DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125276

WRITTEN REQUEST – AMENDMENT 1

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Attention: Karen Robertson
Regulatory Program Management

Dear Ms. Robertson:

Please refer to your correspondence dated March 17, 2017, requesting changes to FDA's November 15, 2012, Written Request for pediatric studies for Actemra (tocilizumab).

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 November 15, 2012, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before ~~May 31, 2018~~ September 30, 2020. Please keep in mind that pediatric exclusivity can attach only to existing exclusivity, if any, 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, if there is unexpired exclusivity that 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 exclusivity is otherwise due to expire.

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 November 15, 2012, as amended by this letter must be submitted to the Agency on or before **September 30, 2020**, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

If FDA has not determined whether Actemra (tocilizumab) is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this Written Request amendment, nor any request for exclusivity made by you,

confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.

Submit reports of the studies as a supplement to an approved BLA 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 to the Office of New Drugs, Immediate Office, Therapeutic Biologics and Biosimilars Team, 10903 New Hampshire Ave, Building 22, Mail Stop 6411, Silver Spring, MD 20993. If you wish to fax it, the fax number is 301-796-9855.

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 Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, MD, MPH
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

Complete Text of Written Request as Amended

I. Systemic Juvenile Idiopathic Arthritis (SJIA)

SJIA comprises only about 10% of all JIA patients,[1] but is associated with disproportionate mortality risk, in large part due to Macrophage Activation Syndrome (MAS), which is unique to SJIA and is associated with 20% mortality risk.[2] The efficacy of tocilizumab (TCZ) for the treatment of SJIA has already been demonstrated, and the intravenous (IV) formulation of TCZ is the only approved treatment for SJIA patients 2 years of age and older. Because SJIA does occur in patients under 2 years of age, additional information allowing for approval in patients less than 2 years of age would be an important public health benefit. Additionally, a subcutaneous (SC) formulation of TCZ would provide a benefit for the SJIA patient population in allowing for the option of self/caregiver-administration which can be done outside the healthcare setting.

II. Polyarticular Course Juvenile Idiopathic Arthritis (PcJIA)

PcJIA is a descriptive term for persistent arthritis of more than 6 weeks in multiple joints, with onset in patients less than 16 years of age. The overall prevalence of JIA is estimated to be 1 to 2 per 1000 children.[1] A limited number of treatments are approved for PcJIA, which include corticosteroids, methotrexate (MTX), the TNF inhibitors etanercept and adalimumab, and the T-cell co-stimulatory modulator abatacept. Because PcJIA patients may not respond to a given treatment or class of treatments, therapies with different mechanisms of action would be an important public health benefit. The efficacy of IV TCZ has been evaluated in a randomized, double-blind, placebo-controlled, withdrawal trial of IV TCZ in PcJIA patients 2 to 17 years of age conducted under the Pediatric Research Equity Act (PREA). In that trial, all patients received IV TCZ in the initial 16 weeks, and responders were then randomized to receive either IV TCZ or placebo infusion until they experienced a flare or 24 weeks had elapsed, whichever occurred earlier. Because patients received active treatment as soon as a disease flare (defined by JIA ACR30 criteria) occurred, the exposure to placebo was limited and no patient experienced uncontrolled or severe disease activity due to placebo treatment. Pediatric patients less than 2 years of age were not included in this study because PcJIA rarely occurs in this age group.

To obtain needed pediatric information on tocilizumab, 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 FD&C Act), as amended by the Food and Drug Administration Amendments Act of 2007 and the Food and Drug Administration Safety and Innovation Act of 2012, and pursuant to section 351(m) of the Public Health Service Act (the PHS Act), as amended by the Biologics Price Competition and Innovation Act of 2009, that you submit information from the studies described below.

***Nonclinical studies*:**

[1] Gabriel SE and K Michaud. Epidemiological Studies in Incidence, Prevalence, Mortality, and Comorbidity of the Rheumatic Diseases. Arthritis Research & Therapy. 2009;11:229.
[2] Sawhney S et al. Macrophage Activation Syndrome: a Potentially Fatal Complication of Rheumatic Disorders. Arch Dis Child. 2001;85:421-426.

