DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125377

WRITTEN REQUEST – AMENDMENT 1

Bristol-Myers Squibb Company
Attention: Kruti Patel, R.Ph.
Associate Director
Global Regulatory Affairs, Safety and Biometrics-US Oncology
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. Patel:

Please refer to your response dated December 10, 2014 to the Pediatric Written Request (WR) for Ipilimumab issued July, 7, 2014, the teleconference between FDA and BMS on June 25, 2015 and the correspondence dated July 20, 2015 in which you provided further justification for the proposal to delete Study 3 from the WR.

(b) (4)

We have reviewed your proposed changes to the ipilimumab WR and the additional justification provided for them. (b) (4)

We are therefore amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on July 7, 2014, remain the same. (Text added is underlined. Text deleted is strikethrough.)

In this submission, the Written Request was amended by removing Study 3 and extending the deadline for submission of the study report from Study 2:

~~**Study 3:**~~
~~A clinical study of ipilimumab in pediatric patients evaluating the anti-tumor activity (i.e., durable objective response rate) of ipilimumab in specified relapsed or treatment-refractory solid tumors other than melanoma. Primary tumors in which ipilimumab activity may be evaluated in this study include, but are not limited to, rhabdomyosarcoma and other soft tissue sarcomas, Ewing sarcoma, osteosarcoma, neuroblastoma, Wilms tumor, Hodgkin's or non-Hodgkin's lymphoma.~~

Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency on or before the following dates:

Study 1: February 1, 2015
Study 2: December, 2018 ~~2017~~
Study 4: To be determined upon discussion with the Division of Oncology Products 2

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 7, 2014, as amended by this letter and by previous amendment dated July 20, 2015, must be submitted to the Agency per the dates listed in attachment 1in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

If FDA has not determined whether ipilimumab is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this Written Request amendment, nor any request for exclusivity made by you, confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.

Submit reports of the studies as a supplement to an approved BLA 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 to the Office of New Drugs, Immediate Office, Therapeutic Biologics and Biosimilars Team, 10903 New Hampshire Ave, Building 22, Mail Stop 6411, Silver Spring, MD 20993. If you wish to fax it, the fax number is 301-796-9855.

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 Gina Davis, Senior Regulatory Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, M.D.
Associate Director for Oncology Sciences
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Attachment 1 - Clean Copy of Written Request as Amended – Amendment 1

ATTACHEMENT 1
WRITTEN REQUEST – AMENDMENT 1

Ipilimumab

Ipilimumab is a fully human monoclonal antibody specific for human cytotoxic T-lymphocyte antigen 4 (CTLA-4/CD152) expressed on a subset of activated T cells. Ipilimumab is thought to behave as a Tcell potentiator via blockade of the inhibitory signal of CTLA-4 resulting in T-cell activation and proliferation. The potential antitumor effect is through enhancement of a T-cell mediated immune response causing lymphocyte infiltration that may result in tumor cell death. This mechanism of action also underlies the toxicity profile of ipilimumab which is notable for immune-mediated adverse reactions including hepatitis, enterocolitis, dermatitis, neuropathies and endocrinopathies. Ipilimumab was approved for the treatment of unresectable or metastatic melanoma in adult patients based on the results of Study MDX010-20, a randomized (3:1:1), double-blind, double-dummy study conducted in 676 previously-treated patients who were randomized to receive ipilimumab in combination with an investigational peptide vaccine (gp100), ipilimumab alone, or gp100 alone. This trial demonstrated a statistically significant improvement in overall survival for the ipilimumab plus gp100 arm compared to the gp100 monotherapy control arm; median survival times were 10 and 6 months respectively.

Pediatric Tumors to be Studied

Melanoma in the pediatric and adolescent populations is rare; however, the incidence across all age groups continues to increase at a rate of approximately 2% per year in individuals< 20 years of age. The estimated incidence of melanoma (all stages) reported in 2008 among children age 0 to 14 years was 2 cases per million in North America. Patients < 20 years of age account for approximately 2% of all melanoma diagnoses, and 15 to19 year old patients account for the vast majority of these cases. Melanoma comprises approximately 8% of all cancers in patients 15 to19 years of age. There is no approved treatment for pediatric patients with metastatic melanoma. Similar to adult patients, surgical resection, if feasible, for limited metastatic disease is recommended. For the small subset of patients with distant metastatic disease, prognosis remains poor, and various agents such as interferon, dacarbazine, temozolomide, sorafenib, or interleukin-2 have been utilized. Studies are limited due to very small numbers of children and adolescents with melanoma to conduct pediatric clinical trials. In addition, age restrictions of current melanoma clinical trials have precluded the enrollment of children and/or adolescents.

