DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT 1

NDA 22307

Eli Lilly and Company
Attention: Peter Morrow, M.Sc.
Director, Global Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Mr. Morrow:

Please refer to your correspondence dated May 24, 2013, requesting changes to FDA's December 19, 2012 Written Request for pediatric studies for EFFIENT®(prasugrel).

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on December 19, 2012, remain the same. (Text added is underlined. Text deleted is strikethrough.)

- *Clinical studies:*

  Study 1 (TACX): An Open-Label, Dose-Ranging Study of Prasugrel in Pediatric Patients with SCD.

  In Study TACX (Parts A and B), a cohort of older children (~~12~~ 8 to <18 years of age) must be evaluated before enrollment of younger children.

- *Patients to be studied:*

  Study 1 (TACX):
  - *Age group in which study will be performed*: patients with SCD ages ≥2 and <18 years of age. The following 3 age groups and numbers of patients will be studied:
    - ≥2 to <6 years: At least ~~12~~ 7 patients must be enrolled; at least ~~11~~ 5 must complete the study
    - ≥6 to <12 years: At least 12 patients must be enrolled; at least ~~11~~ 10 must complete the study
    - ≥12 to <18 years: At least 12 patients must be enrolled; at least ~~11~~ 10 must complete the study

  - *Number of patients to be studied:* At least ~~36~~ 33 pediatric patients with SCD will be enrolled, and a minimum of ~~33~~ 29 patients must complete the study.

  Study 2 (TADO):
  - *Age group in which study will be performed*: patients with SCD ages ≥2 and <18 years of age. The following 3 age groups and numbers of patients will be studied:

- ≥2 to <6 years: At least ~~68 patients (34 prasugrel, 34 placebo)~~ 50 patients (approximately 25 in each blinded treatment group [prasugrel and placebo]) must be enrolled and complete ~~the study treatment period~~ at least 9 months of the double-blind treatment period.
- ≥6 to <12 years: At least ~~68 patients (34 prasugrel, 34 placebo)~~ 70 patients (approximately 35 in each blinded treatment group [prasugrel and placebo]) must be enrolled and complete ~~the study treatment period~~ at least 9 months of the double-blind treatment period.
- ≥12 to <18 years: At least ~~68 patients (34 prasugrel, 34 placebo)~~ 70 patients (approximately 35 in each blinded treatment group [prasugrel and placebo]) must be enrolled and complete ~~the study treatment period~~ at least 9 months of the double-blind treatment period.

- *Number of patients to be studied:* At least 204 pediatric patients with SCD must be enrolled and complete ~~the study treatment period~~ at least 9 months of the double-blind treatment period.

Efficacy Endpoints:

Study 2 (TADO):
The primary efficacy endpoint will be the reduction in the rate of VOC, which will be a composite of the following: pain crisis ~~and~~ or acute chest syndrome. Pain crisis will be defined as a new onset of pain that lasts at least 2 hours for which there is no explanation other than vaso-occlusion and which requires therapy with oral or parenteral opioids or ketorolac, or other analgesics prescribed by a health care provider in a medical setting, such as a hospital, clinic, emergency room visit, or telephone management. Acute chest syndrome will be defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray.

Major secondary efficacy endpoints will include the following:

1. Reduction in the rate of sickle cell-related pain as recorded in patient pain diaries*
2. Reduction in the rate of hospitalization for VOC
3. Reduction in the rate of ~~VOC excluding acute chest syndrome~~ painful crisis
4. Reduction in the rate of acute chest syndrome
5. Reduction in the rate of blood transfusion for complications of SCD
6. Reduction in the intensity of sickle cell-related pain as recorded in patient pain diaries
7. Use of analgesics as measured in patient pain diaries
8. School attendance as measured in patient pain diaries

*The pain diary to be used in this study must include a validated pain scale, to be submitted along with the study protocol for review by the Agency prior to the deadline agreed to herein (see below).

- *Known drug safety concerns and monitoring:*

Study 1 (TACX) *and Study 2* (TADO):

Given the known risk of bleeding associated with prasugrel administration, (a) the proposed pediatric trials must exclude any SCD patient considered to be at high risk for stroke, using currently accepted clinical criteria, and (b) patients must be adequately monitored for bleeding complications during prasugrel treatment and for the duration of the study period. Safety endpoints will include assessment of the following:

- Incidence of hemorrhagic events requiring medical intervention (defined as medical attention, from a trained medical professional, that results in therapy or further investigation)
- Incidence of hemorrhagic TEAEs
- Rate of study drug discontinuation due to hemorrhagic and nonhemorrhagic TEAEs

At a minimum, an external, independent safety reviewer must be utilized in Study TACX for periodic review of study data.

A data safety monitoring board or committee (DSMB/ DSMC) must be utilized in ~~both studies~~ Study TADO for periodic review of study data and for the recommendation of changes as needed.

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

Reports of the studies that meet the terms of the Written Request dated December 19, 2012, as amended by this letter must be submitted to the Agency on or before January 14, 2016, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Reports of the studies 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.

If you have any questions, call Lara Akinsanya, Regulatory Project Manager, at 301-796-9634.

