DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204026

WRITTEN REQUEST – AMENDMENT # 1

Celgene Corporation
Attention: Emmanuel Gutierrez
Senior Manager, Regulatory Affairs
400 Connell Drive, Suite 7000
Berkeley Heights, NJ 07922

Dear Mr. Gutierrez:

Please refer to your correspondence dated May 4 and May 27, 2016, requesting changes to FDA's November 20, 2015, Written Request (WR) for pediatric studies for pomalidomide.

We have reviewed your proposed changes to the pomalidomide WR and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on November 20, 2015, remain the same.

In this submission, the Written Request was amended as follows:

- Removing pediatric low-grade glioma population (pLGG) as one of the recurrent or progressive primary brain tumor types to be studied in Study 2. The rationale provided by Celgene is that this population does not represent an area of high unmet medical need.

- Revising the assessment of the overall response rate (ORR) to be based on the Children's Cooperative Group (COG) response criteria rather than the Reponses Assessment in Neuro-Oncology (RANO) criteria. The rationale provided by Celgene is that COG is more familiar with these criteria and the criteria are otherwise similar.

- Modifying the definition of long-term stable disease (SD) rate as SD sustained for ≥ 6 cycles (instead of months) observed after treatment with pomalidomide. The rational provided by Celgene is that this will be consistent with the Study 1 definition of long-term SD.

- Modifying the due dates for the study reports. The rationale provided is that the patent has been extended.

Reports of the studies that meet the terms of the Written Request dated November 20, 2015, as amended by this letter, must be submitted to the Agency on or before July 19, 2023, 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) with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773.

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

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

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Gina Davis, Senior Regulatory Health Project Manager, Regulatory Project Manager, at 301-796-0704.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, MD
Associate Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Complete Copy of Written Request as Amended

ATTACHMENT 1
WRITTEN REQUEST – AMENDMENT 1

Brain tumors are the most common solid tumors among children. Although overall survival is estimated to be over 70% at 5 years for the less aggressive tumor types such as low-grade gliomas and standard-risk medulloblastoma, these rates drop to below 50% for children with aggressive variants such as high-grade gliomas and diffuse intrinsic pontine glioma. Survival for children with recurrent/progressive disease is much lower. Despite multimodal therapy including surgery, high dose chemotherapy, radiation, autologous hematopoietic cell rescue, biologically targeted agents and antiangiogenic agents, survival have not improved. Pediatric tumors to be studied in this request include recurrent, progressive, or refractory brain tumors.

Pomalidomide is currently approved for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Pomalidomide may be useful for the treatment of central nervous system (CNS) tumors given its mechanism of action and potential ability to cross the blood-brain-barrier. Angiogenesis is important for CNS tumor growth and metastasis and pediatric brain tumors are known to have increased neovascularization and produce angiogenic factors (e.g. vascular endothelial growth factor). Angiogenesis can also be induced indirectly through the recruitment of inflammatory cells. Pomalidomide has demonstrated anti-tumor activity in vitro and in vivo, by several mechanisms including anti-angiogenesis, alterations in inflammatory cytokines and immune modulation, and anti-proliferative activity. Treatment options for patients with CNS tumors are also limited by the presence of the blood-brain barrier which reduces the CNS exposure to chemotherapeutic agents administered. Preclinical studies have demonstrated that pomalidomide has moderate CNS distribution. Clinically, reports of activity of pomalidomide in myeloma with meningeal and CNS involvement suggest that pomalidomide has CNS penetration. The pharmacokinetic (PK) profile of pomalidomide in multiple myeloma (MM) also suggests that it can be co-administered with corticosteroids, which is an advantage for patients with brain tumors who often require treatment with corticosteroids.

Since only patients with recurrent or refractory tumors will be studied, the patients enrolled on this study are intended to be at least 1 year of age thus neonates will likewise be excluded.
To obtain needed pediatric information on pomalidomide and information on the utility of pomalidomide for pediatric patients with brain tumors, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

Nonclinical study(ies):

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

Clinical studies:

Study 1:
A dose-escalation study to determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D), pharmacokinetics (PK), safety, and preliminary efficacy of pomalidomide in children with recurrent, progressive or refractory CNS tumors.

Study 2:
An activity-estimating, parallel disease-specific cohort study of pomalidomide in patients aged 1 to < 21 years with recurrent or progressive primary brain tumors in one of four primary brain tumor types: high-grade glioma, medulloblastoma, ependymoma and diffuse intrinsic pontine glioma (DIPG). This study will provide further information on the anti-tumor activity and safety of pomalidomide in children and young adults and seeks to identify which brain tumors are most sensitive to pomalidomide. This protocol must be reviewed and agreed upon by the FDA prior to patient enrollment.

Study 3:
A study designed to establish the safety and efficacy of pomalidomide, as a single agent or as a component of multi-modality therapy will be conducted if sufficient activity is observed in one or more primary brain tumor types in Study 2. Ideally, this study should be designed to isolate the effectiveness of pomalidomide. This protocol must be reviewed and agreed upon by the Clinical Review Division within FDA prior to enrollment of patients. Efficacy and safety of pomalidomide in patients <21 years of age with recurrent/progressive/refractory brain tumors cannot be extrapolated from the adult experience and will be determined by the studies outlined in the WR.