Although prepubescent patients appear to have different disease characteristics compared to adult melanoma patients (higher likelihood of predisposition syndromes, nodal metastases at diagnosis, nodular or spitzoid histology, thicker lesions and head/face/neck primaries), adolescents are comparable to adult patients with regard to key primary tumor characteristics (primary site, histology, stage at diagnosis, specific genetic mutations, thickness, and level of invasion). Survival data from adult melanoma patients demonstrate a disease stage-dependent outcome that appears to be independent of age in subgroup analyses. Similarly, overall survival in pediatric patients is predicted by melanoma characteristics (e.g., primary site, histology, stage at diagnosis, thickness, and level of invasion) but not age. BMS has provided data to justify the assumption of a similar exposure-response in adolescents compared to adult melanoma patients

receiving ipilimumab. This information, in the setting of a rare and life-threatening disease with lack of alternative therapies, appears to support extrapolation of adult efficacy data for the pediatric development of ipilimumab in adolescent patients with advanced melanoma. Additional investigation of ipilimumab activity in non-melanoma pediatric solid tumors is also warranted. The effectiveness of immunologically-directed treatment (e.g., anti-CTLA4 or anti-PD1 or PD-L1 directed therapy) has not been explored as extensively in pediatric cancers as for many adult tumors; however, at least some childhood cancers (e.g. neuroblastoma, Ewings sarcoma) may benefit from drugs that augment host anti-tumor immune responses.

To obtain needed pediatric information on ipilimumab and information on the utility of ipilimumab in adolescents with melanoma, 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. The occurrence of congenital and infantile melanoma is exceedingly rare as is transplacental metastasis from a maternal melanoma, therefore, investigation of ipilimumab in the neonatal population is not being requested.

- *Nonclinical studies*:

  The nonclinical studies have been completed and results have been reported to FDA prior to the initiation of clinical studies. 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:
  An open label, dose-escalation study of ipilimumab in pediatric patients (aged 1 to 21 years) with refractory cancer .

  Study 2:

  A clinical study of ipilimumab in pediatric patients (12 to $\leq$ 18 years) with unresectable or metastatic melanoma to evaluate PK and safety.

  - Efficacy in adolescent patients (12 to $\leq$ 18 years) will be determined by extrapolation from results observed in adult patients treated with ipilimumab for unresectable or metastatic melanoma.

Study 4:
If further evaluation of ipilimumab is warranted based on results of Studies 1, or 2, ~~or 3,~~ one or more studies will be conducted to establish the safety and efficacy of ipilimumab in specific pediatric indications.

The protocol for study 4 must be submitted for FDA review and approval prior to patient enrollment.

- *Objectives of each study:*

  Study 1:
  - To determine the safety and tolerability of ipilimumab in pediatric patients with solid tumors that are refractory to standard therapy over a range of doses.
  - To assess the pharmacokinetics (PK) of ipilimumab, administered intravenously, in pediatric patients with solid tumors that are refractory to standard therapy.
  - To obtain preliminary evidence of the antitumor activity of ipilimumab in pediatric patients with solid tumors that are refractory to standard therapy.

  Study 2:
  - To estimate ipilimumab clearance (CL) and volume of distribution (Vd) in patients age 12 to ≤ 18 years with unresectable or metastatic melanoma.
  - To assess the safety and tolerability of ipilimumab in patients age 12 to ≤ 18 years with unresectable or metastatic melanoma.
  - To estimate the best overall response rate (BORR) and the response duration in patients age 12 to ≤ 18 years with unresectable or metastatic melanoma.

