DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205437
NDA 206088

WRITTEN REQUEST – AMENDMENT 1

Celgene Corporation
Attention: Gerlee Thomas
Associate Director, Regulatory Affairs
33 Technology Drive
Warren, NJ 07059

Dear Ms. Thomas:

Please refer to your correspondence dated June 6, 2017, requesting changes to FDA's May 29, 2015, Written Request for pediatric studies for apremilast.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on May 29, 2015, remain the same. (Text added is underlined. Text deleted is ~~strikethrough~~.)

Within the section titled: *Clinical Studies*:

- *Study #2:* A Phase 3, multi-center study in subjects ages 6 through 17 years with moderate to severe plaque psoriasis that includes a double-blind, ~~multiple dose level,~~ placebo-controlled treatment phase of 16 weeks to assess the efficacy and safety of apremilast vs. placebo, followed by a 32-week open-label extension treatment period and an 8-week follow-up period. A full protocol must be submitted and agreed upon by the Agency before proceeding with the study.

Within the section titled: Number *of patients to be studied:*

- *Study #1*: At least 32 evaluable subjects of whom at least 16 subjects will be ages 6 through 11 years, and at least 16 subjects will be ages 12 through 17 years. Enrollment should be approximately evenly distributed within age groups and by gender, and there must be a sufficient data to make an adequate assessment of the dose(s) to be evaluated in the Phase 3 efficacy and safety study (Study 2) ~~number of subjects at the lowest ages (i.e., 6, 7 years of age)~~. All subjects must be ~~studied for~~ offered an open-label extension treatment period of 48 weeks and a follow-up period of 8 weeks.

- *Study #2*: at least 150 evaluable subjects ~~on apremilast~~ of whom at least 75 subjects will be ages 6 through 11 years, and at least 75 subjects will be ages 12 through 17 years of age. All subjects must be ~~studied for~~ offered a treatment period of 48 weeks and a follow-up period of 8 weeks.

Within the section titled: *Representation of Ethnic and Racial Minorities:*

- *Efficacy Endpoints: Study #2*
  The ~~co~~ primary efficacy endpoint will be the proportion of subjects who achieve a sPGA score of clear or almost clear, at Week 16 and the major secondary efficacy endpoint will be the proportion of subjects who achieve at least 75% reduction in PASI score (PASI-75) from baseline at Week 16. ~~and the major secondary efficacy endpoint will be the proportion of subjects who achieve a sPGA score of clear or almost clear, at Week 16.~~

Within the section titled: *Statistical information, including power of study(ies) and statistical assessments:*

- *Sample Size Considerations*
  For efficacy, the ~~power~~ sample size calculation should be based upon reliable estimates of treatment effect with at least 80% marginal power to detect a significant difference for both the primary efficacy endpoint and major secondary efficacy endpoint at a two-sided significance level of 0.05. ~~when testing each at the two-sided α = 0.05 significance level~~

- *Efficacy Analysis*
  The primary analysis population will be the Intent-to-Treat (ITT) population, defined as all randomized subjects. As a supportive analysis, the Per-Protocol (PP) population should be used and the criteria used to define the PP population should be pre-specified in the protocol.

  The analysis of the ~~co-~~ primary efficacy endpoint~~s~~, sPGA defined as a score of clear or almost clear at Week 16 ~~PASI-75 at Week 16~~, and ~~success on~~ the major secondary efficacy endpoint, PASI-75 at Week 16, ~~sPGA defined as a score of clear or almost clear at Week 16~~ should be based on the Cochran-Mantel-Haenszel (CMH) test stratified by center. The protocol should pre-specify a pooling algorithm for centers that do not contribute to the CMH analysis due to problems with cells of zero frequency. The protocol should pre-specify a plan to investigate the treatment by center interaction and include a sensitivity analysis to address center outliers if present.

Within the section titled: Timeframe *for submitting reports of the study(ies):*

Reports of the above studies must be submitted to the Agency on or before April 30, 2021 ~~September 30, 2019.~~ 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.

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

Reports of the studies that meet the terms of the Written Request dated May 29, 2015, as amended by this letter, and must be submitted to the Agency on or before April 30, 2021, 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 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.

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.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- 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.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that apremliast 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).

