DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125387/0

BLA APPROVAL
November 18, 2011

Regeneron Pharmaceuticals, Inc.
Attention: Laura Pologe, Ph.D.
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, New York 10591-6707

Dear Dr. Pologe:

Please refer to your Biologics License Application (BLA) dated February 17, 2011, received February 18, 2011, submitted under section 351 of the Public Health Service Act for Eylea (aflibercept).

We acknowledge receipt of your amendments dated February 28, March 10, 18, and 24, April 1, 8, 11 (two), 13 (two), and 29, May 11, 16, 23, and 27, June 3, 7, 9, 16, 20, and 28, July 8, 18, and 19, August 1, 5, 10, 12, and 31, September 1, 7, 12, 20, and 26, October 7, 21, 24, and 27, and November 1, 9, 11, and 17, 2011.

We have approved your BLA for aflibercept effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, aflibercept under your existing Department of Health and Human Services U.S. License No. 1760. Aflibercept is indicated for treatment of neovascular (wet) age-related macular degeneration.

Under this license, you are approved to manufacture aflibercept drug substance intermediate, drug substance, and formulated bulk at (b) (4). The final formulated drug product will be manufactured at (b) (4) The final formulated drug product will be labeled and packaged at (b) (4). You may label your product with the proprietary name Eylea and market it in a (b) (4) single-use vial containing 0.278 mL of 40 mg/mL aflibercept, as part of a final packaged product containing the aflibercept single-use vial, a 19-gauge x 1½-inch 5-micron filter needle, a 30-gauge x ½-inch needle and a 1-mL plastic syringe.

The dating period for aflibercept shall be 15 months from the date of manufacture when stored at 2 - 8°C. The date of manufacture shall be defined as the (b) (4) The expiration date for the packaged product, (aflibercept single-use vials, syringe, needle and filter needle) shall be dependent on the shortest expiration date of any component. (b) (4)

Samsung v. Regeneron
IPR2023-00442
U.S. Pat. 10,130,681
Exhibit 2302

(b) (4)

Results of ongoing stability should be submitted to the annual report.

You are not currently required to submit samples of future lots of aflibercept to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of aflibercept, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

We are approving this application for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 125387**."

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on November 17, 2011, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA STN 125387**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for this application because the product treats a disease that does not exist in pediatric age groups.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of corneal endothelial cell decompensation following the intravitreal administration of Eylea (aflibercept).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of corneal endothelial cell decompensation following the intravitreal administration of Eylea (aflibercept).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1. Provide clinical information from a 1-year (minimum) clinical trial evaluating the adverse effects, if any, on the corneal endothelium following administration of aflibercept.

   The timetable you submitted on October 24, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	March 2012
Trial Completion:	November 2015
Final Report Submission:	May 2016

Submit the protocol to your IND 12462, with a cross-reference letter to this BLA. Submit all final report(s) to your BLA. Prominently identify the submission with the following wording in

bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2. To conduct three drug product hold time studies of the 40 mg/mL vial presentation filled at (b) (4) site. Material will be held at commercial scale, and microbiological samples (total viable count, bacterial endotoxin) will be taken at the end of the hold times. The completed validation report will be submitted as a CBE-0 supplement.

   The timetable you submitted on November 11, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission: November 2012

3. To conduct three drug product hold time studies for the 40 mg/mL vial presentation filled at the (b) (4) site. These studies will include t=0 and end of hold samples for product quality (pH, purity by size exclusion, purity by nrSDS-PAGE, charge variant distribution by IEF, isoaspartate, and potency of aflibercept) evaluation. The completed validation report will be provided as a CBE-0 supplement.

   The timetable you submitted on November 11 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission: June 2012

4. To confirm [redacted] (b) (4) by the aflibercept [redacted] (b) (4) process. The [redacted] (b) (4) study will be performed under protocol on three lots of drug substance produced at the commercial scale. [redacted] (b) (4) will be measured with a validated analytical test method for determining [redacted] (b) (4). The completed method validation and final reports will be submitted in the 2012 annual report by January 2013.

   The timetable you submitted on November 11, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission: January 2013

5. To re-evaluate the release and shelf-life specifications for aflibercept drug product after 30 commercial manufacturing runs to reflect increased manufacturing experience. The revisions to the quality control system, the corresponding data from the 30 commercial manufacturing runs, and the analysis and statistical plan used to evaluate the specifications and any changes to specifications will be provided in a PAS within 60 days after completion of the 30th lot manufactured using the commercial process or by December, 2014, whichever occurs first.

   The timetable you submitted on November 11, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission: December 2014

6. To re-evaluate the release and shelf-life specifications for aflibercept drug substance after 30 commercial manufacturing runs to reflect increased manufacturing experience. The revisions to the quality control system, the corresponding data from the 30 commercial manufacturing runs, and the analysis and statistical plan used to evaluate the specifications and any changes to specifications will be provided in a PAS by within 60 days after completion of the 30th lot manufactured using the commercial process or by June, 2013, whichever occurs first.

   The timetable you submitted on November 11, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission: June 2013

7. To re-evaluate the release and shelf-life specifications for aflibercept drug substance intermediate after 30 commercial manufacturing runs to reflect increased manufacturing experience. The revisions to the quality control system, the corresponding data from the 30 commercial manufacturing runs, and the analysis and statistical plan used to evaluate the specifications and any changes to specifications will be provided in a PAS within 60 days after completion of the 30th lot manufactured using the commercial process or by June, 2014, whichever occurs first.

The timetable you submitted on November 11, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2014

8. To re-evaluate the release and shelf-life specifications for aflibercept formulated bulk after 30 commercial manufacturing runs to reflect increased manufacturing experience. The revisions to the quality control system, the corresponding data from the 30 commercial manufacturing runs, and the analysis and statistical plan used to evaluate the specifications and any changes to specifications will be provided in a PAS within 60 days after completion of the 30th lot manufactured using the commercial process or by June, 2013, whichever occurs first.

   The timetable you submitted on November 11, 2011, states that you will conduct this study according to the following schedule:

   Final Report Submission: June 2013

Submit clinical protocols to your IND 12462 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies and clinical trials to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive

copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

/ Edward Cox, M.D., M.P.H./
Edward Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling