DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203214

WRITTEN REQUEST – AMENDMENT 1

P.F. Prism C.V
c/o Pfizer Inc.
500 Arcola Road
Collegeville, PA 19426-3982

Attention: Alicia Holsey, MS, RAC
Senior Manager, Worldwide Safety and Regulatory

Dear Ms. Holsey:

Please refer to your correspondence dated January 22, 2016, requesting changes to FDA's August 12, 2015, Written Request for pediatric studies for tofacitinib.

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 August 12, 2015, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Drug Information:

Study 1: Appropriate dosing to be identified and agreed upon with the Agency. Dosing will target exposures observed in adult rheumatoid arthritis (RA) patients treated with 5 mg BID regimen.

Study 2: Appropriate dosing to be identified and agreed upon with the Agency. Dosing will ~~target~~ not exceed exposures observed in adult RA patients treated with 5 mg BID regimen.

Study 3: Appropriate dosing to be identified and agreed upon with the Agency. Dosing will ~~target~~ not exceed exposures observed in adult RA patients treated with 5 mg BID or 10 mg BID regimen.

Study 4: Appropriate dosing to be identified and agreed upon with the Agency.

We have the following comment:

> We agree with your proposal to provide efficacy data in a legacy format provided all variables are clearly defined, with derivations carefully documented to link analysis datasets to raw datasets and eCRF files. Further, ensure that the submitted analysis datasets include all data used to generate the results presented in your study report. In addition, provide all programs used for analysis of (i) patient disposition, (ii) each efficacy endpoint proposed for inclusion on the product label, and (iii) each efficacy endpoint which precedes, in the analysis hierarchy, an efficacy endpoint proposed for inclusion on the product label.

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 August 12, 2015, as amended by this letter, must be submitted to the Agency on or before October 31, 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 NDA 203214 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 (240-276-9327) or messenger, to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773.

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, call Sadaf Nabavian, Regulatory Project Manager, at 796-2777.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Deputy Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

Complete Text of Written Request as Amended

BACKGROUND:

These studies investigate the potential use of tofacitinib in the treatment of polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis.

I. Polyarticular Juvenile Idiopathic Arthritis (PJIA)

PJIA is a descriptive term for persistent arthritis of more than 6 weeks in multiple joints, with onset in patients less than 16 years of age. The overall prevalence of juvenile idiopathic arthritis (JIA) is estimated to be 1 to 2 per 1000 children.[1] A limited number of treatments are approved for PJIA, which include corticosteroids, methotrexate (MTX), the TNF inhibitors etanercept and adalimumab, the IL-6 receptor inhibitor tocilizumab, and the T- cell co-stimulatory modulator abatacept. Because PJIA patients may not respond to a given treatment or class of treatments, therapies with different mechanisms of action would be an important public health benefit. Further, tofacitinib, as an oral formulation, may offer an additional desired and more convenient treatment option for this pediatric population.

II. Systemic Juvenile Idiopathic Arthritis (SJIA)

SJIA comprises only about 10% of all JIA patients,[1] but is associated with disproportionate mortality risk, in large part due to Macrophage Activation Syndrome (MAS), which is unique to SJIA and is associated with 20% mortality risk.[2] A limited number of treatments are approved for SJIA, which include the IL-6 receptor inhibitor tocilizumab and the IL-1 inhibitor canakinumab. Off-label therapies for SJIA include use of corticosteroids, methotrexate (MTX), the TNF inhibitors etanercept and infliximab, and the IL-1 therapies like anakinra. Because SJIA patients may not respond to a given treatment or class of treatments, therapies with different mechanisms of action would be an important public health benefit. Further, tofacitinib, as an oral formulation, may offer an additional desired and more convenient treatment option for this pediatric population.

