IND 118981

WRITTEN REQUEST – AMENDMENT 3

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Coletti
Director, Regulatory Affairs
900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877

Dear Ms Coletti:[1]

Please refer to your December 9, 2016 Proposed Pediatric Study Request submitted to IND 118981 for afatinib; our April 7, 2017, Written Request letter for pediatric studies for afatinib; and to your May 12, 2017, notification stating your agreement to the Written Request.

We also refer to the following submissions with requests to amend your Written Request:

- June 14, 2017, amendment to IND 118981, containing revisions to Study 1200.120 titled "Phase I/II Open Label, Dose Escalation Trial to Determine the MTD, Safety, PK and Efficacy of Afatinib Monotherapy in Children Aged ≥1 Year to <18 Years with Recurrent/Refractory Neuroectodermal Tumours, Rhabdomyosarcoma and/or Other Solid Tumours with Known ErbB Pathway Deregulation Regardless of Tumour Histology" reflecting changes necessary to comply with the Written Request; and our August 14, 2017 Written Request—Amendment 1.

- February 7, 2019, correspondence requesting additional changes to FDA's amended Written Request for pediatric studies for afatinib; and our June 5, 2019, Written Request—Amendment 2.

- September 12, 2019, correspondence providing an update (b) (4) ; our October 31, 2019, advice letter advising you to submit an amended Written Request with revisions to the target enrollment and provide rationale for doing so; and your December 23, 2019, correspondence containing additional changes to FDA's amended Written Request for pediatric studies for afatinib.

We have reviewed your proposed changes and are amending the Written Request. For ease of reference, a complete copy of the Written Request, as amended, is attached to

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

this letter. All other terms stated in our Written Request issued on April 7, 2017, and as amended on August 14, 2017 and June 5, 2019, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Reports of the studies that meet the terms of the Written Request dated April 7, 2017, as amended by this letter and by previous amendment dated August 14, 2017 and June 5, 2019, must be submitted to the Agency on or before October 12, 2022, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

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

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[2]

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.

[2] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

If you have any questions, call Idara Udoh, Senior Regulatory Health Project Manager, at 301-796-3074.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, M.D.
Acting Associate Director, Pediatric Oncology
Office of Oncological Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Complete Copy of Written Request as Amended
- Complete Copy of Written Request as Amended (track changes)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201292

WRITTEN REQUEST

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Agnor, MS
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Agnor:

Reference is made to your December 6, 2016 Proposed Pediatric Study Request submitted to NDA 201292 for afatinib.

BACKGROUND:

The studies discussed in this Written Request letter investigate the potential use of afatinib for the treatment of pediatric patients with relapsed or refractory tumors with ErbB1 or ErbB2 pathway dysregulation, based on epidermal growth factor receptor (EGFR) or HER2 protein overexpression or EGFR or HER2 gene amplification, including relapsed or refractory neuroectodermal tumors and rhabdomyosarcomas.

Afatinib is a tyrosine kinase inhibitor that covalently binds the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ERbB4). Binding of afatinib to these receptors irreversibly inhibits auto phosphorylation, resulting in downregulation of ErbB signaling. On July 12, 2013, FDA granted approval to afatinib for use as first line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 (l858R) substitution mutations as detected by an FDA approved test. This approval was based on improvement in progression-free survival for patients treated with afatinib compared with pemetrexed/cisplatin chemotherapy. On April 15, 2016, FDA granted a new indication for afatinib for the treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy. This approval was based on improvement in progression free survival and overall survival for patients treated with afatinib as compared with erlotinib

The ErbB protein family, also known as EGFR family, is a family of four structurally related receptor tyrosine kinases (ErbB1/EGFR, ErbB2/HER2, ErbB3/HER3, ErbB4/HER4). The ErbB family plays an important role in normal embryonic development and constitutive activation of these receptors are involved in pathogenesis and progression of breast and gastric cancers

(ErbB2), lung cancer, squamous cell cancer of the head and neck, and glioblastoma (ErbB1), and lung and ovarian cancer (ErbB4).

