

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125418Orig1s000

MICROBIOLOGY REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51
Silver Spring, MD 20993

Date: 30 July 2012

To: Administrative File, STN 125418/0

From: Michelle Y. Clark-Stuart, MGA, MT (ASCP), Reviewer, CDER/OC/DGMPA/BMAB

Through: Patricia Hughes, Ph. D., Team Leader, CDER/OC/DGMPA/BMAB

Subject: New Biologic License Application (BLA) for treatment, in combination with irinotecan-fluoropyrimidine-based chemotherapy, of patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen # 1760

US License Applicant Product Facility: Sanofi-Aventis US LLC aflibercept (ZALTRIP®) (b) (4)

Indication: treatment of patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen

Dosage: Concentrate for solution for infusion, 25 mg/mL, IV

Due date: 04 August 2012

Recommendation: The drug substance (DS) part of this BLA, as amended, is recommended for approval from a product quality/microbiology and CGMP perspective.

Review Summary:

Aflibercept (VEGF Trap) is a recombinant protein consisting of sequences derived from human vascular endothelial growth factor (VAGF) receptor extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG₁). Aflibercept is a dimeric glycoprotein with a protein molecular weight of 96.9kDa. It contains approximately 15% glycosylation to give a total molecular weight of 115 kDa. The drug substance is derived from Chinese Hamster Ovary (CHO) cells that have been engineered to express aflibercept. (b) (4)

This BLA was submitted in the eCTD format. This review covers the evaluation of the drug substance aspects of the submission from a microbial control and microbiology product quality perspective.

Assessment

The application contains information to support commercial production of the Sanofi-Aventis U.S. aflibercept drug substance [REDACTED] (b) (4)

[REDACTED] This assessment only covers the drug substance aspects of the application. For drug product aspects of the application, please see the review by Kalavati Suvarna.

Drug Substance (3.2.S)

General Information (3.2.S.1)

Aflibercept (VEGF Trap) is a recombinant protein consisting of sequences derived from human vascular endothelial growth factor (VEGF) receptor extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG₁). Aflibercept is a dimeric glycoprotein with a protein molecular weight of 96.9 kDa. It contains approximately 15% glycosylation to give a total molecular weight of 115 kDa. The drug substance is derived from Chinese Hamster Ovary (CHO) cells that have been engineered to express aflibercept. The activation and receptor mediating signaling and pathological activities that endogenous ligands and their cognate receptors bind to are blocked by aflibercept. The aflibercept drug product is a sterile, clear, colorless, non-pyrogenic, preservative-free, pH 6.2 solution, and is supplied as 100 mg and 200 mg single-use vials delivering 4 mL and 8 mL of 25 mg/mL aflibercept solution, respectively. The drug product has been specifically formulated for IV infusion, only. A 1-hour IV infusion of aflibercept at a dosage of 4 mg/kg every 2 weeks in combination with irinotecan-fluoropyrimidine-based chemotherapy for treatment of patients with metastatic colorectal cancer (MCRC) previously treated with an oxaliplatin-containing regimen.

3.2.S.2 MANUFACTURE

3.2.S.2.1 Manufacturer(s)

The drug substance manufacturing, testing, and release sites are provided below:

Drug Substance manufacturing facility

[REDACTED] (b) (4)

End of Production Sample Testing Laboratory

18 Page(s) has been Withheld in Full immediately following this page as B4 (CCI/TS)

Environmental Assessment

A claim for a categorical exclusion from preparing an Environmental Assessment under 21 CFR 25.31(c) was provided by the firm on the grounds the substances associated with this submission occurs naturally in the environment and the actions associated with this submission do not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. The concentration of the active moiety aflibercept in the aquatic environment in the United States is below 1 ppb. Additionally, the firm stated that to the company's knowledge, no extraordinary circumstances exist [21 CFR 25.15 (d)].

cGMP Status

Inspected (b) (4) and classified NAI. This CGMP inspection covered drug substance manufacturing operations and found them acceptable. The (b) (4) profiles were updated and acceptable.