Objective of each study:

Study 1: A dose-escalation trial of pomalidomide for children with recurrent, progressive or refractory CNS tumors

- Primary Objectives
    - To determine the MTD and/or RP2D of pomalidomide, in children with recurrent, progressive or refractory CNS tumors when given once daily for 21 consecutive days of a 28-day course.
    - To describe the toxicity profile and dose-limiting toxicities of pomalidomide in children with recurrent, progressive or refractory CNS tumors.
- Secondary Objectives
    - To explore the preliminary efficacy of pomalidomide in this patient population as defined by radiographic response rate, duration of response, and event free survival (EFS) within the confines of a Phase 1 study. For the purposes of this study, long-term stable disease will be considered a response (defined as stable disease for ≥ 6 courses of treatment).
    - To investigate the relationship between pomalidomide dose and exposure with radiographic response and changes in immune function (for example, T-cell subsets NK cell activity, Granzyme B and circulating levels of IL-12, IL-2, IL-15 and granulocyte-macrophage colony-stimulating factor (GM-CSF).

- Pharmacokinetic Objectives
    - Characterize the PK of pomalidomide in pediatric patients with recurrent, progressive or refractory CNS tumors.

Study 2: A Phase 2 Clinical Study of Pomalidomide Monotherapy for Children and Young Adults With Recurrent, Progressive, or Refractory Primary Brain Tumors

- Primary Objectives
    - To identify the objective response rate (ORR) in children age ≥1 years to <21 with recurrent or progressive primary brain tumors treated with pomalidomide in four distinct primary brain tumor types to identify the specific potential tumor type(s) for further development.
    - To estimate the preliminary long-term stable disease (SD) rate in children and young adults with recurrent or progressive primary brain tumors within the four distinct primary brain tumor types when treated with pomalidomide.
- Secondary Objectives
    - To evaluate the safety of pomalidomide in children age ≥1 years to <21 with recurrent or progressive brain tumors.
    - To estimate the benefit of pomalidomide treatment as characterized by duration of response (DOR) and progression free survival (PFS).
- Pharmacokinetic Objectives
    - Assess the PK of pomalidomide in pediatric patients with recurrent, progressive, or refractory primary brain tumors.

Study 3: The protocol for Study 3 must submitted for FDA review and agreed prior to patient enrollment.

- **Patients to be Studied:**

    - Age group in which studies will be performed: ≥ 1 and <21.

        Note: 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 (including neonates and infants) are more likely to be undergoing first line therapy for their brain tumors and less likely to have already experienced recurrence or progression of disease.

    - Number of patients to be studied:

        - Study 1: (a minimum of 80% of the patients must be < 17 yrs of age)
        - Study 2: (a minimum of 80% of the patients must be <17 yrs of age)
        - Studies 1 and 2: a minimum number of 50 patients must be enrolled

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

- Secondary endpoints
  - Objective response rate (ORR)
  - Duration of response (DOR)
  - Event free survival (EFS)

Study 2

- Primary Endpoints
  - ORR defined as complete response (CR) or partial response (PR) based on Children's Oncology Group (COG) response criteria, observed after treatment with pomalidomide.
  - Long-term SD rate defined as SD sustained for ≥ 6 cycles, SD observed after treatment with pomalidomide.
- Secondary Endpoints
  - DOR
  - PFS

Safety Endpoints:

Study 1

- Incidence and severity of treatment emergent adverse events (TEAEs)

Study 2

- Type, frequency, and severity of adverse events (AEs), and relationship of AEs to study drug

Pharmacokinetic/Pharmacodynamic Endpoints:

- Estimated pomalidomide clearance (CL) and volume of distribution (V_d) from pharmacokinetic samples obtained across all studies from a minimum of 6 patients in each of the following age groups: 1 to < 6, 6 to <12, and ≥ 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.

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 pomalidomide has been established in adults. Clinically significant adverse reactions associated with the use of pomalidomide include fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper respiratory tract infections, back pain and pyrexia.

  Throughout the studies, 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
  - 0.5, 1, 2, 3, 4 or 5 mg capsules in patients able to swallow capsules. Study 1 will only utilize capsules.
  - An age-appropriate formulation will be available for Studies 2 and 3.
- Route of administration
  - Oral

- Regimen
  - Pomalidomide will be administered once daily for 21 days of a 28-day cycle. Dose escalations will be based on toxicities observed during the first cycle of treatment (Cycle 1 Day 1 through initiation of Cycle 2). Four consecutive weeks will constitute one cycle and subsequent cycles will immediately follow as long as criteria to initiate subsequent therapy are met.

In accordance with section 505A(e)(2), if

1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

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

    - Study 1: Dose-escalation will be based on a rolling-6 study design. All statistical analysis will be descriptive. No formal statistical comparisons will be performed.

    - Studies 2 and 3: The statistical analysis plans for Studies 2 and 3 will be agreed upon as part of the protocol review by FDA.

    - Pharmacokinetic analysis: Population PK analysis will be performed using pomalidomide concentration data obtained from all studies. Effect of age and body size on pomalidomide PK will 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 pomalidomide 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 eCTD Specifications* at http://www.fda.gov/Cder/guidances/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency by July 19, 2023. 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);
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4. the exclusivity determination (i.e. granted or denied).

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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.

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/s/

GREGORY H REAMAN
07/13/2016