DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125387

WRITTEN REQUEST

Regeneron Pharmaceuticals, Inc.
Amanda Cook, BSc. (Hons), Dir.Reg.Aff.
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Ms. Cook:

Reference is made to your December 5, 2018, submission to IND 12462 of a Proposed Pediatric Study Request for Eylea (aflibercept) Injection. These studies investigate the potential use of aflibercept in the treatment of retinopathy of prematurity (ROP).

Retinopathy of Prematurity (ROP) is a complex disease process initiated in part by the lack of complete or normal retinal vascularization in premature infants. Retinopathy of prematurity can lead to irreversible blindness. Current nonpharmacologic therapies such as laser photocoagulation and cryotherapy are destructive. There are no approved pharmacologic therapies for ROP. There is publicly available literature which suggests that the use of aflibercept intravitreal injections (IVT) may be useful in delaying this type of retinopathy at doses ranging from 0.4 mg to 1 mg per eye.

To obtain needed pediatric information on aflibercept, 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 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 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: Randomized, parallel group, controlled study of at least 52 weeks duration with a five-year follow-up, including an assessment of retinal photographs. Submission of Week 52 data is required to meet the terms of the Written Request. Five-year follow up must be submitted to the Agency but is not required to meet the terms of the Written Request.

Study 2: Randomized, parallel group, controlled study of at least 52 weeks duration with a five-year follow-up and include an assessment of retinal photographs. Submission of Week 52 data is required to meet the terms of the Written Request. Five-year follow up must be submitted to the Agency but is not required to meet the terms of the Written Request.

Efficacy in premature infants with ROP cannot be extrapolated and will be determined by the studies outlined in the WR. The protocols and statistical analysis plans must be submitted to and agreed upon by the Division.

- *Objective of each study:* The primary objective of the studies is to evaluate the efficacy, safety, and tolerability of intravitreal aflibercept in patients with retinopathy of prematurity.

- *Patients to be studied:*

  - *Age group in which studies will be performed*: Premature infants with ROP

  - *Total number of patients to be studied:* In total (combined from both studies), the clinical studies will study at least 150 premature infants with ROP who have been treated with aflibercept and followed for at least 52 weeks after birth.

  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:* The primary efficacy endpoint will be the absence of active ROP and absence of unfavorable structural outcomes at Week 52 following birth (e.g., retinal detachment) and must be assessed by visualization of the retina (photographic and/or directly by investigators). Safety outcomes must include the collection of adverse experiences as outlined in the agreed-upon protocol.

- *Known safety concerns:* This class of product may theoretically cause systemic inhibition of new vessel formation. The clinical studies planned must each have five-year follow-ups with safety evaluations specified in the agreed-upon protocols.

- *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.

- *Biological product information:*

  - intravitreal injection

- *Statistical information, including power of studies and statistical assessments:* Subjects should be randomized between active treatment and an active standard of care control. The study design may be either a superiority design or a non-inferiority design compared to an established standard of care. The statistical analysis plans must be submitted and agreed upon by the Division and include specifications for handling missing data. Demographic characteristics and adverse experiences should be summarized descriptively and compared for each treatment group.

- *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 aflibercept injection is safe, pure, and potent, 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 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 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 https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.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 https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before September 1, 2025. 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.

  If FDA has not determined whether Eylea (aflibercept) Injection 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 formal pediatric Written Request, 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.

- *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.

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.

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 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 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 Michael Puglisi, Regulatory Project Manager, at 301-796-0791.

Sincerely,

{See appended electronic signature page}

Peter Stein, MD
Director
Office of New Drugs
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/

PETER P STEIN
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