There are no pending or ongoing compliance actions that prevent approval of this BLA. Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation.



Conclusion

- I. The drug substance (DS) part of this BLA, as amended, is recommended for approval from a product quality/microbiology and CGMP perspective.
- II. All other sections of the BLA not related to microbial control and microbial product quality attributes should be reviewed by the OBP/DTP reviewer.
- III. No inspectional follow-up items for drug substance.

cc: WO51: Hughes
WO51: Clark-Stuart
WO22: Pierce
HFD-328, e-CTD Files (STN 125418)

BLA STN 125418/0, Sanofi-Aventis, aflibercept

Archived File: S:\archive\BLA\125418\125418.0.rev.mem.BLA.08-01-12.doc

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/s/

MICHELLE Y CLARK STUART
08/03/2012

TARA R GOOEN
08/03/2012
Acting for Dave Doleski, Division Director, signing per email dated 8/2/12 and 8/3/12



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 51,
Silver Spring, MD 20993

Date: July 25, 2012
To: Administrative File, STN 125418/0
From: Kalavati Suvarna, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Addendum to Quality Micro Review dated July 3, 2012
US License: 1752
Applicant: Sanofi-Aventis, US, LLC
Mfg Facility: Drug Product: Sanofi-Aventis Deutschland GmbH, Industriepark Hoechst, 65926 Frankfurt am Main, Germany. FEI: 3003195501
Product: ZALTRAP® (Aflibercept concentrate for solution; VEGF TRAP)
Dosage: Concentrate for Solution for Infusion (25 mg/mL in 5 mL or 10 mL vials).
Indication: Treatment of patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen.
Due Date: July 27, 2012

Recommendation for Approvability: The sponsor submitted an amendment 0028 dated 7/17/2012, which included responses to the CMC post-marketing commitments. The CMC quality microbiology review dated July 3, 2012, recommended approval of the application pending four post-marketing commitments (PMCs). The applicant agreed to the following 3 PMCs:

Post-marketing commitment 1: 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 CBE-30 supplement.

Final Protocol Submission: 09/30/2012

Final Report Submission: 05/31/2013

Post-marketing commitment 2: 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 CBE-30 supplement.

Final Report Submission : 09/30/2012.

Post-marketing commitment 4: 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 CBE-0 supplement.

Final Report Submission 11/30/2012

For PMC3, the applicant proposed to add a sampling point (b) (4) and set the bioburden limit (b) (4). The (b) (4) bioburden data for (b) (4) batches manufactured using the commercial process after implementation of the change will be submitted as a CBE-0 supplement.

The approach proposed by the applicant is acceptable. The (b) (4) bioburden data from 3 batches is sufficient for this type of change. The PMC 3 should be revised as follows:

Post-marketing commitment 3: To add an (b) (4) 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) bioburden data from 3 batches manufactured using the commercial process after implementation of the change should be submitted as a CBE-0 supplement.

Final Report Submission XX/XX/XXXX (timeline to be provided by applicant)

This review does not change the previous recommendation for approvability. The review is amended merely to include agreed upon revised post-marketing commitment language for PMC 3 and the PMC timelines.

CONCLUSION:

I. Sections 3.2.P of the BLA pertaining to microbial control of the drug product manufacturing process and sterility assurance of the drug product were reviewed. The BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective pending the proposed labeling changes (see section under LABELING) and with the following post-marketing commitments.

II.

Post-marketing commitment 1: 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 CBE-30 supplement by May 31, 2013.

Post-marketing commitment 2: 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 CBE-30 supplement by September 30, 2012.

Post-marketing commitment 3: To add an (b) (4) 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) bioburden data from 3 batches manufactured using the commercial process after implementation of the change should be submitted as a CBE-0 supplement (timeline to be provided by the applicant).

Post-marketing commitment 4: 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 should be submitted as a CBE-0 supplement by November 30, 2012.

