

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125418Orig1s000

CHEMISTRY REVIEW(S)

OBP Review Cover Sheet

BLA STN 125418/0

ZaltrapTM (aflibercept)

Sponsor: sanofi-aventis

**Sarah Kennett, Ph.D.
Division of Monoclonal Antibodies**

Product Quality Review Data Sheet

1. **BLA#** STN 125418/0
2. **REVIEW #:** 1
3. **REVIEW DATE:** July 6, 2012
4. **REVIEWER(s):** Sarah Kennett, Ph.D.
Chana Fuchs, Ph.D., Team Leader

5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS TO DATE:**

<u>Communication/Documents</u>	<u>Date</u>
Pre-BLA meeting	5-12-2011
Information Request	3-26-2012
Filing Communication with Deficiencies (IR)	4-2-2012
Information Request	5-21-2012
Information Request	6-1-2012
Information Request	6-11-2012
Information Request	6-18-2012
Teleconference	6-29-2012
Teleconference	7-5-2012

6. **SUBMISSIONS REVIEWED TO DATE:**

<u>Submissions Reviewed</u>	<u>Document Date</u>
125418/0.0 (original submission)	2-3-2012
125418/0.1	3-2-2012
125418/0.4	3-30-2012
125418/0.5	4-3-2012
125418/0.9	4-18-2012
125418/0.12	4-30-2012
125418/0.15	5-10-2012
125418/0.17	5-30-2012
125418/0.19	6-1-2012
125418/0.21	6-8-2012
125418/0.22	6-18-2012
125418/0.23	6-22-2012
125418/0.24	6-27-2012
125418/0.25	6-29-2012
CMC sections intended for submission the week of July 8, 2012, via email; if these sections are changed in the official submission to the BLA, an amendment to this review will be generated.	7-6-2012

7. NAME & ADDRESS OF APPLICANT:

Name: sanofi-aventis U.S. LLC
Address: 55 Corporate Drive, Bridgewater, NJ 08807
Representative: Elma Fernandes, Ph.D.
Telephone: (908) 981-5000
Fax: (877) 332-5512

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Zaltrap™
Non-proprietary/USAN: Aflibercept
Code name: VEGF Trap, AVE0005
Common name: Vascular endothelial growth factor receptor type VEGFR-1
((b) (4) human immunoglobulin domain 2 fragment) fusion
protein with vascular endothelial growth factor receptor type
VEGFR-2 ((b) (4) human immunoglobulin domain 3
fragment) fusion protein with immunoglobulin G1 ((b) (4) Fc
fragment), dimer
Drug Review Status: Priority
Chemical Type: recombinant fusion protein of human VEGFR1 Ig domain 2,
human VEGFR2 Ig domain 3, and human IgG1 Fc

9. PHARMACOLOGIC CATEGORY: Therapeutic recombinant fusion protein of human VEGFR1 Ig domain 2, human VEGFR2 Ig domain 3, and human IgG1 Fc**10. DOSAGE FORM:** Injection**11. STRENGTH/POTENCY:**

- The concentration of Zaltrap (aflibercept) Drug Product is 25 mg/ml.
- Potency is defined as IC₅₀ of the sample relative to IC₅₀ of the reference standard in a proprietary VEGF-stimulated reporter gene assay and an ELISA-based binding assay.
- Potency specification is (b) (4) of reference standard as measured by the cell-based assay and (b) (4) of reference standard as measured by the binding assay.
- Dating period for vial drug product is 36 months when stored at 2-8°C.
- 100 mg or 200 mg of aflibercept is filled into either 5 ml glass vials or 10 ml glass vials, respectively.

12. ROUTE OF ADMINISTRATION: Intravenous injection

(b) (4)

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

(b) (4)

14. PRIMARY STRUCTURE, PHARMACOLOGICAL CATEGORY, MAIN SPECIES MOLECULAR WEIGHT, HOST SOURCE, MAIN GLYCOSYLATION

STRUCTURE/S:

Aflibercept is a dimeric IgG1 fusion protein. The Fc portion of human IgG1 is fused to human vascular endothelial growth factor receptor (VEGFR)-derived peptide domains. VEGFR2 extracellular Ig domain 3 is fused to the Fc region, and VEGFR1 extracellular Ig domain 2 is fused to the VEGFR2 domain.

(b) (4)

The theoretical (unglycosylated) molecular weight is 96.9 kD, and the experimental molecular weight is 115 kD. The isoelectric point is (b) (4).

