DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202806

WRITTEN REQUEST

Novartis Pharmaceuticals Corporation
Attention: Amita Chaudhari, M.Sc.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Chaudhari:

Reference is made to your August 31, 2015, revised Proposed Pediatric Study Request (PPSR) for Tafinlar (dabrafenib) capsules.

We also refer to our January 11, 2016, comments regarding the revised PPSR, our January 12, 2016, teleconference to discuss alternative study designs for Study 2, and to your January 27, 2016, response to our January 11, 2016, comments.

BACKGROUND:

These studies investigate the potential use of dabrafenib in the treatment of pediatric patients with relapsed or refractory solid tumors containing BRAF V600 activating mutations and in the treatment of adolescent patients with unresectable or metastatic melanoma containing BRAF V600 activating mutations.

Despite the improvements in survival observed in the last three decades as a result of the multidisciplinary approach applied overall to pediatric solid tumors, including brain tumors, the prognosis for patients with recurrent or metastatic disease remains poor.

Dabrafenib (Taflinar®) is an oral kinase inhibitor with activity against some mutated forms of BRAF kinase. It was approved in 2012 as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Dabrafenib, in combination with trametinib, was subsequently approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test.

BRAF is a protein that mediates the RAS-RAF-MEK-ERK signaling pathway and is involved in a variety of cellular functions including cell proliferation, cell cycle arrest, terminal differentiation, and apoptosis. Multiple cancer-associated mutations have been identified in the BRAF gene, including the

V600E activating mutation which has been identified at a high frequency in certain cancer types. While BRAF inhibition with dabrafenib has been associated with tumor response in adult patients with BRAF V600 mutant melanoma, it is not clear that a similar rate of response can be generalized across all BRAF V600 mutant tumor types. Children and adolescents with refractory solid tumors harboring the BRAF V600 mutation are a population with limited treatment options in which the safety and efficacy of dabrafenib should be evaluated. Pediatric cancers that express the BRAF V600 mutation in a subpopulation of patients include recurrent or advanced melanoma, Langerhans cell histiocytosis (LCH), low- and high-grade gliomas, and papillary thyroid cancer (PTC).

Melanoma in the pediatric population is rare; however, the incidence across all age groups continues to increase at a rate of approximately 2% per year in individuals less than 20 years of age. 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). Additionally, survival in both the adult and pediatric populations is predicted by characteristics of the melanoma (e.g., primary site, histology, stage at diagnosis, thickness, and level of invasion) but not by age. This information supports extrapolation of tumor response data from adults with melanoma treated with dabrafenib to adolescent patients, if the systemic exposures achieved in adolescent patients are similar to that in adults.

The incidence of pediatric high grade glioma (HGG) in the United States is approximately 0.85 per 100,000 (CBTRUS, 2012). The most common HGGs are anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM). Other less common pediatric HGGs include anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic ganglioglioma, anaplastic pilocytic astrocytoma and giant cell glioblastoma and gliosarcoma. After primary treatment with surgery and adjuvant chemotherapy and/or radiotherapy, the majority of patients with HGG develop recurrent disease. There is no accepted second-line therapy in clinical practice, and the literature reports approximately 10% response rates for patients who have failed frontline therapy and are treated with temozolomide. The median survival after initial diagnosis of a HGG is eighteen to twenty-four months. BRAF V600E mutations have been detected in approximately 10% of pediatric HGGs, and there are case reports of durable responses observed in pediatric patients with HGG treated with vemurafenib. This information supports the evaluation of dabrafenib in pediatric patients with HGGs with BRAF V600 activating mutations. Additionally, given the improved treatment effect observed in adult patients with BRAF mutant melanoma when dabrafenib is combined with trametinib as compared to dabrafenib alone, evaluation of the combination regimen may be worth exploring in this molecular subset of pediatric HGGs.

Other pediatric tumors that harbor BRAF V600 mutations include low-grade glioma (LGG), LCH and PTC. Although there are effective first-line local and systemic therapies for these conditions, patients with multiply recurrent or progressive disease after failing primary therapy have limited treatment options. These usually consist of further cytotoxic chemotherapy which has generally not been shown to impact survival, and in some cases of refractory LCH, allogeneic stem cell transplantation (SCT). Salvage cytotoxic chemotherapy regimens and SCT are associated with significant treatment-related morbidity and mortality. For the subgroup of patients with refractory BRAF V600 mutation positive disease, dabrafenib may offer an improved safety profile and therapeutic benefit.