Neuroectodermal tumors comprise a variety of pediatric malignancies derived from the portion of the ectoderm of the early embryo which gives rise to the central and peripheral nervous systems. Neuroectodermal tumors include high grade gliomas (HGG), diffuse intrinsic pontine gliomas (DIPG), refractory low grade astrocytomas (RLGA), neuroblastomas (NB), ependymomas (EM), and medulloblastomas/primitive neuroectodermal tumors (M/PNET).

Limited evidence shows a correlation between ErbB dysregulation and tumor histology in neurogenic tumors. Preclinical evidence suggests that ErbB pathway dysregulation is also present in rhabdomyosarcoma (RMS). Data from the literature shows the following:

- **EGFR**: The prognostic significance of EGFR expression has been evaluated in intracranial EM. Analysis of 68 sporadic tumors which included 29 pediatric samples revealed that the EGFR protein status subdivides intracranial grade II EMs into two different risk groups, and concluded that EGFR overexpression represents an independent prognostic marker and correlates with poor prognosis. In addition, several studies also reported significant overexpression of EGFR in pediatric DIPGs and HGGs. In rhabdomyosarcoma, EGFR is overexpressed in 50% of cases
- **HER2**: HER2 expression has been evaluated in patients diagnosed with neurogenic tumors, particularly medulloblastoma. In one study of 22 medulloblastoma samples, from both children and adults, 11 tumors showed solid expression of HER2 in 10 to 50% of neoplastic cells. In rhabdomyosarcoma HER2 was identified in 33% of cases and was more common in the alveolar subtype.
- **ErbB4**: Overexpression of ErbB4 with concomitant low EGFR expression is associated with refractory neuroblastoma.

While there are no FDA-approved drugs for pediatric neuroectodermal tumors and rhabdomyosarcomas, there are commonly used treatment regimens for newly diagnosed neuroectodermal tumors and rhabdomyosarcomas that prolong disease-free survival. However, once patients develop recurrent/refractory disease, treatment options are limited and outcomes are poor.

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) conducted a biomarker study that assessed the prevalence of ErbB dysregulation in tissue samples from pediatric patients with relapsed and recurrent neuroectodermal tumors including HGG, DIPG, RLGA, EM, M/PNETs, NB, and RMS and evaluated the technical feasibility of testing biomarkers indicative for ErbB dysregulation in the clinical setting.

In the biomarker study, seven different tumor types from a total of 277 pediatric patients were analyzed (48 EM, 48 HGG, 45 M/PNETs, 40 RLGA, 4 DIPG, 26 RMS, and 66 NB). Tumors were tested for the following biomarkers in order to establish useful cutoffs and qualify assay systems for later use in clinical trials:

- EGFR gene amplification using FISH
- EGFR protein expression determined using immunohistochemistry (IHC)
- HER2 protein expression using IHC
- HER2 gene amplification using dual-hapten dual-color *in situ* hybridization (DDish)

Based on the results of the biomarker study, BI proposes that tumors meeting two or more of the following criteria have evidence of ErbB dysregulation and may therefore be susceptible to treatment with afatinib:

- EGFR gene amplification (FISH): Either EGFR/Cen7[1] ≥ 2.0 or ≥10% of cells with ≥15 copies or ≥40% of cells with ≥ 4 copies or gene cluster in ≥10% of cells.
- HER2 gene amplification (DDISH): Her2/CEP17[2] ≥ 2.0
- EGFR protein expression: H-score > 150 (membrane staining)
- HER2 protein expression: H-score > 0 (membrane staining)

To obtain needed pediatric information on afatinib for the treatment of pediatric tumors with ErbB1 or ErbB2 dysregulation, 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 BI submits information from the studies described below. As discussed below neonates are not included in this Written Request.

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.

BI must submit the results of analytical validation studies for the planned biomarker assays, preferably in neuroectodermal tumor tissues and rhabdomyosarcomas, demonstrating the reliability and reproducibility of these assays.

CLINICAL STUDIES

- **Study 1(Study 1200.120):** A multicenter, open-label, two-part trial to identify a pediatric dose, assess the pharmacokinetics, and investigate the anti-tumor activity of afatinib when administered for the treatment of pediatric tumors with known ErbB pathway dysregulation.