15. RELATED/SUPPORTING DOCUMENTS:

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²
(b) (4)	III	(b) (4)	(b) (4)	4	N/A
	III			4	N/A
	III			4	N/A
	III			4	N/A
	V			4	N/A

Action codes for DMF Table:

4 – Sufficient information in application

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

16. CONSULT STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Environmental Assessment	Approval	2/23/2012	Sarah Kennett
OBP Carton and Vial labeling	Initial Review includes comments to sponsor; however most requirements met.	6/27/2012	Kimberly Rains
BMAB and DMA- memo for Drug Substance review	Waived	5/10/2012	Michelle Clark-Stuart Sarah Kennett
BMAB- memo for Drug Product review	Waived	7/3/2012	Kalavati Suvarna Sarah Kennett

17. INSPECTIONAL ACTIVITIES

A pre-approval inspection (PAI) for aflibercept drug substance production (b) (4) was conducted (b) (4) by BMAB reviewers Kalavati Suvarna and Lakshmi Narasimhan and product reviewer Sarah Kennett under BLA 125387 (aflibercept, Eylea). (b) (4)

A form 483 was issued at the end of this inspection. Observations made during the inspection pertain to inadequate microbial control strategy for (b) (4) QA documents that do not assure appropriate production record review and release of commercial material. This inspection was classified VAI. A cGMP inspection was performed (b) (4); this inspection was classified NAI. (b) (4)

Inspection of Sanofi-Aventis Deutschland GmbH, the drug product manufacturing site, was waived based on the compliance history, current GMP status, and previous inspections (b) (4). Additional information requested for review due to the waiving of the inspection is incorporated into the appropriate section of the BLA review.

All other facilities listed in the BLA, including contract facilities for mycoplasma, viral, and sterility testing, were not inspected as part of this BLA. Inspections were not conducted for this BLA as these sites have been inspected as part of the GMP inspection program and are in compliance as per 21 CFR 210, 211, and 600.

18. RECOMMENDATIONS ON APPROVABILITY

The data submitted in this Biologics License Application support the conclusion that the manufacture of Zaltrap™ (aflibercept) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been

sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. It is recommended that Zaltrap™ (aflibercept) be approved for human use (under conditions specified in the package insert).

QUALITY UNIT ASSESSMENT

I. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

The review of module 3.2 is provided below. A review of the product immunogenicity assays is included at the end of the primary review document.

II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

- a. **ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION**
As specified in 21 CFR 25.31(b), sanofi-aventis states that this Biologic License Application (BLA) qualifies for a categorical exclusion to the environmental assessment (EA) requirement based on the estimated concentration of the substance at the point of entry into the aquatic environment being below 1 ppb. Sanofi-aventis states that to their knowledge, no extraordinary circumstances exist.
- b. **PACKAGE INSERT**
CMC Review and comments on package insert were provided directly to the team and are incorporated in the approved package insert.
- c. **DRUG PRODUCT LABEL**
CMC review of DP label was generated under a separate consult to Kimberley Rains, OBP, with secondary and tertiary review by Sarah Kennett and Patrick Swann, respectively.

III. LIST OF DEFICIENCIES TO BE COMMUNICATED

There are no CMC-related deficiencies precluding approval of this BLA.

A list of PMC's can be found at the end of this document and in the quality team leader's executive summary.

IV. ADMINISTRATIVE

A. **Reviewer's Signature**

Product Quality Reviewer: Sarah Kennett, Ph.D.

B. **Endorsement Block**

Product Division Team Leader: Chana Fuchs, Ph.D.

Product Division Deputy Director: Patrick Swann, Ph.D.

Product Division Director: Kathleen Clouse, Ph.D.

C. **cc Block**

OBP Office Director: Steven Kozlowski, M.D.

Clinical Division Director (DOP2): Patricia Keegan, M.D.

Division of Monoclonal Antibodies File: BLA STN 125418

191 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

SARAH B KENNETT
07/06/2012

CHANA FUCHS
07/06/2012

PATRICK G SWANN
07/06/2012

KATHLEEN A CLOUSE STREBEL
07/06/2012

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form Version 1.0

Instructions:

The review team should email this form to the email account “CDER-TB-EER” to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing¹ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: August 04, 2012

Applicant Name: Sanofi-Aventis US LLC

U.S. License #: 1752

STN(s): 125418

Product(s): Zaltrap (Aflibercept)

Short summary of application: Original BLA –TB-EER request

FACILITY INFORMATION

Manufacturing Location:

Firm Name: Sanofi-Aventis Deutschland GmbH,

Address: Building H600, Industriepark Hoechst, 65926 Frankfurt am Main, Germany.