In summary, dabrafenib has the potential to provide therapeutic benefit to pediatric patients with solid tumors with BRAF V600 activating mutations, which include unresectable or recurrent melanoma, LCH, low- and high-grade gliomas, and PTC. Efficacy in the subgroup of adolescent patients (12 through 18 years) with unresectable or metastatic BRAF V600 mutation positive melanoma could be determined by extrapolation from results observed in adult patients treated with dabrafenib alone or in combination with trametinib for the same indication. Efficacy in pediatric patients less than 12 years of age with melanoma and in patients 12 months to ≤ 18 years of age with BRAF V600 mutation positive solid tumors other than melanoma cannot be extrapolated from adult data and will be determined by the studies outlined in the Written Request. If there is encouraging antitumor activity observed with dabrafenib in initial studies, this Written Request additionally calls for evaluation of dabrafenib alone or in combination in patients with BRAF V600 mutation positive HGGs. Similar to other oncology drug development programs, objective response rate (ORR) and duration of response will be evaluated in early studies to detect potential antitumor activity signals, and progression free survival (PFS) is considered an acceptable surrogate endpoint to reasonably predict clinical benefit and can be used to assess efficacy in later studies.

FDA is not requesting studies in neonates because the occurrence of a refractory solid tumor with a BRAF V600E mutation in this population is rare. Additionally, based on nonclinical studies showing evidence of greater renal toxicity in rats less than 22 days old suggesting a higher risk for renal tubular injury for humans less than 12 months old, infants from birth up to 1 year of age will not be studied.

To obtain needed pediatric information on dabrafenib, 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: An open label, single arm, two-part study of dabrafenib in pediatric patients with refractory BRAF V600 mutation positive solid tumors.

- Part 1 will consist of a dose-escalation phase with a rolling six design to determine the recommended phase 2 dose (RP2D) of dabrafenib in specific age groups.
- Part 2 will consist of an expansion phase in four disease-specific cohorts (BRAF V600 mutation positive HGG, LGG, LCH, and other refractory BRAF V600 mutated tumors) treated at the RP2D to further characterize PK and evaluate safety and preliminary efficacy of dabrafenib.

Study 2: An open label, single arm, study of dabrafenib in pediatric patients with refractory, relapsed or progressive BRAF V600 mutation positive high grade glioma who have progressed after at least one line of therapy.

Study 3: An open-label, randomized, controlled study of dabrafenib alone or in combination in pediatric patients with BRAF mutation positive HGG, following standard of care surgical and adjuvant radiation therapy.

Study 4: If further evaluation of dabrafenib is warranted based on results of Study 1, one or more studies will be conducted to establish the safety and efficacy of dabrafenib in other pediatric refractory BRAF V600 mutation positive solid tumors.

- Study 1 must be completed before initiating enrollment in Study 2 to inform dosing.
- A protocol, including a statistical analysis plan, for studies 2, 3and 4 must be submitted for FDA review and approval prior to initiating enrollment.

Efficacy of dabrafenib alone or in combination with trametinib in adolescent patients (12 to less than 18 years of age) with unresectable or metastatic BRAF V600 mutation positive melanoma will be supported by extrapolation utilizing dabrafenib PK data from adolescent patients with melanoma or BRAF V600 mutation positive solid tumors other than melanoma and exposure-response relationships observed in adult patients with unresectable or metastatic BRAF V600 mutation positive melanoma treated with dabrafenib alone or in combination with trametinib.

Objectives of each study:

Study 1

- To determine the optimal safe and tolerable dose(s) of dabrafenib that achieves similar exposures to those achieved in adults, for chronic dosing in pediatric patients with relapsed or refractory BRAF V600-mutation positive solid tumors.
- To characterize the PK of dabrafenib in adolescent patients to support extrapolation of efficacy for the BRAF V600 mutation-positive unresectable or metastatic melanoma indication.
- To assess preliminary single-agent anti-tumor activity of dabrafenib.
- To assess the acceptability and palatability of the age-appropriate powder for oral suspension formulation and the acceptability of the capsules.

Study 2

- To estimate the overall response rate (ORR) and the response duration in pediatric patients with locally confirmed BRAF V600 mutation positive HGGs.
- To characterize the PK, safety and tolerability of dabrafenib in pediatric patients with BRAF V600 mutation positive HGG.