- III. CMC product specific information and data should be reviewed by the OBP reviewer.
- IV. The drug product manufacturing site, Sanofi-Aventis Deutschland GmbH, located at Industriepark Hoechst, 65926 Frankfurt am Main, Germany (FEI: 3003195501) was inspected April 23-30, 2012 by IOG. The classification of this inspection is NAI. The facility has an acceptable compliance status.

The alternate drug product labeling and packaging site, Sanofi-Aventis US LLC located at 6239-6244 Lemay Ferry Road, Saint Louis, MO 63129. USA (FEI: 1000117606) was inspected February 29, 2012 – March 14, 2012 by KAN-DO and classified as VAI (b) (4). The facility has an acceptable compliance status.

SIGNATURES/DISTRIBUTION LIST

Primary BMAB Reviewer: Kalavati Suvarna, Ph.D.

Date:

Concurring BMAB Team leader: Patricia. F. Hughes, Ph.D.

Date:

cc:

OND/OHOP/DOP2/Pierce, Melanie

Building 51/OC/OMPQ/DGMPA/BMAB Hughes, Patricia

OND/OHOP/DOP2/Lemery, Steven

OND/OHOP/DOP2/Casak, Sandra

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/s/

KALAVATI C SUVARNA

07/27/2012

Addendum to Quality Micro Review.

PATRICIA F HUGHES TROOST

07/27/2012



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Office of Manufacturing and Product Quality
Biotech Manufacturing and Assessment Branch

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Kalavati Suvarna, Ph.D.
TEAM LEADER: Patricia Hughes, Ph.D.

BLA	125418/0
APPLICANT	Sanofi-Aventis, US, LLC.
US LICENSE NUMBER	1752
SUBMISSION REVIEWED	Original BLA
PRODUCT	ZALTRAP® (Aflibercept concentrate for solution; VEGF TRAP)
MANUFACTURING FACILITY	Drug Product: Sanofi-Aventis Deutschland GmbH, Industriepark Hoechst, 65926 Frankfurt am Main, Germany. FEI: 3003195501
INDICATION	Treatment of patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen.
DOSAGE FORM	Concentrate for Solution for Infusion (25 mg/mL in 5 mL or 10 mL vials).
SUPPORTING DOCUMENTS	BB-IND-9948, Type III DMF (b) (4); Type III DMF (b) (4), Type III DMF (b) (4) Type III DMF (b) (4), and Type V DMF (b) (4)
CDER RECEIPT DATE	February 03, 2012
REVIEW ASSIGN DATE	February 15, 2012
REVIEW COMPLETE DATE	July 3, 2012
GRMP GOAL DATE	July 6, 2012
PDUFA GOAL DATE	August 03, 2012
PROJECT MANAGER	Melanie Pierce
DIVISION	Division of Oncology Products 2
TO	S:\archive\BLA\125418\STN125418.rev.mem.BLA.07-03-2012.doc

1. PRODUCT QUALITY MICROBIOLOGY SUMMARY

I. EXECUTIVE SUMMARY

The subject of this BLA is aflibercept, a recombinant protein consisting of sequences derived from the human vascular endothelial growth factor (VEGF) receptor extracellular domains fused to the Fc portion of human immunoglobulin G1 (IgG1). Aflibercept acts as a soluble decoy receptor that binds VEGF-A, VEGF-B, and PlGF, thereby inhibiting the binding and activation of these cognate VEGF receptors. It is produced by recombinant technology in Chinese hamster ovary (CHO) cells. (b) (4)