- 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 your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be 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 these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301)796-5376.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written as Amended

Complete Copy of Written Request as Amended

BACKGROUND:
These studies investigate the potential use of apremilast in the treatment of pediatric patients with moderate to severe plaque psoriasis who are candidates for systemic or phototherapy.
Psoriasis occurs in children ages 2 through 17 years. In the U.S., a regional study of a pediatric population residing in southern California from 2007 to 2008, reported a psoriasis prevalence of 19 per 10,000 patients[1]. In addition, the same report revealed that the prevalence of psoriasis in pediatric patients, ages 2 through 5 years, is 3 per 10,000 for males and 4 per 10,000 for females. The prevalence of moderate to severe psoriasis in children who are candidates for systemic or phototherapy, would be lower than the total population of children with psoriasis ages 2 through 5 years. Therefore, studies in psoriasis patients less than 6 years of age (including neonates) would be impossible or highly impracticable.

- Moderate to severe psoriasis does occur in children ages 6 through 17 years although with a lower prevalence than in adults. Studies in adults are complete and apremilast was approved for the treatment of moderate to severe psoriasis in adults. Thus, it is feasible to conduct studies in pediatric patients ages 6 through 17 years with moderate to severe psoriasis. Although the clinical presentation and course of psoriasis is similar in adults and pediatric patients, it is not known whether the exposure- response relationship in children is the same as for adults for this first-in-class drug for psoriasis. Therefore, in addition to a dose-finding, pharmacokinetics and safety trial, a safety and efficacy trial in pediatric subjects is needed as well.

- To obtain needed pediatric information on apremilast, 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 studies*: Based on our review of the available non-clinical toxicology data, including data from your juvenile animal toxicology study in mice, no additional animal studies are required at this time to support the clinical studies described in this Written Request.

- *Clinical studies:*
  - *Study #1:* A Phase 2, multi-center, open-label safety and pharmacokinetic (PK) dose-finding study, with a 48-week open-label extension treatment period and an 8-week follow-up period, in subjects ages 6 through 17 years with moderate to severe plaque psoriasis. A full protocol must be submitted and agreed upon by the Agency before proceeding with the study.

[1] Wu JJ, Black NH, Smith N, Porter AH, Jacobsen SJ, Koebnick C. Low prevalence of psoriasis among children and adolescents in a large multiethnic cohort in southern California. J AM Acad Dermatol. 2011 Nov: 65 (5): 957-64.

- *Study #2:* A Phase 3, multi-center study in subjects ages 6 through 17 years with moderate to severe plaque psoriasis that includes a double-blind, placebo-controlled treatment phase of 16 weeks to assess the efficacy and safety of apremilast vs. placebo, followed by a 32-week open-label extension treatment period and an 8-week follow-up period. A full protocol must be submitted and agreed upon by the Agency before proceeding with the study.

Efficacy in subjects ages 6 through 17 years cannot be fully extrapolated and will be determined by the studies outlined in the WR.

- *Objective of each study:*
  Study #1: To select a dose based on the PK and safety of apremilast in adolescents and children (ages 6 through 17 years) with moderate to severe plaque psoriasis.

  Study #2: To assess the clinical efficacy and safety of apremilast compared to placebo in adolescents and children (ages 6 through 17 years) with moderate to severe plaque psoriasis.
  - *Patients to be Studied* (*Study #1 and Study #2):*
    - *Age group in which studies will be performed*: Subjects ages 6 through 17 years
    - *Entry Criteria* (*Study #1* and *Study #2*)
      - Psoriasis Area Severity Index PASI score ≥12; and
      - Body surface area (BSA) ≥10%; and
      - Psoriasis Global Assessment sPGA ≥3 (moderate)
      - Candidates for systemic or phototherapy
    - *Exclusion Criteria: Study #2*
      - Use of corticosteroids by any route of administration likely to have a systemic effect during the baseline period.
  - *Number of patients to be studied:*
    - *Study #1*: At least 32 evaluable subjects of whom at least 16 subjects will be ages 6 through 11 years, and at least 16 subjects will be ages 12 through 17 years. Enrollment should be approximately evenly distributed within age groups and by gender, and there must be a sufficient data to make an adequate assessment of the dose(s) to be evaluated in the Phase 3 efficacy and safety study (Study 2). All subjects must be offered an open-label extension treatment period of 48 weeks and a follow-up period of 8 weeks.

    - *Study #2*: at least 150 evaluable subjects of whom at least 75 subjects will be ages 6 through 11 years, and at least 75 subjects will be ages 12 through 17 years of age. All subjects must be offered a treatment period of 48 weeks and a follow-up period of 8 weeks.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial

minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*
  - *Pharmacokinetic Endpoints: Study #1and Study 2??*
    The pharmacokinetic endpoints for Studies #1 and 2: Standard Pharmacokinetic (PK) parameters and/or population-based PK parameters in the two age groups will be assessed [e.g., Maximum concentration (C_{max}), Time to achieve maximum concentration (T_{max}), Area under the concentration time curve (AUC), Apparent clearance (CL/F), Apparent volume of distribution (Vss/F), Terminal half-life ($t_{1/2}$), etc.] as appropriate. Exposure- response relationships (with respect to key clinical efficacy endpoints) and covariate analysis to identify relevant covariates should be explored in all subjects.