Study 3

- To compare the centrally confirmed progression free survival (PFS) of patients with BRAF V600E mutated HGG treated with dabrafenib alone or in combination to the PFS of patients treated with temozolomide.
- To compare confirmed response rates and duration of responses across treatment arms.
- To assess overall survival.
- To further characterize the population PK, safety and tolerability of dabrafenib alone or in combination in pediatric patients with BRAF V600 mutation positive HGG.

Study 4

- To estimate the ORR and response durations, and PFS in subgroups of pediatric patients with specific relapsed or refractory BRAF V600 mutation positive solid tumors other than melanoma and HGG.
- To further assess safety and tolerability in pediatric patients with BRAF V600 mutation positive refractory solid tumor (s).

- *Patients to be Studied:*

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

    Studies 1, 2, 3 and 4: Patients 1 to ≤18 years of age

  - *Number of patients to be studied:*

    Study 1: At least 48 patients, with at least 40 patients evaluable for response assessment.

    Part I - At least 6 patients; additional recruitment will depend on the occurrence of dose-limiting toxicities.

    Part II – At least 40 patients in order to enroll at least 10 evaluable patients for each disease-specific expansion cohort.

    Study 2: At least 20 patients.

    Additional patients may be enrolled in Study 2 to ensure that there are at least 20 patients with centrally confirmed BRAF V600 mutation, independently confirmed histologic Grades III & IV glioma by WHO criteria, and baseline measurable disease by Response Assessment in Neuro-Oncology (RANO) that is confirmed by a Blinded Independent Review Committee (BIRC).

Study 3: The sample size will be estimated based on the final study design and statistical analysis plan.

Study 4: The sample size will be estimated based on the final study design and statistical analysis plan.

A sufficient number of adolescent patients evaluable for dabrafenib PK across all studies to support extrapolation of efficacy of dabrafenib alone or in combination with trametinib in the treatment of adolescent patients with unresectable or metastatic BRAF V600 mutation positive melanoma.

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:*

  Efficacy Endpoints

  Study 1

  - Overall response rate (ORR) and duration of response according to Response Criteria in Solid Tumors version 1.1 (RECIST 1.1) for solid tumors, RANO criteria for gliomas and response criteria for LCH as defined in the 2009 Histiocyte Society Evaluations and Treatment Guidelines**.**
  - Acceptability, including palatability, of the oral suspension as assessed by a palatability questionnaire.

  Study 2

  - Primary endpoint - ORR and duration of responses as determined by central review according to RANO criteria. Investigator-assessed ORR is acceptable for treatment decisions.
  - Secondary endpoints - Overall survival (OS) and progression free survival (PFS).

  Study 3

  - Primary endpoint - PFS as determined by central review according to RANO criteria**.**
  - Secondary endpoints - ORR, duration of response and OS.

  Study 4

  - PFS, ORR and duration of responses. Other efficacy endpoints will be determined based on the disease being evaluated.

Safety Endpoints

- The primary endpoint for Study 1 is determination of the RP2D of dabrafenib in pediatric patients based on achievement of similar dabrafenib systemic exposures to those in adults or maximum tolerated dose (MTD) defined as the dose level below that which produces a dose limiting toxicity (DLT) in at least one third of evaluable patients during Cycle 1 of treatment, whichever occurs first.

- Safety outcomes for all studies must include a description 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, vital signs, routine laboratory parameters, growth parameters including effect on growth plates, and assessment of Tanner stages.

- The following known adverse events must be actively monitored: skin toxicity, ocular disorders, serious febrile reactions, hyperglycemia.

Pharmacokinetic/Pharmacodynamic Endpoints

Estimated dabrafenib clearance (CL) and volume of distribution (Vd) from pharmacokinetic samples obtained across all studies from a sufficient number of patients 12 to ≤ 18 years of age and a minimum of 8 patients in each of the following age groups: 1 to < 6 and 6 to < 12 years of age. Combine data from all completed studies to develop PK and pharmacodynamic models to explore exposure-response relationships for measures of safety and activity.