    - Part 1: Dose finding to determine the dose limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, and pharmacokinetics of afatinib

[1] EGFR/Cen7 is a DNA-FISH probe designed to detecton increase in copy number of the EGFR gene
[2] Chromosome enumeration probe 17 (CEP17)

- Part 2: An activity-estimating, disease-specific parallel cohort study of afatinib in patients aged 1 to <18 years with relapsed or refractory tumors with evidence of ErbB-dysregulation based upon the presence of overexpression or amplification of EGFR or HER2 using the criteria established in the companion biomarker study. The study will have three tumor-specific cohorts: HGG ≥ 5 patients; EM ≥ 5 patients, DIPG ≥ 4 patients. In addition to these three disease-specific cohorts, the trial will include a histology-agnostic cohort of patients with refractory tumors, including those which were studied for biomarker feasibility or other tumors that fulfill the biomarker screening criteria; this cohort will have a minimum of five patients. The amendment to Part 2 of the ongoing trial 1200.120 must be reviewed and agreed upon by the FDA prior to enrollment.

- **Study 2:** Study(ies) designed to establish the safety and effectiveness of afatinib, as a single agent or as a component of multi-modality therapy in neuroectodermal tumors or rhabdomyosarcoma, if sufficient antitumor activity is observed in one or more tumor types in Part 2 of Study 1. Include in the study detailed information and support for the *in vitro* diagnostic device(s) used for patient selection. Design the study to isolate the effectiveness of afatinib. This protocol must be reviewed and agreed upon by FDA prior to enrollment of patients.

Efficacy in patients aged ≥1 to < 18 cannot be extrapolated and will be determined by the studies outlined in the WR.

OBJECTIVES OF EACH STUDY:

- **Study 1:**
  - Part 1:
    - Primary objectives: Determine the maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D), safety, and pharmacokinetics of afatinib in pediatric patients. The MTD of afatinib as monotherapy will be determined in the pediatric patient population across all applicable tumor types based on the occurrence of dose limiting toxicities (DLTs).
    - Secondary objectives: Explore the preliminary objective response by investigator assessment according to the protocol-specified response evaluation criteria for each tumor type studied.
  - Part 2:
    - Primary objectives: Determine the objective response rate (ORR) and duration of response (DOR) in children age ≥1years to <18 years in three disease specifc cohorts of pediatric patients with relapsed or refractory tumors.
    - Secondary objectives: Evaluation of progression free survival, and pharmacokinetics of afatinib.

- **Study 2:** The protocol and statistical analysis plan (SAP) for Study 2 must be submitted to FDA for review and agreement prior to patient enrollment in this study.

PATIENTS TO BE STUDIED

- Age group in which study(ies) will be performed: children ages 1 to < 18.

  The 1-year lower age limit for these studies was selected because it is highly unlikely that patients younger than 1 year of age would have exhausted other available treatment options at the time of entry into these studies. Patients less than 1 years of age are more likely to be undergoing first line therapy for their tumors and less likely to have already experienced recurrence or progression of disease. For this reason, neonates will not be included.

- Number of patients to be studied:
  - **Study 1**
    - Part 1: a minimum of 17 patients
    - Part 2: A minimum of 5 patients each in the HGG and EM cohorts, a minimum of 4 patients in the DIPG cohort and a minimum of 5 patients in the histology-agnostic cohort, for a minimum of 20 patients in total; a total of 50 patients over all 4 cohorts is planned.

  - **Study 2**: The protocol for Study 2 must be submitted for FDA review and agreed upon prior to patient enrollment

  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

- Safety Endpoints:
  - **Study 1**
    - Primary endpoint: Identification of dose limiting toxicity, determination of the maximum tolerated dose and the recommended phase 2 dose of afatinib
    - Other endpoints: overall incidence and Common Terminology Criteria for Adverse Events (CTCAE) grade of adverse events, as well as relatedness of adverse events to treatment, events leading to dose reduction, events leading to permanent treatment discontinuation, adverse events of special interest (AESI), and causes of death. The following adverse events are considered AESI and must be actively monitored: hepatic injury, diarrhea, reduced renal function, keratitis, and cardiac failure.
  - **Study 2**: The protocol for Study 2 must be submitted for FDA review and agreed upon prior to patient enrollment. The sponsor should request an amendment to the Written Request accordingly.

