DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125418/0 **BLA APPROVAL**

sanofi-aventis, U.S., LLC
Attention: Elma Fernandes, Ph.D.
Director, Global Regulatory Affairs
55 Corporate Drive
Mail Stop 55D-225A
Bridgewater, NJ 08807

Dear Dr. Fernandes:

Please refer to your Biologics License Application (BLA) dated February 3, 2012, submitted under section 351 of the Public Health Service Act for ZALTRAP® (ziv-aflibercept).

We acknowledge receipt of your amendments dated March 2, 2012, March 12, 2012, March 22, 2012, March 30, 2012, April 3, 2012, April 9, 2012, April 11, 2012, April 13, 2012, April 18, 2012, April 24, 2012, April 27, 2012, April 30, 2012, May 7, 2012, May 8, 012, May 10, 2012, May 25, 2012, May 30, 2012, June 1, 2012 (2), June 4, 2012, June 8, 2012, June 18, 2012, June 22, 2012, June 27, 2012, June 29, 2012, July 9, 2012, July 13, 2012, July 17, 2012, July 20, 2012, July 23, 2012, August 1, 2012 (2) and August 2, 2012.

LICENSING

We have approved your BLA for ZALTRAP (ziv-aflibercept), effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, ZALTRAP under your existing Department of Health and Human Services U.S. License No. 1752. ZALTRAP, in combination with 5-flourouracil, leucovorin, irinotecan-(FOLFIRI), is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture ziv-aflibercept drug substance at (b) (4) (b) (4). The final formulated product will be manufactured, filled, labeled, and packaged at Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany and labeled and packaged at sanofi-aventis, U.S., LLC in Saint Louis, MO. You may label your product with the proprietary name, ZALTRAP, and will market it in 5 mL and 10 mL vials at a concentration of 25 mg/mL in a single-use vial.

DATING PERIOD

The dating period for ZALTRAP shall be 36 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of (b) (4) of the formulated drug product. The dating period for your drug substance shall be (b) (4) from the date of manufacture when stored at ≤ -20°C in bags or bottles.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of ZALTRAP 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 ZALTRAP, 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.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, 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 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be 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.

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, 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 125418/0**." Approval of this submission by FDA is not required before the labeling is used.

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

ADVISORY COMMITTEE

Your application for ziv-aflibercept was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a biologic in the intended population.

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 necessary studies are impossible or highly impracticable because the disease/condition does not exist in children.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

1. To submit a final report from the pediatric trial COG-AVDL0714 (NCT00622414) entitled "Aflibercept in treating young patients with relapsed or refractory solid tumors," that was completed in August 2011. The final report should include primary and derived datasets including demographic datasets, pharmacokinetic/pharmacodynamic datasets, adverse events datasets, laboratory datasets, and tumor response datasets.

The timetable you submitted on July 17, 2012, states that you will conduct this trial according to the following schedule:

Final Report Submission: August 2013

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

We remind you of your postmarketing commitments:

2. To add conductivity testing to the DP release specification. The analytical method protocol, qualification report, proposed acceptance criterion, and data used to set the

proposed acceptance criterion will be provided in a Changes Being Effected in 30 Days supplement by November 30, 2012.

The timetable you submitted on July 17, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission: November 2012

3. To re-evaluate the release and shelf-life specifications for ziv-aflibercept drug product after 30 commercial manufacturing runs tested using the current specification methods. The revisions to the quality control system, the corresponding data, and the analysis and statistical plan used to evaluate the specifications and any changes to specifications will be provided in a prior approval supplement by December 30, 2016

The timetable you submitted on July 17, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2016

4. To re-evaluate the release and shelf-life specifications for ziv-aflibercept drug substance after 30 commercial manufacturing runs tested using the current specification methods. The revisions to the quality control system, the corresponding data, and the analysis and statistical plan used to evaluate the specifications and any changes to specifications will be provided in a PAS by December 30, 2016.

The timetable you submitted on July 17, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2016

5. To conduct a study to evaluate impact of worst case (b) (4) using a validated container closure integrity test. The study protocol and data should be submitted as a Changes Being Effected in 30 Days supplement.

The timetable you submitted on July 17, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: September 2012
Final Report Submission: May 2013

6. To evaluate the interference of the red dye with product in the dye ingress test method used for the stability program. A spectrophotometric method should be used to assess dye ingress. The method should be correlated with the microbial ingress test method performed under the same experimental conditions. The study protocol and data should be submitted as a Changes Being Effected in 30 Days supplement.

The timetable you submitted on July 17, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission: September 2012

7. To add an additional sampling point after the first (b) (4) and prior to the final (b) (4) and to set the limit for this sample (b) (4). The (b) (4) (b) (4) bioburden data from 3 batches manufactured using the commercial process after implementation of the change should be submitted as a Changes Being Effected supplement.

The timetable you submitted on August 1, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2014

8. To conduct a shipping qualification study to assess the ability of the commercial shipper to maintain temperature during three shipments of minimum loads from Frankfurt to the US Distribution Center. The protocol and data from the shipping qualification study should be submitted as a Changes Being Effected supplement.

The timetable you submitted on July 17, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission: November 2012

Submit clinical protocols to your IND 9948 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 or requirement {506B, Accelerated Approval, PREA, or 505(o)} in your annual progress report of postmarketing studies 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**."

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
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), 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 Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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.

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

MEDWATCH-TO-MANUFACTURER PROGRAM

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.

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 Melanie Pierce, Senior Regulatory Health Project Manager, at (301) 796-1273.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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

/s/

RICHARD PAZDUR
08/03/2012