The studies outlined in this Written Request are designed to evaluate the safety and efficacy of tofacitinib in the treatment of PJIA and SJIA patients 2 years and older. The efficacy of tofacitinib in PJIA and SJIA patients 2 to <18 years of age may not be fully extrapolated and will be determined by the randomized, double-blind, placebo-controlled withdrawal studies in PJIA patients 2 to <18 years (Study 2), and in patients 2 to <18 years with active SJIA (Study 3). Pediatric patients less than 2 years of age, including neonates, will not be included in these

[1] Gabriel SE and K Michaud. Epidemiological Studies in Incidence, Prevalence, Mortality, and Comorbidity of the Rheumatic Diseases. Arthritis Research & Therapy. 2009;11:229.

[2] Sawhney S et al. Macrophage Activation Syndrome: a Potentially Fatal Complication of Rheumatic Disorders. Arch Dis Child. 2001;85:421-426.

studies because PJIA and SJIA rarely occur in this age group and because of the difficulty with diagnosing these conditions in this age group.

The safety concerns with tofacitinib include serious infections, including tuberculosis and opportunistic infections, malignancy, including lymphoma and non-melanoma skin cancer, and laboratory abnormalities, including abnormal hematologic parameters, lipid parameter changes, liver enzymes, serum creatinine elevation, and gastrointestinal perforations.

To obtain needed pediatric information on tofacitinib, 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.

***Nonclinical study(ies)*:**

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: A multiple-dose pharmacokinetic (PK) study in juvenile polyarticular idiopathic arthritis (PJIA) patients ages 2 to <18 years. The PK study must be completed before the efficacy trial(s) to inform dosing.

Study 2: A randomized withdrawal, double-blind placebo-controlled efficacy study in polyarticular juvenile idiopathic arthritis (PJIA) patients ages 2 to <18 years.

Study 3: A randomized withdrawal, double blind, placebo controlled study to evaluate the efficacy, safety and pharmacokinetics of tofacitinib in children 2 to <18 years with active systemic juvenile idiopathic arthritis (SJIA).

Study 4: An open-label long-term follow-up study in JIA patients ages 2 to <18 years who have previously participated in tofacitinib studies for treatment of JIA. Patients from Studies 1 through 3 may be rolled over into Study 4. Only interim results from Study 4 will be submitted.

Objective of each study:

Study 1: PK study in PJIA patients ages 2 to <18 years
The primary objective is to characterize the pharmacokinetics of tofacitinib in PJIA patients. Secondary objectives include the evaluation of safety.

Study 2: Efficacy study in PJIA patients ages 2 to <18 years
To compare the efficacy and safety of tofacitinib to placebo in PJIA patients.

Study 3: Efficacy study in SJIA patients ages 2 to <18 years
To evaluate the efficacy, safety, and pharmacokinetics of tofacitinib to placebo in SJIA patients with active systemic features.

Study 4: Long-term safety and tolerability of tofacitinib in JIA patients ages 2 to <18 years
To assess long-term safety of tofacitinib for treatment of JIA patients.

Patients to be studied:

- *Age group in which study will be performed:*

Studies 1 through 4 will enroll patients 2 to <18 years old.

- *Number of patients to be studied:*

Study 1: At least 24 males and females with PJIA aged 2 to <18 yrs to be divided into three cohorts: 12 to <18 years, 6 to <12 years, and 2 to <6 years.

Study 2: Enroll at least 170 patients with PJIA with a minimum of 20 patients in each of the following age groups: 12 to <18 years, 6 to <12 years, and 2 to <6 years old.

Study 3: Enroll at least 100 patients with active SJIA with at least 12 patients in each of the following age groups: 12 to <18 years, 6 to <12 years, and 2 to <6 years old.

Study 4: Enroll at least 240 patients with JIA ages 2 to <18 for assessment of long-term safety. Interim report containing at minimum 75 patients treated for at least 24 months must be submitted.

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.

Study endpoints:

Study 1: PK study in PJIA patients ages 2 to <18 years

- ☐ Pharmacokinetic endpoints will include oral clearance (CL/F), area under the curve plasma concentration-time profile of the dosing interval τ at steady state (AUCτ), Cmax, Tmax, PK sampling adequate for non-compartmental analysis (1 ml blood per sample; samples at pre-dose 0.5, 1, 2, 4 and 8 hours post-dose) on Day 5.

- ☐ Taste acceptability of the oral solution on Day 1 may be included as secondary endpoint.

- ☐ Safety endpoints:
  Safety outcomes must include: adverse events, tolerability, vital signs, and laboratory parameters.

- ☐ Exploratory endpoints:
  Efficacy parameters will be regarded as exploratory and may include Physician Global Assessment of disease activity, Parent/patient Global Assessment of overall well-being, Number of joints with limitation of movement, Number of joints with active arthritis.

Study 2: Efficacy study in PJIA patients ages 2 to <18 years

- ☐ Efficacy Endpoints:
  - The primary efficacy endpoint will be the occurrence of disease flare (according to Pediatric Rheumatology Clinical Study Group/Pediatric Rheumatology International Trials Organization [PRCSG/PRINTO] Disease Flare criteria) at Week 26 of the double-blind phase.

  - Secondary efficacy endpoints will include:
    - Occurrence of disease flare (according to PRCSG/PRINTO Disease Flare criteria) at various time points
    - Time to disease flare
    - JIA ACR30-50-70-90 response at various time points
    - Change from baseline in each JIA ACR core set variable at various time points
    - Additional secondary endpoints may be agreed upon with the Agency

- ☐ PK parameters will be regarded as secondary endpoints and may include Cmax, Cmin and AUC. Sparse PK sampling will be collected for exposure-response analysis.

- ☐ Safety endpoints will include adverse events, vital signs, and laboratory parameters. Safety outcomes of special interest will include serious infections, laboratory abnormalities with neutrophils, lymphocytes, platelets, lipids, and liver enzymes, malignancies, including lymphoma and non-melanoma skin cancer, gastrointestinal perforations, and validated assessments of growth and pubertal development.

- ☐ A Data Monitoring Committee (DMC) must be included because the study is being performed in children. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees.

Study 3: Efficacy study in SJIA patients ages 2 to <18 years

- ☐ Efficacy endpoints:
  - The primary efficacy endpoint will be the time to disease flare during the double-blind randomized-withdrawal phase. Flare is defined as the recurrence of fever (>38ºC lasting for 2 or more consecutive days); a worsening of 30% or more in three or more of the six variables of the JIA core set, with no more than one variable improving by 30% or more or discontinuation of treatment, except in the case of discontinuation because of inactive disease at 24 weeks or more. If the Physician or parent global scores are used in the definition of flare, then there must be an increase of at least 2 units on a 0-10 VAS scale. If the number of active joints or number of joints with loss of motion is used in the definition of flare, then there must be an increase of at least 2 joints. If the ESR is used in the definition of flare, then the value at the visit in which flare is being assessed must be out of the normal range.

  - Secondary efficacy endpoints will include:
    - Occurrence of disease flares in the double blind phase.
    - Occurrence of achieving tapering of corticosteroids at the end of the open-label active treatment period
    - Response of adapted Pediatric ACR JIA 30/50/70/90 during the open-label and double-blind Phase
    - Resolution of fever
    - Change from baseline in each ACR Pediatric core variable at various time points
    - Additional secondary endpoints may be agreed upon with the Agency

- ☐ PK endpoints will be regarded as secondary endpoints and may include Cmax, Cmin, and AUC. PK endpoints may also be assessed during the open-label, run-in phase. Sparse PK sampling will be collected for exposure-response analysis.

- ☐ Safety endpoints will include adverse events, vital signs, and laboratory parameters. Safety outcomes of special interest will include serious infections, laboratory abnormalities with neutrophils, lymphocytes, platelets, lipids, and liver enzymes, malignancies, including lymphoma and non-melanoma skin cancer, macrophage activation syndrome, gastrointestinal perforations, and validated assessments of growth and pubertal development.

- ☐ A Data Monitoring Committee (DMC) must be included because the study is being performed in children and the possibility of serious toxicity with

tofacitinib. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees.

Study 4: Long-term safety and tolerability of tofacitinib in JIA patients ages 2 to <18 years

- ☐ *Safety endpoints:*
  Safety outcomes must include: adverse events, tolerability, vital signs and laboratory parameters. Safety will also focus on serious infections, laboratory abnormalities with neutrophils, lymphocytes, platelets, lipids, and liver enzymes, malignancies, including lymphoma and non-melanoma skin cancer, gastrointestinal perforations, and validated assessments of growth and pubertal development.

- ☐ A Data Monitoring Committee (DMC) must be included because the study is being performed in children and the possibility of serious toxicity with tofacitinib. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees.

Known Drug Safety concerns and monitoring:

You will monitor for:

- Serious infections, including tuberculosis and opportunistic infections
- Laboratory abnormalities with neutrophils, lymphocytes, platelets, lipids, and liver enzymes
- Malignancies, including lymphoma and non-melanoma skin cancer
- Gastrointestinal perforations
- Other serious safety concerns
- Live vaccines should not be given with tofacitinib
- Tofacitinib should not be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.

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.

Drug information:

- *dosage form (all studies)*
  Tofacitinib oral solution (1 mg/mL)

Tofacitinib 5 mg film coated tablet

- *route of administration (all studies)*
  Oral
- *regimen*
  Studies 1 through 4: Twice daily (BID).

  Study 1: Appropriate dosing to be identified and agreed upon with the Agency. Dosing will target exposures observed in adult rheumatoid arthritis (RA) patients treated with 5 mg BID regimen.

  Study 2: Appropriate dosing to be identified and agreed upon with the Agency. Dosing will not exceed exposures observed in adult RA patients treated with 5 mg BID regimen.

  Study 3: Appropriate dosing to be identified and agreed upon with the Agency. Dosing will not exceed exposures observed in adult RA patients treated with 5 mg BID or 10 mg BID regimen.

  Study 4: Appropriate dosing to be identified and agreed upon with the Agency.

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.

Statistical information, including power of study(ies) and statistical assessments:

- *Study 1: PK study in PJIA patients ages 2 to <18 years*
  The sample size of 24 pediatric patients (8 per age group) will provide 80% probability that the ideal recommended dose resulting from the clearance estimate would achieve a systemic exposure within 66% to 150% of the targeted exposure (5 mg BID). The 66-150% criterion was based on the exposure-response relationships of tofacitinib for efficacy and safety in the adult RA population, which is consistent with the recommended dosage adjustments for various intrinsic and extrinsic factors in the current product label for AUC increases of greater than 50%. Non-compartmental analysis of plasma concentration-time data and non-linear mixed effects analysis of PK data will be performed to determine parameters. The PK parameters from the non-compartmental analysis will be summarized descriptively.

- *Study 2 (Efficacy study in PJIA patients ages 2 to <18 years) and Study 3 (Efficacy study in SJIA patients ages 2 to <18 years)*
  The studies must have a pre-specified, detailed statistical analysis plan appropriate to the study design and outcome measure. The protocol and statistical analysis plan must be submitted to the Division for review. You must obtain agreement on the final protocol prior to initiation of the studies and on the statistical analysis plan prior to unblinding of randomized treatment codes.

- *Study 4: Long-term safety and tolerability of tofacitinib in JIA patients ages 2 to <18 years*
  Interim results on the accrued safety data available on a minimum of 75 patients enrolled in the study and treated for at least 24 months will be required. Safety and efficacy data will be summarized by descriptive statistics over time. Descriptive statistics on the incidence of serious infections, laboratory abnormalities, malignancies, including lymphoma and non-melanoma skin cancer, macrophage activation syndrome, gastrointestinal perforations, should be provided and compared to the expected rate of these events based on historical controls.

***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 tofacitinib 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 (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. 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):

Full report for Studies 1, 2, and 3, and an interim report for Study 4 must be submitted to the Agency on or before October 31, 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.

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

/s/

MARY H PARKS
07/12/2016