- *Known Drug Safety concerns and monitoring:*
  BRAF inhibition can result in the development of, or acceleration of, actinic keratosis, keratoacanthomas and squamous cell carcinoma (SCC); therefore, a risk management plan for the potential occurrence of skin findings, including squamous cell carcinoma, will be utilized for pediatric patients, and will be based on what has been put into place for the adult clinical studies of dabrafenib. Specifically, routine dermatologic evaluations will be included in all pediatric clinical trials. Dermatological examinations will include examination of skin and assessment of any skin changes. Biopsy in or around skin lesions that change during the study will be obtained, if clinically indicated. Skin photography of new non-melanoma skin lesions or non-melanoma lesions that change during the study will be obtained and requested to be forwarded to the Sponsor. Details regarding the lesion documentation by photography will be included in protocol procedure manuals.

  Dabrafenib can result in the development of uveitis, including iritis. Pediatric patients enrolled in dabrafenib studies will be monitored for visual signs and symptoms of uveitis including change in vision, photophobia, and eye pain. The study protocols will provide dose modification guidelines for ocular toxicity and instruct investigators to obtain ophthalmologic specialty consultation for new ocular symptoms.

Dabrafenib treatment can result in serious febrile reactions and hyperglycemia. Standard vital sign and laboratory parameter monitoring will be included in all pediatric studies.

- *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:* capsule formulation for children able to swallow capsules, dispersible tablet, or powder for oral suspension formulations.

  - *route of administration:* oral

  - *regimen:*

    Study 1*:* The starting total daily dose for dabrafenib is 3.0 mg/kg. Dose escalation will proceed based on toxicities observed during the first cycle of treatment and PK data.

    Studies 2, 3 and 4: Dabrafenib will be administered at the recommended phase 2 dose established in Study 1.

    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 studies and statistical assessments:*

Study 1
The primary endpoint will be defining the RP2D of dabrafenib in pediatric patients. This trial will use a Rolling Six dose-escalation design to evaluate the toxicity profile of dabrafenib. All statistics will be descriptive.

Study 2
The primary endpoint will be ORR. Utilizing a null and alternative hypothesis of 10% and 40% respectively, 20 evaluable subjects will be enrolled. With an actual type I error rate (α) of 0.038 and 92.8% power, the trial is designed to stop early for futility if the predictive probability of success falls below 6.4%. After the first 10 subjects have been enrolled, regular interim analyses will be conducted in order to determine whether the stopping criteria has been met.

The Bayesian prior probability used in determining the design was Beta (0.25, 0.75), a vaguely informative prior distribution with an effective sample size of 1 subject and a mean response rate of 25%. Under the null hypothesis, if the true response rate is 10%, the expected sample size of the design is 12.5 subjects and probability of early termination is 91.6%. Under the alternative hypothesis, if the true response rate is 40%, the expected sample size of the design is 19.6 subjects and probability of early termination is 5.3%. Success at the conclusion of the study will be defined as the posterior probability that the ORR >10% being greater than 89.9%. In addition to considering the recommendations of this non-binding futility analyses, final decisions on stopping enrollment will depend on the totality of the data collected. Should the recommendation to stop for futility be disregarded in favor of a decision to continue the trial based on the totality of the data, the overall type I error rate of the expansion phase will be inflated. In order to adjust for this, a nominal type I error of 5% will be used at the end of the main study.

Additional subjects may be enrolled to ensure that there are at least 20 evaluable patients with independently confirmed HGG, baseline measurable disease by RANO and centrally confirmed BRAFV600 mutation.

Patients will not be replaced when they discontinue the study due to: Progression (symptomatic or otherwise), toxicity related to dabrafenib, or lack of efficacy.

Study 3
The primary endpoint will be progression free survival (PFS). The study will enroll a sufficient sample size such that the trial is adequately powered to detect a clinically meaningful improvement in PFS.

Study 4
The analytic plan will be determined based on the disease being evaluated.

Pharmacokinetic analysis:
Studies must be prospectively powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for dabrafenib in the adolescent (12 to ≤ 18 years) age group with at least 80% power. Population PK analysis should be performed using dabrafenib concentration data obtained from all studies. Effect of age and body size on dabrafenib PK should be assessed. The relationship between systemic drug exposure and selected efficacy and toxicity endpoints may be explored.

- *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 dabrafenib 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):* Reports of Studies 1 and 2 must be submitted to the Agency on or before January 31, 2019. Upon receipt and evaluation of the study report, a decision will be made regarding design, conduct, and report submission deadlines for Studies 3 and 4. This information will require submission of a proposal to amend this Written Request if Studies 3 and 4 are not warranted. 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 studies. 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 studies, 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 studies 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 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 Norma Griffin, Lead Regulatory Health Project Manager, at 301-796-4255.

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

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
03/01/2016