- Efficacy Endpoints:
  - **Study 1**
    - The primary efficacy endpoint will be ORR and duration of response (DOR) as assessed by the investigator according to the protocol-specified response evaluation criteria for the given tumor type, assessed every 8 weeks until progression of disease.
    - Secondary endpoints: progression free survival (PFS), for descriptive purposes only, defined as the duration of time from the date of first treatment until the date of the first documented progression or death due to any cause, tumor shrinkage, and overall survival defined as the duration from the date of first treatment to the date of death

  - **Study 2**
    - If the results of any cohort in Part 2 of Study 1 indicate sufficient anti-tumor activity, Study 2 will be a confirmatory trial designed to establish efficacy of afatinib as a single agent or as a component of multi-modality therapy. This protocol must be reviewed and agreed upon by the FDA prior to patient enrollment. An amendment to the Written Request should be requested accordingly.

- Pharmacokinetic Endpoints:
  - **Study 1**
    Estimated apparent clearance (CL/F) and volume of distribution (Vd/F) of afatinib from pharmacokinetic (PK) samples obtained across all studies from a minimum of 20 patients ≥ 2 to < 12 years of age.
    - Include PK evaluation for enrolled patients < 2 years of age and ≥ 12 years of age. Population PK analysis should be performed using afatinib concentration data obtained from all studies.
    - Assess the effects of age, weight, and other relevant covariates on the PK of afatinib.
    - Combine data from all completed studies to develop PK/PD models to explore exposure-response relationships for measures of safety and efficacy/activity as the data allow.

A Data Monitoring Committee (DMC) must be included. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

KNOWN DRUG SAFETY CONCERNS AND MONITORING

The tolerability and safety of afatinib has been established in adults. Clinically significant adverse reactions associated with the use of afatinib include diarrhea, bullous and exfoliative skin disorders, (including toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome), interstitial lung disease, hepatic toxicity, and keratitis. Diarrhea is the most common adverse reaction observed in patients who received afatinib occurring in 96% of patients, with Grade 3-4

occurring in 15% or patients. Renal impairment as a consequence of diarrhea occurred in 6% of patients treated with afatinib, of which 1.3% were Grade 3. Cases of pneumonitis/ILD have been reported in 1.6% of adult patients treated with afatinib; of these, 0.4% were fatal. Grade 3 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions, occurred in 0.2% of adult patients treated with afatinib. The overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 90%, and the incidence of Grade 3 cutaneous reactions was 16%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 7%. Post marketing cases consistent with toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS) have been reported in patients receiving afatinib. Approximately 10% of patients treated with afatinib experienced liver test abnormalities, of which 0.2% were fatal. Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye occurred in 0.7% of patients treated with afatinib of which 0.05% of patients experienced Grade 3 keratitis.

Throughout the studies described herein, all patients will be monitored for safety concerns including the adverse reactions listed above. These data will be assessed periodically along with all other safety parameters for any potential risks that may not be foreseeable from the known adult exposure or from preclinical findings. A patient whose symptoms are not manageable with allowable medications will be discontinued from the study and treated according to local treatment guidelines.

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:
  - Film coated tablets: 20 mg, 30 mg, 40 mg, (b) (4) film-coated tablets (the dose of afatinib in the film-coated tablets is related to the free base equivalent of afatinib dimaleate)
  - (b) (4)
- Route of Administration:
  - Oral. An age-appropriate formulation will be used in Study 1 and Study 2.
- Regimen:
  - Part 1: The starting dose was 80% of the adult dose based on allometric scaling and was increased to 100% of the adult dose based on allometric scaling. The 100% of allometric scaling exceeded the MTD of afatinib because 2 of 5 evaluable patients experienced a DLT.

- Part 2: The MTD/RP2D determined in Part 1 was 80% of the recommended adult dose per m^2 body surface using allometric scaling. This is the dose to be used in Part 2 of the trial.

DRUG FORMULATION

In accordance with section 505A(e)(2) of the Federal, Food, Drug and Cosmetic Act, 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

- **Study 1**
  - Part 1
    - A Rolling-6 dose-escalation design will be used to identify the maximum tolerated dose or RP2D and evaluate the toxicity profile of afatinib in pediatric patients.