FEI: 3003195501

Short summary of manufacturing activities performed: Drug product manufacturing. The application states aflibercept manufacturing takes place (b) (4)

Inspected by IOG from 9/6/10-9/16/10 and classified OAI for sterile processing operations. A warning letter was sent to the firm in February 2011. The firm received a follow up CGMP inspection from 4/23/12-4/30/12 to verify corrective actions to deviations in the 2/2011 warning letter. This inspection was performed by IOG. An FDA

¹The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

483 was not issued and the inspection is initially classified NAI. DIDQ has reviewed the available case materials and finds this site acceptable for the purposes of this BLA.

Manufacturing Location:

Firm Name: Sanofi-Aventis US LLC

Address: 6239-6244 Lemay Ferry Road, Saint Louis, MO 63129. USA.

FEI: 1000117606

Short summary of manufacturing activities performed: Drug product labeling

Inspected by KAN-DO from 2/29/12-3/14/12 and classified VAI. This was a CGMP inspection of this licensed repackager/labeling facility. This facility has a currently acceptable (b) (4) profile history.

OVERALL RECOMMENDATION:

There are no pending or ongoing compliance actions with the facilities listed in this TB-EER that prevent approval of this BLA.

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

/s/

MAHESH R RAMANADHAM
07/03/2012

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:

The review team should email this form to the email account “CDER-TB-EER” to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing¹ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: August 04, 2012

Applicant Name: Sanofi-Aventis US LLC

U.S. License #: 1752

STN(s): 125418

Product(s): Zaltrap (Aflibercept)

Short summary of application: Original BLA –TB-EER request

FACILITY INFORMATION

Manufacturing Location:

Firm Name: Sanofi-Aventis Deutschland GmbH,

Address: Building H600, Industriepark Hoechst, 65926 Frankfurt am Main, Germany.

FEI: 3003195501

Short summary of manufacturing activities performed: Drug product manufacturing. The application states aflibercept manufacturing takes place (b) (4)

Inspected by IOG from 9/6/10-9/16/10 and classified OAI for sterile processing operations. A warning letter was sent to the firm in February 2011. The firm received a follow up CGMP inspection and to verify corrective actions to deviations in the 2/2011 warning letter from 4/23/12-4/30/12. This inspection was performed by IOG. An FDA 483 was not issued and the inspection is initially classified OAI. Action on this BLA

¹The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

should not be taken until this inspection classification is finalized within CDER Office of Compliance.

Manufacturing Location:

Firm Name: Sanofi-Aventis US LLC

Address: 6239-6244 Lemay Ferry Road, Saint Louis, MO 63129. USA.

FEI: 1000117606

Short summary of manufacturing activities performed: Drug product labeling

Inspected by KAN-DO from 2/29/12-3/14/12 and initially classified VAI. This was a CGMP inspection of this licensed repackager/labeling facility. This facility has previously acceptable (b) (4) profile history.

OVERALL RECOMMENDATION:

Action on this BLA should not be taken until this inspection classification of Sanofi Duetschland is finalized within CDER Office of Compliance. Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation.

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

/s/

MAHESH R RAMANADHAM
05/16/2012

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:

The review team should email this form to the email account “CDER-TB-EER” to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing¹ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: 08/04/12

Applicant Name: Sanofi-Aventis U. S. LLC

U.S. License #: 1752

STN(s): 125418/0

Product(s): alibercept (Zaltrap[®])

Short summary of application: Treatment in combination with irinotecan-fluoropyrimidine - based chemotherapy, of patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen.

FACILITY INFORMATION

Manufacturing Location: (b) (4)

Firm Name: (b) (4)

Address: (b) (4)

FEI: (b) (4)

Short summary of manufacturing activities performed: Drug substance manufacturing process (b) (4)

¹The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

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

OVERALL RECOMMENDATION:

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.

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

/s/

MAHESH R RAMANADHAM
05/16/2012

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

BLA/NDA Number: 125418/0 **Applicant:** sanofi-aventis U.S. LLC **Stamp Date:** Feb. 3, 2012
Established/Proper Name: aflibercept **BLA/NDA Type:** Priority

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 <input type="checkbox"/> including list of all establishment sites and their registration numbers	Y Y	
Comprehensive Table of Contents	N	Not necessary
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: <input type="checkbox"/> PI –non-annotated <input type="checkbox"/> PI –annotated <input type="checkbox"/> PI (electronic) <input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Insert <input type="checkbox"/> package and container <input type="checkbox"/> diluent <input type="checkbox"/> other components <input type="checkbox"/> established name (e.g. USAN) <input type="checkbox"/> proprietary name (for review)	Y Y Y N N Y Y N Y N Y Y	Not necessary Not necessary Not applicable Not applicable