  Study 4:
  - To establish the effectiveness of ipilimumab in the proposed study population.
  - To assess safety and tolerability in patients age 1 to ≤ 18 years with specific primary cancer(s) based on the results of Study 3,
  - To assess the PK of ipilimumab in patients age 1 to ≤ 18 years with specific primary cancer(s), including assessment of drug interactions if appropriate.

- *Patients to be Studied:*

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

    Study 1: Patients 1 to 21 years of age.
    Study 2: Patients 12 to ≤ 18 years of age.
    Study 4: Patients 1 to ≤ 18 years of age, if appropriate

  - *Number of patients to be studied:*

    Study 1:
    At least 30 patients, including at least 6 patients enrolled at the highest dose tolerable for each of the following age groups: children 1 to 12 years of age and adolescents 12 to ≤ 18 years of age.

    Study 2:
    At least 30 patients, with at least 20 patients treated at approved dosing regimen for ipilimumab (3 mg/kg as an intravenous infusion every 21 days for up to 4 cycles).

Study 4:
A sufficient number of patients to establish the safety and effectiveness of ipilimumab for the treatment of one or more specific pediatric primary solid tumors.

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:*

  - *Pharmacokinetic/Pharmacodynamic Endpoints:*

    All studies:
    Ipilimumab trough concentrations obtained from samples collected in a minimum of 8 patients in each of the following age groups: 1 to < 12 years and 12 to < 18 years from the start of ipilimumab treatment through the last dose. The age groups are based on the identification of an apparent age-dependent maximum tolerated dose identified in Study 1.

    Study 2:
    Estimated ipilimumab CL and Vd from samples collected from an adequate number of adolescents age 12 to < 18 years old with unresectable or metastatic melanoma to target a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of CL and Vd of ipilimumab with 80% power.

  - *Efficacy Endpoints*

    Study 1:
    Best objective response rate (ORR) and duration of responses using RECIST 1.1 criteria.

    Study 2:
    ORR and duration of responses using RECIST 1.1 criteria.

    Study 4:
    Evidence of clinical benefit, including overall survival, event-free survival, and/or progression-free survival.

  - *Safety Endpoints:*

    Study 1:
    The key endpoint for Study 1 will be defining the age appropriate MTD and recommended phase 2 dose of ipilimumab in pediatric patients based on the frequency of observed dose-limiting toxicities. The rate and clinical course of adverse events including, but not limited to, ipilimumab-induced immune-related AEs, will be evaluated. The type, frequency, duration, and severity of laboratory abnormalities will also be analyzed.

Study 2:
Characterization of safety will include descriptive analyses of adverse events, including the incidence, severity, and clinical outcomes of all adverse events, and the incidence, severity, and clinical outcomes of severe, serious and fatal adverse events. Type, frequency, duration, and severity of laboratory abnormalities will also be analyzed using descriptive statistics.

Study 4:
Characterization of safety, by primary cancer type if appropriate and by overall study population, will include descriptive analyses of adverse events, including the incidence, severity, and clinical outcomes of all adverse events, and the incidence, severity, and clinical outcomes of severe, serious and fatal adverse events. The type, frequency, duration, and severity of laboratory abnormalities will also be analyzed using descriptive statistics.

- *Known Drug Safety concerns and monitoring:* For adults treated with ipilimumab at doses of 3 mg/kg administered intravenously every 3 weeks, the most frequently reported adverse reactions are fatigue, diarrhea, pruritus, rash, and colitis. Ipilimumab has also resulted in severe and fatal immune-mediated reactions due to T-cell activation and proliferation in adults. Therefore, the eligibility criteria for all studies will exclude patients with chronic autoimmune disorders and patients with known liver and/or endocrine dysfunction. Study 1 will incorporate a stopping rule in the event that 2 of 6 patients experience grade 4 non-hematologic toxicity or grade 5 toxicity that is at least possibly related to ipilimumab and occurs within one month of receiving any dose of ipilimumab. All clinical study protocols will incorporate surveillance for such immune-mediated events, close monitoring of patients, and an algorithm for medical management of anticipated adverse reactions.