- A total of 17 patients will be enrolled and treated in the dose finding portion of Study 1.

- Part 2
  - Given the single arm trial design and the small number of patients in each histology-defined cohort, statistics will be descriptive only.

- **Study 2**
  - The protocol and statistical analysis plan for Study 2 must be reviewed and agreed upon by FDA prior to patient enrollment.

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 afatinib 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 the above studies must be submitted to the Agency on or before October 12, 2022. 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.

If you have any questions, call Idara Udoh, Senior Regulatory Health Project Manager, at 301-796-3074.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, M.D.
Associate Director, 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GREGORY H REAMAN
06/05/2019 04:33:46 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201292

WRITTEN REQUEST

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Agnor, MS
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Agnor:

Reference is made to your December 6, 2016 Proposed Pediatric Study Request submitted to NDA 201292 for afatinib.

BACKGROUND:

The studies discussed in this Written Request letter investigate the potential use of afatinib for the treatment of pediatric patients with relapsed or refractory tumors with ErbB1 or ErbB2 pathway dysregulation, based on epidermal growth factor receptor (EGFR) or HER2 protein overexpression or EGFR or HER2 gene amplification, including relapsed or refractory neuroectodermal tumors and rhabdomyosarcomas.

Afatinib is a tyrosine kinase inhibitor that covalently binds the kinase domains of EGFR (ErbB1), HER2 (ErbB2), and HER4 (ERbB4). Binding of afatinib to these receptors irreversibly inhibits auto phosphorylation, resulting in downregulation of ErbB signaling. On July 12, 2013, FDA granted approval to afatinib for use as first line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 (l858R) substitution mutations as detected by an FDA approved test. This approval was based on improvement in progression-free survival for patients treated with afatinib compared with pemetrexed/cisplatin chemotherapy. On April 15, 2016, FDA granted a new indication for afatinib for the treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy. This approval was based on improvement in progression free survival and overall survival for patients treated with afatinib as compared with erlotinib

The ErbB protein family, also known as EGFR family, is a family of four structurally related receptor tyrosine kinases (ErbB1/EGFR, ErbB2/HER2, ErbB3/HER3, ErbB4/HER4). The ErbB family plays an important role in normal embryonic development and constitutive activation of these receptors are involved in pathogenesis and progression of breast and gastric cancers

(ErbB2), lung cancer, squamous cell cancer of the head and neck, and glioblastoma (ErbB1), and lung and ovarian cancer (ErbB4).

Neuroectodermal tumors comprise a variety of pediatric malignancies derived from the portion of the ectoderm of the early embryo which gives rise to the central and peripheral nervous systems. Neuroectodermal tumors include high grade gliomas (HGG), diffuse intrinsic pontine gliomas (DIPG), refractory low grade astrocytomas (RLGA), neuroblastomas (NB), ependymomas (EM), and medulloblastomas/primitive neuroectodermal tumors (M/PNET).

Limited evidence shows a correlation between ErbB dysregulation and tumor histology in neurogenic tumors. Preclinical evidence suggests that ErbB pathway dysregulation is also present in rhabdomyosarcoma (RMS). Data from the literature shows the following:

- **EGFR**: The prognostic significance of EGFR expression has been evaluated in intracranial EM. Analysis of 68 sporadic tumors which included 29 pediatric samples revealed that the EGFR protein status subdivides intracranial grade II EMs into two different risk groups, and concluded that EGFR overexpression represents an independent prognostic marker and correlates with poor prognosis. In addition, several studies also reported significant overexpression of EGFR in pediatric DIPGs and HGGs. In rhabdomyosarcoma, EGFR is overexpressed in 50% of cases
- **HER2**: HER2 expression has been evaluated in patients diagnosed with neurogenic tumors, particularly medulloblastoma. In one study of 22 medulloblastoma samples, from both children and adults, 11 tumors showed solid expression of HER2 in 10 to 50% of neoplastic cells. In rhabdomyosarcoma HER2 was identified in 33% of cases and was more common in the alveolar subtype.
- **ErbB4**: Overexpression of ErbB4 with concomitant low EGFR expression is associated with refractory neuroblastoma.