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: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> compatible file formats <input type="checkbox"/> navigable hyper-links <input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays <input type="checkbox"/> summary reports reference the location of individual data and records <input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y Y Y Y Y Y	
Companion application received if a shared or divided manufacturing arrangement	Y N	Not applicable

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	N	Not necessary
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
<input type="checkbox"/> Drug Substance	Y	
<input type="checkbox"/> Drug Product	Y	
<input type="checkbox"/> Facilities and Equipment	Y	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y	
<input type="checkbox"/> Novel Excipients	Y N	Not applicable
<input type="checkbox"/> Executed Batch Records	Y	
<input type="checkbox"/> Method Validation Package	Y	
<input type="checkbox"/> (b) (4)	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	N	Not necessary
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	Y	
<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	
<input type="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> (b) (4)		
<input type="checkbox"/> (b) (4)		
<input type="checkbox"/> (u) (4) storage and shipping		
<input type="checkbox"/> control of materials	Y	
<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	
<input type="checkbox"/> (b) (4)		
<input type="checkbox"/> justification of specifications		
<input type="checkbox"/> stability		

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<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"> ○ specifications <ul style="list-style-type: none"> ○ justification of specs. ○ analytical procedures ○ analytical method validation ○ batch analyses <input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> □ summary □ post-approval protocol and commitment □ pre-approval <ul style="list-style-type: none"> ○ protocol ○ results ○ method validation 	<p align="center">Y</p>	
Drug Product [3.2.P] [Dosage Form] <input type="checkbox"/> description and composition <input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> ○ preservative effectiveness ○ 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)} & sterility assurance: <ul style="list-style-type: none"> ○ ^{(b) (4)} validation ○ Component, container, 	<p align="center">Y</p> <p align="center">Y</p> <p align="center">Y N</p> <p align="center">Y</p> <p align="center">Y</p> <p align="center">Y</p> <p align="center">Y</p> <p align="center">Y</p> <p align="center">Y</p>	<p align="center">Not applicable</p>

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<p>closure (b) (4) and sterilization validation</p> <ul style="list-style-type: none"> 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>Y</p> <p>N</p> <p>Y</p> <p>Y</p> <p>Y</p>	<p>The method validation/transfer package is not complete. An information request for submission of a complete package was sent to the sponsor on March 26. As an alternative, the sponsor was requested to confirm that DP lot release and stability testing would be done (b) (4) (a clinical testing site where methods were originally validated) with appropriately validated or qualified assays and to provide the validation/qualification reports for Zaltrap (i.e. DP in the oncology formulation). In their March 28 response, the sponsor stated that 3 tests will be performed (b) (4); an additional validation report was submitted for (b) (4) testing, and the validation report for testing polysorbate in DP will be submitted by the end of April. Formal qualification reports for compendial methods used at Sanofi will be submitted in May; qualification reports for testing DP (b) (4) were submitted.</p>
<p>Diluent (vials or filled syringes) [3.2P']</p> <ul style="list-style-type: none"> <input type="checkbox"/> description and composition of diluent <input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> o preservative effectiveness o container-closure integrity <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) 	<p>Y N</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/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> batch formula		
<input type="checkbox"/> description of manufacturing process for production through finishing, including formulation,	Y N	
<input type="checkbox"/> (b)(4) labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	
<input type="checkbox"/> controls of critical steps (b)(4)	Y N	
<input type="checkbox"/> process validation (b)(4)	Y N	
<input type="checkbox"/> & sterility assurance: <ul style="list-style-type: none"> o (b)(4) validation o Component, container, closure (b)(4) and sterilization validation 	Y N	
<ul style="list-style-type: none"> o Validation (b)(4) 	Y N	
<ul style="list-style-type: none"> o Environmental Monitoring Program 	Y N	
<ul style="list-style-type: none"> 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), 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 <ul style="list-style-type: none"> o specifications (vial, (b)(4) drawings) o availability of DMF & LOAs 	Y N	
<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"> o protocol o results 		
Other components to be marketed (full description and supporting data, as		Not applicable

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
of manufacture		
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y	
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	
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	
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	Y Y Y	
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	Not applicable
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? **Yes** **No**

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.

Product Quality Reviewer(s) Date

Branch Chief/Team Leader/Supervisor Date

Division Director Date

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

/s/

SARAH B KENNETT
03/29/2012

CHANA FUCHS
03/29/2012

KATHLEEN A CLOUSE STREBEL
03/29/2012