  - *Efficacy Endpoints: Study #2*
    The primary efficacy endpoint will be the proportion of subjects who achieve a sPGA score of clear or almost clear, at Week 16 and the major secondary efficacy endpoint will be the proportion of subjects who achieve at least 75% reduction in PASI score (PASI-75) from baseline at Week 16.

  - *Safety Endpoints: Study #1 and Study #2*
    - Safety outcomes must include: adverse events, gastrointestinal adverse events, psychiatric adverse events, growth parameters (e.g., height, weight). Growth parameters must include a baseline period of at least 16 weeks, a treatment period of at least 48 weeks, and a follow-up period of at least 8 weeks.

    - The following adverse events, based on the drug's known adverse event profile, must be monitored for the duration of the study:
      a. Diarrhea (frequency, duration and associated symptoms) monitored daily through use of symptom diaries;
      b. Other gastrointestinal adverse events including anorexia, nausea, and abdominal pain monitored every 4 weeks during the placebo-controlled period and every 8 weeks until the end of study;
      c. Depression, suicidal thoughts and behavior using the Columbia-Suicide Severity Rating Scale (C-SSRS) assessed at baseline and monitored every 4 weeks during the placebo-controlled period, every 8 weeks until the end of study, and at any unplanned visits at which other clinical assessments are needed; and
      d. Impaired growth: height (using a stadiometer) and weight assessed at baseline and monitored every 4 weeks during the placebo-controlled period and every 8 weeks until the end of study; Tanner staging assessed at baseline and at the end of study.

  - A Data Monitoring Committee (DMC) must be employed.

  - All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- *Known Drug Safety concerns and monitoring:* Depression; suicidal thoughts and ideation; weight loss or lack of weight gain; and diarrhea.

- *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 to this Written Request.

- *Drug information:*
  - *dosage form:* tablet
  - *route of administration:* oral
  - *regimen:* will be based on results of the PK study (*Study #1*)

  Use an age-appropriate formulation in the studies 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),
  1) if 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) if 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 prepared 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 preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation 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:*
- A statistical analysis plan must be submitted and agreed upon with the Agency.

  - *Sample Size Considerations*
    For efficacy, the sample size calculation should be based upon reliable estimates of treatment effect with at least 80% marginal power to detect a significant difference for both the primary efficacy endpoint and major secondary efficacy endpoint at a two-sided significance level of 0.05.

  - *Efficacy Analysis*
    The primary analysis population will be the Intent-to-Treat (ITT) population, defined as all randomized subjects. As a supportive analysis, the Per-Protocol (PP) population should be used and the criteria used to define the PP population should be pre-specified in the protocol.

    The analysis of the primary efficacy endpoint, sPGA defined as a score of clear or almost clear at Week 16, and the major secondary efficacy endpoint, PASI-75 at Week 16, should be based on the Cochran-Mantel-Haenszel (CMH) test stratified by center. The protocol should pre-specify a pooling algorithm for centers that do not contribute to the CMH analysis due to problems with cells of zero frequency. The protocol should pre-specify a plan to investigate the treatment by center interaction and include a sensitivity analysis to address center outliers if present.

    With respect to the primary efficacy analysis, the protocol will describe the estimand of primary interest. If the estimand of interest is the treatment effect in all patients randomized regardless of adherence, you should include provisions to limit the missing data through study design and education of investigators and patients, and pre-specify analysis methods to account for missing data for the primary and key secondary efficacy analyses. We recommend designs that encourage continued collection of efficacy data even after study treatment discontinuation. If you believe the treatment effect in all patients randomized regardless of adherence is not the most clinically important estimand, the protocol should specify which estimand is of most clinical importance and why. Statistical methods to quantify this estimand should be specified in the protocol.

- *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 apremilast is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of

the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequire ments/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before April 30, 2021. 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.

Reports of the studies that meet the terms of the Written Request dated May 29, 2015, as amended by this letter, and must be submitted to the Agency on or before April 30, 2021, 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 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.

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. Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows

- 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,

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    - the exclusivity determination (i.e., granted or denied).

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- 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 may be 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 these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

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

/s/

JULIE G BEITZ
10/30/2017