ZALTRAP (final formulated aflibercept drug product) is proposed to be available at 25 mg/mL concentration, in 5 mL or 10 mL single use vials, containing withdrawable amount of 100 mg/4 mL or 200 mg/8 mL aflibercept, respectively. It is to be diluted before administration. The proposed dose of ZALTRAP® is 4 mg/kg administered as an intravenous infusion. This review covers microbial control of the drug product manufacturing process and sterility assurance aspects of the drug product as described in the original BLA and amendments (eCTD sequences 0001 dated 3/3/2012; 0004 dated 3/30/2012; 0010 dated 4/18/2012; 0015 dated 5/10/2012; 0018 dated 6/1/2012, 0020 dated 6/4/2012; 0022 dated 6/18/2012; and 0025 dated 6/29/2012). For a review of the microbial controls in drug substance manufacture, please see the review by Michelle Clark-Stuart. The drug substance is manufactured (b) (4) under Sanofi control. The drug product is manufactured at Sanofi-Aventis Deutschland GmbH, Industriepark Hoechst, 65926 Frankfurt am Main, Germany. The proposed shelf-life for drug product is 36 months at 2°C- 8°C protected from light.

II. Recommendation and Conclusion on Approvability

Sections 3.2.P of the BLA pertaining to microbial control of the drug product manufacturing process and sterility assurance of the drug product were reviewed. The BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective pending proposed labeling changes (see section on LABELING) and with the following post-marketing commitments.

Post-marketing commitment 1: 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 CBE-30 supplement by September 2012.

Post-marketing commitment 2: 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 CBE-30 supplement by September 2012.

Post-marketing commitment 3: (b) (4)
The (b) (4)

bioburden data from (b) (4) batches manufactured using the commercial process (b) (4) should be submitted as a CBE-0 supplement (timeline to be provided by the applicant).

Post-marketing commitment 4: 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 should be submitted as a CBE-0 supplement by November 2012.

The drug product manufacturing site is Sanofi-Aventis Deutschland GmbH located at Industriepark Hoechst, 65926 Frankfurt am Main, Germany (FEI: 3003195501). The site was inspected April 23-30, 2012 by IOG and the inspection is classified as NAI. The facility has an acceptable compliance status.

The alternate drug product labeling and packaging site, Sanofi-Aventis US LLC located at 6239-6244 Lemay Ferry Road, Saint Louis, MO 63129, USA (FEI: 1000117606) was inspected February 29, 2012 – March 14, 2012 by KAN-DO and classified as VAI (b) (4). The facility has an acceptable compliance status.

2. PRODUCT QUALITY MICROBIOLOGY ASSESSMENT

Introduction:

VEGF Trap (aflibercept) is a recombinant dimeric glycoprotein consisting of specific domains of the human VEGF receptors, VEGF-R1 and VEGF-R2, fused to the Fc portion of an IgG1 molecule. (b) (4)

The drug substance (DS) for ZALTRAP® is manufactured for Sanofi-Aventis U.S. LLC (b) (4). The drug product (DP) is manufactured at a SANOFI affiliate site in Frankfurt, Germany. Sanofi Aventis US LLC retains control of all manufacturing steps for aflibercept drug substance and drug product as the Sponsor for BLA 125418.

In addition to the original submission, amendments eCTD sequence numbers 0001 dated 3/3/2012 (updated manufacturing schedule), 0004 dated 3/30/2012 (clarification related to DMF information), 0010 dated 4/18/2012 (control of critical steps in drug product manufacture, protocol for microbial control during storage of diluted drug product, and batch analyses update), 0015 dated 5/10/2012 (response to drug product information request of 4/27/2012), 0018 dated 6/1/2012 (drug product specification), 0020 dated 6/4/2012 (microbial control of diluted product study results), 0022 dated 6/18/2012 (stability update), and 0025 dated 6/29/2012 (response to information request of 6/26/2012) are reviewed here.

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/s/

KALAVATI C SUVARNA
07/03/2012

PATRICIA F HUGHES TROOST
07/03/2012

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

BLA Number: STN 125418 **Applicant:** SANOFI-AVENTIS U.S. LLC **Stamp Date:** 03-Feb-2012