While there are no FDA-approved drugs for pediatric neuroectodermal tumors and rhabdomyosarcomas, there are commonly used treatment regimens for newly diagnosed neuroectodermal tumors and rhabdomyosarcomas that prolong disease-free survival. However, once patients develop recurrent/refractory disease, treatment options are limited and outcomes are poor.

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) conducted a biomarker study that assessed the prevalence of ErbB dysregulation in tissue samples from pediatric patients with relapsed and recurrent neuroectodermal tumors including HGG, DIPG, RLGA, EM, M/PNETs, NB, and RMS and evaluated the technical feasibility of testing biomarkers indicative for ErbB dysregulation in the clinical setting.

In the biomarker study, seven different tumor types from a total of 277 pediatric patients were analyzed (48 EM, 48 HGG, 45 M/PNETs, 40 RLGA, 4 DIPG, 26 RMS, and 66 NB). Tumors were tested for the following biomarkers in order to establish useful cutoffs and qualify assay systems for later use in clinical trials:

- EGFR gene amplification using FISH
- EGFR protein expression determined using immunohistochemistry (IHC)
- HER2 protein expression using IHC
- HER2 gene amplification using dual-hapten dual-color *in situ* hybridization (DDish)

Based on the results of the biomarker study, BI proposes that tumors meeting two or more of the following criteria have evidence of ErbB dysregulation and may therefore be susceptible to treatment with afatinib:

- EGFR gene amplification (FISH): Either EGFR/Cen7[1] ≥ 2.0 or ≥10% of cells with ≥15 copies or ≥40% of cells with ≥ 4 copies or gene cluster in ≥10% of cells.
- HER2 gene amplification (DDISH): Her2/CEP17[2] ≥ 2.0
- EGFR protein expression: H-score > 150 (membrane staining)
- HER2 protein expression: H-score > 0 (membrane staining)

To obtain needed pediatric information on afatinib for the treatment of pediatric tumors with ErbB1 or ErbB2 dysregulation, 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 BI submits information from the studies described below. As discussed below neonates are not included in this Written Request.

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.

BI must submit the results of analytical validation studies for the planned biomarker assays, preferably in neuroectodermal tumor tissues and rhabdomyosarcomas, demonstrating the reliability and reproducibility of these assays.

CLINICAL STUDIES

- **Study 1(Study 1200.120):** A multicenter, open-label, two-part trial to identify a pediatric dose, assess the pharmacokinetics, and investigate the anti-tumor activity of afatinib when administered for the treatment of pediatric tumors with known ErbB pathway dysregulation.

    - Part 1: Dose finding to determine the dose limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, and pharmacokinetics of afatinib

[1] EGFR/Cen7 is a DNA-FISH probe designed to detecton increase in copy number of the EGFR gene
[2] Chromosome enumeration probe 17 (CEP17)

- Part 2: An activity-estimating, disease-specific parallel cohort study of afatinib in patients aged 1 to <18 years with relapsed or refractory tumors with evidence of ErbB-dysregulation based upon the presence of overexpression or amplification of EGFR or HER2 using the criteria established in the companion biomarker study. The study will have three tumor-specific cohorts: HGG ≥ 5 patients; EM ≥ 5 patients, DIPG ≥ 4 patients~~with histology to be determined based on accrual. The specific cohorts will be determined based on the time to accrue a minimum of five patients each~~. In addition to these three disease-specific cohorts, the trial will include a histology-agnostic cohort of patients with refractory tumors, including those which were studied for biomarker feasibility or other tumors that fulfill the biomarker screening criteria; this cohort will ~~also~~ have a minimum of five patients. ~~The four cohorts will remain open to enrollment until all have accrued at least five patients each.~~ The amendment to Part 2 of the ongoing trial 1200.120 must be reviewed and agreed upon by the FDA prior to enrollment.