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 pharmacokinetic and safety study of IV TCZ in SJIA patients under 2 years of age.

- ☐ Efficacy of IV TCZ in SJIA patients under 2 years of age will be supported by the demonstrated efficacy of IV TCZ in SJIA patients 2 years of age and older that supported the approval of IV TCZ for this age group.

Study 2: Long-term safety and tolerability study of IV TCZ in PcJIA patients ages 2 to 17 years who were enrolled in the randomized, double-blind, placebo-controlled withdrawal trial of IV TCZ and who are participating in the 64-week, open-label, extension period.

- ☐ The efficacy of IV TCZ in PcJIA patients 2 to 17 years of age cannot be extrapolated and will be determined by the randomized, double-blind, placebo-controlled withdrawal portion of the trial that has been completed and submitted to the Agency.

Study 3: A study of the pharmacokinetics, pharmacodynamics, and safety of SC TCZ in patients with SJIA 2 to 17 years of age.

- ☐ Efficacy of SC TCZ in SJIA patients 2 to 17 years old will be supported by the demonstrated efficacy of IV TCZ in SJIA patients 2 years of age and older that supported the approval of IV TCZ for this age group.

Study 4: A study of the pharmacokinetics, pharmacodynamics, and safety of SC TCZ in patients with PcJIA ages 2 to 17 years.

- ☐ Efficacy of SC TCZ in PcJIA patients 2 to 17 years of age will be supported by a demonstration of efficacy of IV TCZ in PcJIA patients 2 to 17 years of age.

- ☐ An efficacy trial of IV TCZ in PcJIA patients 2 to 17 years of age must be completed before proceeding to a pharmacokinetics/safety study of the SC formulation of TCZ in PcJIA patients 2 to 17 years of age in order to better define the subcutaneous dose regimen.

Objective of each study:

Study 1: Systemic Juvenile Idiopathic Arthritis under 2 years of age
The primary objective of this study is to evaluate the pharmacokinetics (PK) and safety of IV TCZ over 12 weeks of treatment in patients less than 2 years of age with SJIA, and the secondary objective is to evaluate safety of IV TCZ over 12 weeks in combination with stable ongoing therapy. The exploratory objective is to evaluate pharmacodynamic (PD) and age-appropriate efficacy outcomes of TCZ over 12 weeks in combination with stable ongoing therapy.

Study 2: Long-term safety and tolerability of IV TCZ in Polyarticular-course Juvenile Idiopathic Arthritis ages 2 to 17
The objective of this study is to evaluate the long-term safety and tolerability of IV TCZ in patients with PcJIA ages 2 to 17 years who were enrolled in the randomized, double-blind, placebo-controlled withdrawal trial assessing the efficacy and safety of IV TCZ in patients with active PcJIA and who are participating in the 64-week, open-label extension period.

Study 3: Subcutaneous PK-PD Bridging Study in SJIA
The primary objective of this study is to evaluate the pharmacokinetics (PK), pharmaco-dynamics (PD), and safety of TCZ in patients with SJIA following SC administration for 14 weeks. Specifically, the aim will be to achieve a similar Cmin range with the SC route of administration to that observed with the IV route of administration in the study that served as the basis for approval of IV TCZ in SJIA. The exploratory objective is to evaluate efficacy of TCZ in combination with stable ongoing therapy in patients with SJIA following SC administration for 14 weeks.

Study 4: Subcutaneous PK-PD Bridging Study in PcJIA
The primary objective of this study is to evaluate the pharmacokinetics (PK), pharmaco-dynamics (PD), and safety of TCZ in patients with PcJIA following SC administration for l4 weeks. Specifically, the proposed objective is to achieve a similar range of exposures with the SC route as that observed with the IV route of administration in the randomized, double-blind, placebo-controlled withdrawal trial that serves as the pivotal study to support the use of IV TCZ in PcJIA patients ages 2 to 17 years. The exploratory objective is to evaluate efficacy of TCZ in combination with stable ongoing therapy in patients with PcJIA following SC administration for l4 weeks.

