AUC_{0-t}, AUC_{0-5}, AUC_{5-t}, $t_{1/2}$, λz, CL/F, Vz/F, Vss, AUC_{0-tau}, and C_{trough}. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available at https://www.fda.gov/downloads/drugs/guidances/ucm425885.pdf.

Study 3: Pediatric Open-Label Safety Study in patients age 4 to 12 years (at the time of entry into Study 1 or 2 or at the time of enrollment if directly enrolled into Study 3) with ADHD

- *Objective study:* The primary objective of Study 3 is to evaluate the, long-term safety of this formulation of amphetamine in the treatment of attention deficit hyperactivity disorder.

- *Patients to be Studied:*
  - *Age group in which study will be performed*: Pediatric patients 4 to 12 years-old with ADHD. The age and diagnosis will be assessed at the time of entry into Study 1 or Study 2 or at the time of enrollment if directly enrolled into Study 3.
  - Patients from Study 2 may be directly enrolled in Study 3 upon completion of Study 2.

  - *Inclusion and Exclusion Criteria*
    - Screening procedures and inclusion and exclusion criteria must be agreed upon by the Agency in the protocol.
    - Patients must have a DSM-5-defined diagnosis of ADHD, assessed using a clinically-validated and age-appropriate instrument for diagnosing psychiatric illnesses in children and confirmed with a structured clinical interview of patients and caregivers conducted by a clinician with appropriate clinical training and expertise in diagnosing psychiatric disorders in children.
    - For 4 to 5 year-old patients, study subjects must:
      - Have previously undergone an adequate course of non-pharmacological treatment

        or
      - Meet prespecified ADHD severity criteria and, in the investigator's opinion, the child's condition must be severe enough to warrant enrollment in this trial without having undergone non-pharmacological treatment.

  - *Number of patients to be studied:*

- The gender distribution of participants in this study must reflect the distribution of those affected with this condition.
- The overall minimum number of patients with 6 months' exposure is 60
- If determined to be safe, no fewer than forty 4 to 5 year-old patients should be enrolled in Study 3.

- *Study endpoints:*
  Safety Endpoints: The safety study must include the identical safety assessments required in the controlled study, including adverse events, tolerability, vital signs, laboratory parameters, and growth parameters. All adverse events must be monitored until symptom resolution or until the condition stabilizes.
    - You must collect adequate longer-term safety data.The longer-term safety data could come from an open-label study, e.g., a longer-term open-label extension study from the controlled efficacy trials, or from a separate longer-term open safety study(ies). No minimum number of patients completing longer-term safety study are being required, because preliminary data indicate lack of efficacy in 4 to 12 year olds.

Data Monitoring Committee
A Data Monitoring Committee (DMC) must be included. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

Known Drug Safety concerns and monitoring
Active surveillance for insomnia and decreased appetite leading to weight loss are required.

Extraordinary results
In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

Representation of Ethnic and Racial Minorities
The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Pediatric Formulation
Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate

formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), 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 indicating you have not marketed the new pediatric formulation.

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 prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, 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 preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

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

Labeling that may result from the study(ies)
You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that SHP-465 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). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

Format and types of reports to be submitted
You must submit full study reports for Study 1 and Study 2 by March 15, 2019. Any safety data collected from Study 3 will be submitted in an abbreviated report within 120 days of your NDA supplement submission (June 28, 2019.) In addition, the reports must include

information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) 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, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

Timeframe for submitting reports of the study(ies)
Reports of the above studies 1 and 2 must be submitted to the Agency on or before March 15, 2019. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request
Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) 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.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are 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 to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, 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, complete response); or
4) the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

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

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 are 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 submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, contact Latrice Wilson, PharmD, Regulatory Project Manager, at latrice.wilson@fda.hhs.gov or (240) 402-5317.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELLIS F UNGER
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