Established/Proper Name: ZALTRAP® **BLA/NDA Type:** Original

On initial overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed	Y	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling:	Y	OBP lead; Microbial control for diluted drug product reviewed by BMAB
<input type="checkbox"/> PI –non-annotated	Y N	
<input type="checkbox"/> PI –annotated	Y	
<input type="checkbox"/> PI (electronic)	Y N	
<input type="checkbox"/> Medication Guide	Y N	
<input type="checkbox"/> Patient Insert	Y N	
<input type="checkbox"/> package and container	Y N	
<input type="checkbox"/> diluent	Y N	
<input type="checkbox"/> other components	Y N	
<input type="checkbox"/> established name (e.g. USAN)	Y N	
<input type="checkbox"/> proprietary name (for review)	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y N	
<input type="checkbox"/> legible	Y	
<input type="checkbox"/> English (or translated into English)	Y	
<input type="checkbox"/> compatible file formats	Y	
<input type="checkbox"/> navigable hyper-links	Y	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y N	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y N	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a shared or divided manufacturing	Y N	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

Examples of Filing Issues	Yes?	If not, justification, action & status
arrangement		

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	Facilities and Equipment information is included in the Appendix section and manufacturer's are listed in the drug substance and drug product section. Microbial methods validation data included for drug product. (b) (4)
<input type="checkbox"/> Drug Substance	Y	
<input type="checkbox"/> Drug Product	Y	
<input type="checkbox"/> Facilities and Equipment	Y N	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y N	
<input type="checkbox"/> Novel Excipients	Y	
<input type="checkbox"/> Executed Batch Records	Y	
<input type="checkbox"/> Method Validation Package	Y N	
<input type="checkbox"/> (b) (4)	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		Defer to OBP.
<input type="checkbox"/> general info	Y N	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	
<input type="checkbox"/> description of manufacturing process and process control	Y N	
<input type="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> (b) (4)		
<input type="checkbox"/> (b) (4)		
<input type="checkbox"/> (b) (4) storage and shipping		
<input type="checkbox"/> control of materials	Y N	OBP has the lead.
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		
<input type="checkbox"/> cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps (b) (4)	Y N	Defer to OBP; bioburden IPCs for BMAB review.
(b) (4)		

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> <input type="checkbox"/> justification of specifications <input type="checkbox"/> stability <input type="checkbox"/> process validation (prospective plan, results, analysis, and conclusions) <input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> <input type="checkbox"/> specifications <input type="checkbox"/> justification of specs. <input type="checkbox"/> analytical procedures <input type="checkbox"/> analytical method validation <input type="checkbox"/> batch analyses <input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results <input type="checkbox"/> method validation 	<p>Y</p> <p>Y N</p> <p>Y N</p> <p>Y</p> <p>Y</p> <p>Y</p> <p>Y N</p> <p>Y</p> <p>Y</p>	<p>OBP has the lead; Validation data, microbial control strategy, process hold times, (b) (4) for BMAB review.</p> <p>Defer to OBP.</p> <p>Defer to OBP.</p> <p>OBP has the lead; compendia or equivalent microbial analytical procedures for BMAB review.</p> <p>OBP has the lead; bioburden & endotoxin evaluation in BMAB review.</p> <p>Defer to OBP.</p> <p>OBP has the lead; bioburden for BMAB review.</p>
<p>Drug Product [3.2.P] [Dosage Form]</p> <ul style="list-style-type: none"> <input type="checkbox"/> description and composition <input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> <input type="checkbox"/> preservative effectiveness <input type="checkbox"/> container-closure integrity <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) <input type="checkbox"/> batch formula <input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, (b) (4) labeling and packaging (including all steps performed at outside [e.g., contract] facilities) <input type="checkbox"/> controls of critical steps (b) (4) <input type="checkbox"/> process validation (b) (4) 	<p>Y</p> <p>Y</p> <p>Y N</p> <p>Y</p> <p>Y</p> <p>Y</p> <p>Y</p> <p>Y</p>	<p>1. Study on microbial control after dilution missing.</p> <p>2. Container closure dye integrity tests with closure (b) (4) performed. Relationship to microbial ingress not included. Review issues.</p> <p>3. Bacterial retention tests (b) (4) included in process validation section.</p>