Patients to be studied:

- *Age group in which studies will be performed*:
  - Study 1: SJIA patients less than 2 years of age
  - Study 2: PcJIA patients 2 to 17 years of age
  - Study 3: SJIA patients 2 to 17 years of age
  - Study 4: PcJIA patients 2 to 17 years of age

- *Number of patients to be studied:*
  - Study 1: Enroll sufficient numbers of SJIA patients less than 2 years of age to support assessment of safety and PK. The final number must include at least 10 SJIA patients.
  - Study 2: Enroll at least 160 patients with polyarticular course JIA, 2 to 17 years of age, who have been treated in the randomized withdrawal trial.
  - Study 3, SC PK-PD Bridging Study in SJIA: Enroll sufficient numbers of patients to determine the SC dosing regimen that approximates the relevant PK exposure parameters of the IV SJIA dose regimen.
  - Study 4, SC PK-PD Bridging Study in PcJIA: Enroll sufficient numbers of patients to determine the SC dosing regimen that approximates the relevant PK exposure parameters of the IV PcJIA dose regimen.

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.

Study endpoints:

Study 1: in SJIA patients less than 2 years old

☐ *Pharmacokinetic Endpoints:*
The pharmacokinetic endpoints for this study must include Cmin, Cmax, and AUC_{2weeks} at Week 12.

Efficacy parameters will be regarded as exploratory and may include Physician Global Assessment of disease activity, Parent/patient Global Assessment of overall well-being, Number of joints with limitation of movement, Number of joints with active arthritis, Systemic features (fever and rash), ESR, CRP, and ferritin. Pharmacodynamic (PD) parameters will be considered exploratory and may include sIL-6R.

☐ *Safety Endpoints:*
Safety outcomes must include: adverse events, tolerability, vital signs, and laboratory parameters. Immunogenicity will be assessed by anti-TCZ antibodies

Study 2: Long-term Safety and Tolerability of IV TCZ in PcJIA patients ages 2 to 17

☐ *Safety Endpoints:*
Safety outcomes must include: adverse events, tolerability, vital signs, and laboratory parameters. Immunogenicity will be assessed by anti-TCZ antibodies.

Study 3: Subcutaneous PK-PD Bridging Study in SJIA Patients under 2 years of age

☐ *Pharmacokinetic Endpoints:*
The pharmacokinetic endpoints for SC PK-PD bridging study in SJIA patients must include Cmin, Cmax, Tmax, T1/2 and AUC_{τ} at steady state.

☐ *Pharmacodynamic Endpoints:*
Pharmacodynamic (PD)/efficacy parameters will be regarded as exploratory and may include Physician Global Assessment of disease activity, Parent/patient Global Assessment of overall well-being, Number of joints with limitation of movement, Number of joints with active arthritis, Systemic features (fever and rash), ESR, CRP, ferritin and sIL-6R.

☐ *Safety Endpoints:*
Safety outcomes must include: adverse events, tolerability, vital signs, and laboratory parameters. Immunogenicity will be assessed by anti-TCZ antibodies.

Study 4: Subcutaneous PK-PD Bridging Study in PcJIA Patients
☐ *Pharmacokinetic Endpoints:*

The pharmacokinetic endpoints for SC PK-PD bridging study in PcJIA patients must include Cmin, Cmax, Tmax, T1/2, and AUC_{τ} at steady state.

☐ *Pharmacodynamic/Efficacy Endpoints:*
Pharmacodynamic /efficacy parameters will be regarded as exploratory and may include Physician Global Assessment of disease activity, Parent/patient Global Assessment of overall well-being, Number of joints with limitation of movement, Number of joints with active arthritis, ESR, CRP, and sIL-6R.

☐ *Safety Endpoints:*
Safety outcomes must include: adverse events, tolerability, vital signs, and laboratory parameters. Immunogenicity will be assessed by anti-TCZ antibodies.