- **Study 2:** Study(ies) designed to establish the safety and effectiveness of afatinib, as a single agent or as a component of multi-modality therapy in neuroectodermal tumors or rhabdomyosarcoma, if sufficient antitumor activity is observed in one or more tumor types in Part 2 of Study 1. Include in the study detailed information and support for the *in vitro* diagnostic device(s) used for patient selection. Design the study to isolate the effectiveness of afatinib. This protocol must be reviewed and agreed upon by FDA prior to enrollment of patients.

Efficacy in patients aged ≥1 to < 18 cannot be extrapolated and will be determined by the studies outlined in the WR.

OBJECTIVES OF EACH STUDY:

- **Study 1:**
  - Part 1:
    - Primary objectives: Determine the maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D), safety, and pharmacokinetics of afatinib in pediatric patients. The MTD of afatinib as monotherapy will be determined in the pediatric patient population across all applicable tumor types based on the occurrence of dose limiting toxicities (DLTs).
    - Secondary objectives: Explore the preliminary objective response by investigator assessment according to the protocol-specified response evaluation criteria for each tumor type studied.
  - Part 2:
    - Primary objectives: Determine the objective response rate (ORR) and duration of response (DOR) in children age ≥1years to <18 years in three disease specifc cohorts of pediatric patients with relapsed or refractory tumors.
    - Secondary objectives: Evaluation of progression free survival, and pharmacokinetics of afatinib.

- **Study 2:** The protocol and statistical analysis plan (SAP) for Study 2 must be submitted to FDA for review and agreement prior to patient enrollment in this study.

PATIENTS TO BE STUDIED

- Age group in which study(ies) will be performed: children ages 1 to < 18.

  The 1-year lower age limit for these studies was selected because it is highly unlikely that patients younger than 1 year of age would have exhausted other available treatment options at the time of entry into these studies. Patients less than 1 years of age are more likely to be undergoing first line therapy for their tumors and less likely to have already experienced recurrence or progression of disease. For this reason, neonates will not be included.

- Number of patients to be studied:
  - **Study 1**
    - Part 1: a minimum of 17 patients
    - Part 2: A minimum of 5 patients each in the HGG and EM cohorts, a minimum of 4 patients in the DIPG cohort ~~each of the three disease-specific cohorts~~ and a minimum of 5 patients in the histology-agnostic cohort, for a minimum of 20 patients in total; a total of 50 patients over all 4 cohorts is planned.

  - **Study 2**: The protocol for Study 2 must be submitted for FDA review and agreed upon prior to patient enrollment

  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

- Safety Endpoints:
  - **Study 1**
    - Primary endpoint: Identification of dose limiting toxicity, determination of the maximum tolerated dose and the recommended phase 2 dose of afatinib
    - Other endpoints: overall incidence and Common Terminology Criteria for Adverse Events (CTCAE) grade of adverse events, as well as relatedness of adverse events to treatment, events leading to dose reduction, events leading to permanent treatment discontinuation, adverse events of special interest (AESI), and causes of death. The following adverse events are considered AESI and must be actively monitored: hepatic injury, diarrhea, reduced renal function, keratitis, and cardiac failure.
  - **Study 2**: The protocol for Study 2 must be submitted for FDA review and agreed upon prior to patient enrollment. The sponsor should request an amendment to the Written Request accordingly.

- Efficacy Endpoints:
  - **Study 1**
    - The primary efficacy endpoint will be ORR and duration of response (DOR) as assessed by the investigator according to the protocol-specified response evaluation criteria for the given tumor type, assessed every 8 weeks until progression of disease.
    - Secondary endpoints: progression free survival (PFS), for descriptive purposes only, defined as the duration of time from the date of first treatment until the date of the first documented progression or death due to any cause, tumor shrinkage, and overall survival defined as the duration from the date of first treatment to the date of death

  - **Study 2**
    - If the results of any cohort in Part 2 of Study 1 indicate sufficient anti-tumor activity, Study 2 will be a confirmatory trial designed to establish efficacy of afatinib as a single agent or as a component of multi-modality therapy. This protocol must be reviewed and agreed upon by the FDA prior to patient enrollment. An amendment to the Written Request should be requested accordingly.

- Pharmacokinetic Endpoints:
  - **Study 1**
    Estimated apparent clearance (CL/F) and volume of distribution (Vd/F) of afatinib from pharmacokinetic (PK) samples obtained across all studies from a minimum of 20 patients ≥ 2 to < 12 years of age.
    - Include PK evaluation for enrolled patients < 2 years of age and ≥ 12 years of age. Population PK analysis should be performed using afatinib concentration data obtained from all studies.
    - Assess the effects of age, weight, and other relevant covariates on the PK of afatinib.
    - Combine data from all completed studies to develop PK/PD models to explore exposure-response relationships for measures of safety and efficacy/activity as the data allow.

A Data Monitoring Committee (DMC) must be included. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

KNOWN DRUG SAFETY CONCERNS AND MONITORING

The tolerability and safety of afatinib has been established in adults. Clinically significant adverse reactions associated with the use of afatinib include diarrhea, bullous and exfoliative skin disorders, (including toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome), interstitial lung disease, hepatic toxicity, and keratitis. Diarrhea is the most common adverse reaction observed in patients who received afatinib occurring in 96% of patients, with Grade 3-4

occurring in 15% or patients. Renal impairment as a consequence of diarrhea occurred in 6% of patients treated with afatinib, of which 1.3% were Grade 3. Cases of pneumonitis/ILD have been reported in 1.6% of adult patients treated with afatinib; of these, 0.4% were fatal. Grade 3 cutaneous reactions characterized by bullous, blistering, and exfoliating lesions, occurred in 0.2% of adult patients treated with afatinib. The overall incidence of cutaneous reactions consisting of rash, erythema, and acneiform rash was 90%, and the incidence of Grade 3 cutaneous reactions was 16%. In addition, the incidence of Grade 1-3 palmar-plantar erythrodysesthesia syndrome was 7%. Post marketing cases consistent with toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS) have been reported in patients receiving afatinib. Approximately 10% of patients treated with afatinib experienced liver test abnormalities, of which 0.2% were fatal. Keratitis, characterized as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain, and/or red eye occurred in 0.7% of patients treated with afatinib of which 0.05% of patients experienced Grade 3 keratitis.

Throughout the studies described herein, all patients will be monitored for safety concerns including the adverse reactions listed above. These data will be assessed periodically along with all other safety parameters for any potential risks that may not be foreseeable from the known adult exposure or from preclinical findings. A patient whose symptoms are not manageable with allowable medications will be discontinued from the study and treated according to local treatment guidelines.

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:
  - Film coated tablets: 20 mg, 30 mg, 40 mg, (b) (4) film-coated tablets (the dose of afatinib in the film-coated tablets is related to the free base equivalent of afatinib dimaleate)
  - (b) (4)
- Route of Administration:
  - Oral. An age-appropriate formulation will be used in Study 1 and Study 2.
- Regimen:
  - Part 1: The starting dose was 80% of the adult dose based on allometric scaling and was increased to 100% of the adult dose based on allometric scaling. The 100% of allometric scaling exceeded the MTD of afatinib because 2 of 5 evaluable patients experienced a DLT.

- Part 2: The MTD/RP2D determined in Part 1 was 80% of the recommended adult dose per m^2 body surface using allometric scaling. This is the dose to be used in Part 2 of the trial.

DRUG FORMULATION

In accordance with section 505A(e)(2) of the Federal, Food, Drug and Cosmetic Act, 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

- **Study 1**
  - Part 1
    - A Rolling-6 dose-escalation design will be used to identify the maximum tolerated dose or RP2D and evaluate the toxicity profile of afatinib in pediatric patients.

- A total of 17 patients will be enrolled and treated in the dose finding portion of Study 1.

- Part 2
  - Given the single arm trial design and the small number of patients in each histology-defined cohort, statistics will be descriptive only.

- **Study 2**
  - The protocol and statistical analysis plan for Study 2 must be reviewed and agreed upon by FDA prior to patient enrollment.

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 afatinib 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 the above studies must be submitted to the Agency on or before October 12, 2022. 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.

If you have any questions, call Idara Udoh, Senior Regulatory Health Project Manager, at 301-796-3074.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, M.D.
Associate Director, 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GREGORY H REAMAN
06/05/2019 04:33:46 PM

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

/s/

GREGORY H REAMAN
04/29/2020 03:33:11 PM