Sincerely,

{See appended electronic signature page}

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

Attachment (Complete Clean Copy of Written Request as amended)

NDA 22307 **WRITTEN REQUEST**

Eli Lilly and Company
Attention: Peter Morrow, M.Sc.
Director, Global Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Mr. Morrow:

Reference is made to your April 30, 2012 Proposed Pediatric Study Request for EFFIENT® (prasugrel).

These studies investigate the potential use of prasugrel in the prevention of vaso-occlusive crises (VOC) in pediatric patients with sickle cell disease (SCD) 2 to <18 years of age.

SCD is a genetic disorder characterized by a point mutation in the β-globin chain of hemoglobin, and affects an estimated 1 in 5,000, or ~70,000 people in the U.S. Complications include: acute chest syndrome, stroke, splenic sequestration crisis, aplastic crisis, hemolytic crisis, vaso-occlusive crisis (VOC), priapism, osteomyelitis, overwhelming post-(auto) splenectomy infection (OPSI), acute papillary necrosis of the kidney, chronic renal failure due to sickle cell nephropathy, and pulmonary hypertension, among other complications. Currently there are no approved drugs for the treatment of SCD in the pediatric population. The development of safe and effective agents for this indication would thus address a currently unmet medical need and would provide a significant public health benefit.

Efficacy in pediatric patients with SCD cannot be extrapolated from available data in adult patients with acute coronary syndrome and will be determined by the studies outlined in the Written Request (WR). The incidence of pain crises in patients with SCD is lower in the first 2 years of life, particularly in neonates, corresponding to greater levels of circulating fetal hemoglobin (HbF) compared to later childhood. Accordingly, neonates and pediatric patients less than 2 years of age will not be studied. The age group requested for study is 2 to <18 years of age.

To obtain needed pediatric information on prasugrel, 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 data, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*

  Study 1 (TACX): An Open-Label, Dose-Ranging Study of Prasugrel in Pediatric Patients with SCD.

In Study TACX (Parts A and B), a cohort of older children (8 to <18 years of age) must be evaluated before enrollment of younger children.

Study 2 (TADO): A Phase 3, Double-Blind, Randomized, Efficacy and Safety Comparison of Prasugrel and Placebo in Pediatric Patients with SCD

The PK/PD study (TACX) must be completed before, and used to inform dosing in, the efficacy trial (TADO). Results of trial TACX and relevant adult data used to propose pediatric dose(s) must be submitted along with the final protocol for TADO before initiation of trial TADO. Justification of the proposed dose and trial design for TADO must be agreed upon by the Agency before initiation of the trial. This may require additional dose exploration if the available information is not adequate.

- *Objective of each study:*

  Study 1 (TACX): To identify the dose(s) of prasugrel to be studied in TADO, and to assess the tolerability of prasugrel in pediatric patients with SCD.

  Study 2 (TADO): To assess the efficacy and safety of prasugrel for the reduction of VOC in pediatric patients with SCD.

- *Patients to be studied:*

  Study 1 (TACX):
  - *Age group in which study will be performed*: patients with SCD ages ≥2 and <18 years of age. The following 3 age groups and numbers of patients will be studied:
    - ≥2 to <6 years: At least 7 patients must be enrolled; at least 5 must complete the study
    - ≥6 to <12 years: At least 12 patients must be enrolled; at least 10 must complete the study
    - ≥12 to <18 years: At least 12 patients must be enrolled; at least 10 must complete the study

  - *Number of patients to be studied:* At least 33 pediatric patients with SCD will be enrolled, and a minimum of 29 patients must complete the study.

  Study 2 (TADO):
  - *Age group in which study will be performed*: patients with SCD ages ≥2 and <18 years of age. The following 3 age groups and numbers of patients will be studied:
    - ≥2 to <6 years: At least 50 patients (approximately 25 in each blinded treatment group [prasugrel and placebo]) must be enrolled and complete at least 9 months of the double-blind treatment period
    - ≥6 to <12 years: At least 70 patients (approximately 35 in each blinded treatment group [prasugrel and placebo]) must be enrolled and complete at least 9 months of the double-blind treatment period
    - ≥12 to <18 years: 70 patients (approximately 35 in each blinded treatment group [prasugrel and placebo]) must be enrolled and complete at least 9 months of the double-blind treatment period

- *Number of patients to be studied:* At least 204 pediatric patients with SCD must be enrolled and complete at least 9 months of the double-blind treatment period.

- *Study design:*

  Study 1 (TACX): A Phase 2 PK and PD dose escalation and dose-ranging (Part A) and dose tolerability (Part B) study.

  Study 2 (TADO)*:* Phase 3, randomized, double-blind, placebo-controlled trial in which patients are randomized 1:1 to receive either prasugrel or placebo for at least 9 months and up to a maximum of 24 months. Evaluation of all patients must continue through a follow-up period of 4 weeks after last dose of study drug.

  Study 1 (TACX) and *Study 2* (TADO):
  The collection of PK data must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution with 80% power for prasugrel in each age group. This means, a minimum of 10 patients in each age group of ≥ 2 to < 12 years and ≥ 12 to <18 years must be sampled for pharmacokinetics in studies TACX and TADO combined. This requirement may be met by collecting PK in either study alone or throughout both studies. Pharmacokinetic samples must be collected through approaches such as rich sampling or optimal sparse sampling. Such data must then be appropriately analyzed using methods such as mixed effects modeling or noncompartmental analysis.

- *Study endpoints:*

  ☐ *Pharmacokinetic Endpoints:*

  Study 1 (TACX) and/or *Study 2* (TADO): Prasugrel apparent clearance and volume of distribution must be determined from either or both *Study 1* and *Study 2*.

  ☐ *Pharmacodynamic Endpoints:*

  Study 1 (TACX) and *Study 2* (TADO): Data from study TACX and TADO must be used to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness. The Review Division must agree on the PD endpoint(s) to be used in Study 1 & Study 2.

  Efficacy Endpoints:

  Study 2 (TADO):
  The primary efficacy endpoint will be the reduction in the rate of VOC, which will be a composite of the following: pain crisis or acute chest syndrome. Pain crisis will be defined as a new onset of pain that lasts at least 2 hours for which there is no explanation other than vaso-occlusion and which requires therapy with oral or parenteral opioids or ketorolac, or other analgesics prescribed by a health care provider in a medical setting such as a hospital, clinic, emergency room visit, or telephone management. Acute chest syndrome will be defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray.

Major secondary efficacy endpoints will include the following:

1. Reduction in the rate of sickle cell-related pain as recorded in patient pain diaries*
2. Reduction in the rate of hospitalization for VOC
3. Reduction in the rate of painful crisis
4. Reduction in the rate of acute chest syndrome
5. Reduction in the rate of blood transfusion for complications of SCD
6. Reduction in the intensity of sickle cell-related pain as recorded in patient pain diaries
7. Use of analgesics as measured in patient pain diaries
8. School attendance as measured in patient pain diaries

*The pain diary to be used in this study must include a validated pain scale, to be submitted along with the study protocol for review by the Agency prior to the deadline agreed to herein (see below).

☐ *Safety Endpoints:*

Study 1 (TACX) *and Study 2* (TADO):
Safety endpoints will include assessment of the following:

- Incidence of hemorrhagic events requiring medical intervention (defined as medical attention, from a trained medical professional, that results in therapy or further investigation)
- Incidence of hemorrhagic treatment-emergent adverse events (TEAEs)
- Tolerability of prasugrel compared to placebo as measured by the rate of study drug discontinuation due to hemorrhagic and nonhemorrhagic TEAEs

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.

- *Known drug safety concerns and monitoring:*

Study 1 (TACX) *and Study 2* (TADO):
Given the known risk of bleeding associated with prasugrel administration, (a) the proposed pediatric trials must exclude any SCD patient considered to be at high risk for stroke, using currently accepted clinical criteria, and (b) patients must be adequately monitored for bleeding complications during prasugrel treatment and for the duration of the study period. Safety endpoints will include assessment of the following:

- Incidence of hemorrhagic events requiring medical intervention (defined as medical attention, from a trained medical professional, that results in therapy or further investigation)
- Incidence of hemorrhagic TEAEs
- Rate of study drug discontinuation due to hemorrhagic and nonhemorrhagic TEAEs

At a minimum, an external, independent safety reviewer must be utilized in Study TACX for periodic review of study data.

A data safety monitoring board or committee (DSMB/ DSMC) must be utilized in Study TADO for periodic review of study data and for the recommendation of changes as needed.

- *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*
    An age-appropriate formulation must be used (see below).

  - *route of administration*
    Study drug will be administered orally (PO), per the labeled route of administration (PO) for prasugrel.

  - *regimen*
    Dosing and regimen for in Study 2 (TADO) must be supported by the results in Study 1 (TACX).

    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 compounded 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 compounding an age-appropriate formulation from commercially available ingredients that

are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies 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 2 must have a detailed statistical plan. A preliminary statistical analysis plan must be submitted for comment prior to initiating the efficacy and safety study, and you must obtain agreement on the final statistical plan prior to 25% enrollment.

  Study 2 must be designed with at least 85% statistical power to detect a clinically meaningful treatment effect at a Type I error rate of 5% (two-sided). You must obtain agreement with the Division with regard to the treatment effect prior to initiating the study. For the purpose of satisfying the Written Request, this treatment effect might, for example, be defined as a 35% reduction in the VOC rate.

  To ensure that the study is adequately powered, you should obtain an estimate of the overall event rate from an interim analysis, and then follow a pre-specified rule to adjust the sample size to achieve the specified target power. You may estimate the overall event rate based on a blinded and pooled analysis of all groups, in which case no alpha-spending adjustment is required for this interim analysis. If, however, you want to perform an efficacy assessment at this or some other interim analysis, an appropriate alpha adjustment would be required.

- *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 prasugrel 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 FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.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/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before January 14, 2016. 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.

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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, call Lara Akinsanya, Regulatory Project Manager, at 301-796-9634.

Sincerely,

{See appended electronic signature page}

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

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

/s/

GREGORY H REAMAN
07/24/2013