Known drug safety concerns and monitoring:

You will monitor for:
Serious infections
Gastrointestinal perforations
Laboratory monitoring for neutrophils, platelets, lipids, and liver enzyme abnormalities
Hypersensitivity reactions, including anaphylaxis
Live vaccines should not be given with tocilizumab
Other serious safety concerns

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*
  - Intravenous (IV): Solution for intravenous infusion.
  - Subcutaneous (SC): Solution for subcutaneous injection.
- *route of administration*
  - Study 1: IV
  - Study 2: IV
  - Study 3: SC
  - Study 4: SC
- *regimen*
  - Study 1: SJIA, 12 mg/kg IV every 2 weeks

- Study 2: PcJIA, weight <30 kg—8 mg/kg or 10 mg/kg (patients randomized to either dose); weight ≥30 kg—8 mg/kg; all doses given IV every 4 weeks.
- Study 3: SJIA, Appropriate regimen to be identified
- Study 4: PcJIA, Appropriate regimen to be identified

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), if

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

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

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

Statistical information, including power of studies and statistical assessments:

- Study 1: SJIA in patients less than 2 years of age: This is a descriptive study in SJIA patients under 2 years of age. Enroll sufficient numbers of SJIA patients less than 2 years of age to support assessment of safety and PK. The final number must include at least 10 patients.

- Study 2: Long-term Safety and Tolerability of IV TCZ in PcJIA patients ages 2 to 17: This is a descriptive study to evaluate safety outcomes and immunogenicity in patients who participated in the randomized withdrawal study of IV TCZ in PcJIA patients ages 2 to 17.

- Study 3: SC PK-PD Bridging Study in SJIA: A pediatric PK study must be prospectively powered to target a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution with 80% power in the age group to be studied. The proposed sample size must be based on the above criterion utilizing inter-subject PK variability from Study WA18221. In order to calculate the sample size, the method under "Sample Size Calculation for Rich PK Sampling Design Intended for NCA Analysis" in the paper by Wang Y et al. (*Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies, J Clin Pharmacol published online December 12, 2011*) should be followed. An alternative method to compute the 95% CI without involving the empirical Bayesian estimate is also described in the cited paper (under "Sample Size Calculation for Sparse/Rich PK Sampling Design Intended for popPK Analysis").

- Study 4: SC PK-PD Bridging Study in PcJIA: A pediatric PK study must be prospectively powered to target a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution with 80% power in the age group to be studied. In order to calculate the sample size, the method under "Sample Size Calculation for Rich PK Sampling Design Intended for NCA Analysis" in the paper by Wang Y et al. (*Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies, J Clin Pharmacol published online December 12, 2011*) should be followed. An alternative method to compute the 95% CI without involving the empirical Bayesian estimate is also described in the cited paper (under "Sample Size Calculation for Sparse/Rich PK Sampling Design Intended for popPK Analysis").

  Key PK and PD parameters to be assessed and how they will be analyzed will depend on findings from the pivotal IV TCZ study in PcJIA patients ages 2 to 17. Agreement on the details of the statistical analysis plan for study 4 must be reached with FDA prior to study start.

Labeling that may result from the studies:

You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the FD&C Act, regardless of whether the studies demonstrate that tocilizumab is safe, pure, and potent, or whether such study results are inconclusive in the studied pediatric populations or subpopulations, the labeling must include information about the results of the studies. Under section 505A(k)(2) of the FD&C 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 studies.

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 studies 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 FD&C 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 600.80 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 ICH guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before September 30, 2020. Please keep in mind that pediatric exclusivity can attach only to existing exclusivity, if any, 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, if there is unexpired exclusivity that 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 exclusivity is otherwise due to expire.

Response to Written Request:

Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC WRITTEN REQUEST STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies must be submitted as a biologics license application (BLA) or as a supplement to your approved BLA 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 Office of New Drugs, Immediate Office, Therapeutic Biologics and Biosimilars Team, 10903 New Hampshire Ave, Building 22, Mail Stop 6411, Silver Spring, MD 20993. If you wish to fax it, the fax number is 301-796-9855.

In accordance with section 505A(k)(1) of the FD&C 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 reports. 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., pending or withdrawn after the supplement was filed);
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, 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 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.

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

/s/

CURTIS J ROSEBRAUGH
06/27/2017