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<p>(b) (4) & sterility assurance:</p> <ul style="list-style-type: none"> o (b) (4) validation o Component, container, closure (b) (4) and sterilization validation o Validation (b) (4) o Environmental Monitoring Program o (b) (4) validation o Other needed validation data (hold times) <p><input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients (b) (4))</p> <p><input type="checkbox"/> control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)</p> <p><input type="checkbox"/> reference standards or materials</p> <p><input type="checkbox"/> container closure system [3.2.P.7]</p> <ul style="list-style-type: none"> o specifications (vial, (b) (4) drawings) o availability of DMF & LOAs o administration device(s) <p><input type="checkbox"/> stability</p> <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> o protocol o results o method validation 	<p></p> <p>Y N</p> <p>Y</p> <p>Y N</p> <p>Y</p> <p>Y</p> <p>Y</p>	<p></p> <p>Defer to OBP</p> <p></p> <p>Defer to OBP</p> <p>CCI dye ingress test information and DMF LOA included</p> <p></p>
<p>Diluent (vials or filled syringes) [3.2P']</p> <p><input type="checkbox"/> description and composition of diluent</p> <p><input type="checkbox"/> pharmaceutical development</p> <ul style="list-style-type: none"> o preservative effectiveness o container-closure integrity <p><input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites)</p>	<p>Y N</p> <p>Y N</p> <p>Y N</p> <p>Y N</p>	<p>Not applicable</p>

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

CTD Module 3 Contents	Present?	If not, justification, action & status
involved)	Y N	
<input type="checkbox"/> batch formula		
<input type="checkbox"/> description of manufacturing process for production through finishing, including formulation,	Y N	
(b)(4) labeling and packaging	Y N	
(including all steps performed at outside [e.g., contract] facilities)	Y N	
<input type="checkbox"/> controls of critical steps (b)(4)		
<input type="checkbox"/> process validation (b)(4)	Y N	
& sterility assurance:		
o (b)(4) validation		
o Component, container, closure (b)(4)		
and sterilization	Y N	
validation		
o Validation (b)(4)		
	Y N	
o Environmental	Y N	
Monitoring Program		
o (b)(4) sterilization		
validation		
o Other needed validation data (hold times)	Y N	
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients (b)(4)		
(b)(4), other novel		
excipients)	Y N	
<input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
<input type="checkbox"/> reference standards	Y N	
<input type="checkbox"/> container closure system		
o specifications (vial, (b)(4)		
drawings)		
o availability of DMF & LOAs	Y N	
<input type="checkbox"/> stability		
<input type="checkbox"/> summary		
<input type="checkbox"/> post-approval protocol and commitment		
<input type="checkbox"/> pre-approval		
o protocol		
o results		
Other components to be marketed (full		OBP Lead

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

Examples of Filing Issues	Yes?	If not, justification, action & status
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	Defer to OBP
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	Defer to OBP; Container closure integrity studies reviewed by BMAB
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	Defer to OBP; endotoxin and container closure data reviewed by BMAB
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	N Y N Y N Y N	Rabbit pyrogen and sterility test as specified by regulations
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	Additional floor diagrams for drug product manufacturing will be requested
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	List of shared equipment will be requested

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Microbiological studies in support of the storage time of diluted aflibercept-DP have not been provided. Please provide a summary of a risk assessment and a report from studies that show adventitious microorganisms do not grow under the storage conditions for the diluted aflibercept DP. The report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product dilution and storage. It is generally accepted that growth is evident when the population increases more than 0.5 Log₁₀. The test should be run at the label's recommended storage conditions and be conducted for 2 to 3-times the label's recommended storage period and using the label recommended fluids. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.

Michelle Clark-Stuart- Drug Substance

Kalavati Suvarna – Drug Product

2/22/2012

Product Quality Microbiology Reviewer(s)

Date

Branch Chief/Team Leader/Supervisor

Date

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

/s/

KALAVATI C SUVARNA
03/28/2012

MICHELLE Y CLARK STUART
03/28/2012

PATRICIA F HUGHES TROOST
03/28/2012