  The safety and efficacy of ipilimumab in pregnant women has not been established. Animal toxicology studies demonstrate an increased incidence of abortion, stillbirths and postnatal deaths in monkeys who received ipilimumab during pregnancy and developmental abnormalities in infant monkeys exposed to ipilimumab in utero. All patients of childbearing potential enrolled in the above studies must therefore use highly effective contraception during treatment and for 5 months after the end of treatment. Pregnancy tests for women of childbearing potential will be conducted at screening, at defined time points while on study, and during safety follow-up.

  Patients on the above studies will be followed for toxicity for a minimum of 90 days following the last dose of ipilimumab and until any related adverse event resolves, returns to baseline or is deemed irreversible. Patients will be followed for long-term survival information.

  The safety and efficacy of ipilimumab in pregnant women has not been established. Animal toxicology studies demonstrate an increased incidence of abortion, stillbirths and postnatal deaths in monkeys who received ipilimumab during pregnancy and developmental abnormalities in infant monkeys exposed to ipilimumab in utero. All patients of childbearing potential enrolled in the above studies must therefore use highly effective contraception during treatment and for 5 months after the end of treatment. Pregnancy tests

for women of childbearing potential will be conducted at screening, at defined time points while on study, and during safety follow-up.

Patients on the above studies will be followed for toxicity for a minimum of 90 days following the last dose of ipilimumab and until any related adverse event resolves, returns to baseline or is deemed irreversible. Patients will be followed for long-term survival information.

Specific monitoring for immune-induced endocrinopathies and other auto-immune reactions will occur at regular, protocol-specified timepoints. Guidelines for mitigation and/or management of such will be provided in the protocol. All studies will be conducted under the oversight of a Data and Safety Monitoring Committee.

- *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:* Solution for injection (200 mg/40 mL vial and 50 mg/10 mL vial)
  - *Route of administration:* Intravenous
  - *Regimen:*

- *Statistical information, including power of studies and statistical assessments:*

Study 1:
This trial will use a 3+3 dose escalation design to study the toxicity profile of ipilimumab at doses tolerable in adult trials. All statistics will be descriptive. The highest dose tolerated will be defined as the dose level immediately below the level at which ≥ 2 patients in a cohort of 2 to 6 patients experienced a DLT attributable to ipilimumab. Safety outcomes will include an analysis of adverse events, including the incidence of adverse events, severe adverse events, serious adverse events, and fatal adverse events. The rate of severe immune-related adverse events including, but not limited to, enterocolitis, dermatitis, hepatitis, endocrinopathies and neuropathies will be evaluated. Type, frequency, and severity of laboratory abnormalities will also be analyzed for each cohort. Safety analyses will be performed in aggregate, by dosing cohort, and by age group (< 12 years of age and 12 to ≤ 21 years of age).

Tumor response will be assessed using the RECIST 1.1 criteria. Patients will be considered evaluable for tumor response if they complete at least one cycle of therapy, or if they experience progressive disease prior to that time.

Study 2:
The primary safety endpoints will be reported using descriptive statistics. ORR will be assessed using RECIST 1.1 criteria and 95% exact CI will be provided; however, an extrapolation approach will be utilized for determining efficacy in adolescent melanoma patients.

With regard to PK collection, Study 2 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 CL and Vd of ipilimumab with 80% power in pediatrics aged 12 to ≤ 18 years administered a dose of 3 mg/kg. The choice of the sample size and sampling scheme for the study must be justified. Either non-compartmental analysis (NCA) based on rich pharmacokinetics sampling or population pharmacokinetic modeling analysis based on sparse PK sampling can be applied to achieve this precision standard. After initial data from the study are evaluated, if the goals for characterizing pharmacokinetics across the intended age range are not achieved, the sample size must be increased as necessary to meet the goals of the study.

Study 4:

A statistical analysis plan with the protocol will be submitted to the Agency for review prior to enrolling patients onto Study 4.

Protocols for Studies 2, and 4 must be reviewed and approved by the Agency prior to patient enrollment.

Labeling that may result from the studies: You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that ipilimumab 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/FormsSubmissionRequire ments/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 must be submitted to the Agency on or before the following dates:

  Study 1: February 1, 2015
  Study 2: December, 2018
  Study 4: To be determined upon discussion with the Division of Oncology Products 2

  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, HFD-600, Metro Park North IV, 7519 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/

GINA M DAVIS
04/11/2016

GREGORY H REAMAN
04/11/2016