CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125418Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	13 Jul 2012
From	Steven Lemery, M.D., M.H.S.
Subject	Cross-Discipline Team Leader Review
BLA #	STN 125418/0
Applicant	sanofi-aventis, U.S., LLC
Date of Submission	03 Feb 2012
PDUFA Goal Date	03 Aug 2012
Proprietary Name / Established Name	Zaltrap / aflibercept
Dosing Regimen	Single-use vials (25 mg/mL): 100 mg/4 mL, 200 mg/8 mL
Proposed Indication(s)	Aflibercept in combination with irinotecan-fluoropyrimidine-based chemotherapy is indicated for patients with metastatic colorectal cancer (mCRC) previously treated with an oxaliplatin-containing regimen
Recommended:	*Approval pending final agreement on labeling and Post-Marketing Commitments*

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1. Introduction

FDA received a BLA (STN 125418) from Sanofi-aventis for aflibercept (proposed trade-name Zaltrap) on 03 Feb 2012. Sanofi-aventis requested marketing authorization for the use of aflibercept in combination with irinotecan-fluoropyrimidine-based chemotherapy for patients with metastatic colorectal cancer (mCRC) previously treated with an oxaliplatin-containing regimen.

The following section describes the primary issues identified during the review of this application:

1.1 One versus two trials

The primary issue considered during the review of this application was whether the results of a single adequate and well-controlled trial were sufficient to support approval. FDA Guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf, accessed 12 Jul 2007) identified characteristics that can contribute to the conclusion that results from a single study can support an efficacy claim. The characteristics identified were (a) large multicenter study; (b) consistency across study subsets; (c) multiple studies in a single study; (d) multiple endpoints involving different events; and (e) statistically very persuasive finding. Results of the VELOUR trial submitted in support of this BLA satisfied all of these characteristics except (c).

VELOUR was a large, randomized (1:1), multi-national trial that enrolled over 1,200 patients with previously treated mCRC. Patients in VELOUR received aflibercept plus FOLFIRI chemotherapy or placebo plus FOLFIRI chemotherapy. Table 1, copied from the statistical review, summarizes the efficacy results from VELOUR. The results (demonstrating that aflibercept plus FOLFIRI prolonged overall survival in patients with previously treated mCRC) were statistically robust and supported by consistent results in subgroup analyses.

Table 1 Summary of Efficacy Results

	Placebo (n=614)	**Aflibercept (n=612)**
Overall survival		
# of events	460	403
Median (in mos.)	12.1	13.5
Stratified HR (95% CI)	0.816 (0.713, 0.934)	
p-value	0.0032	
Progression free survival		
# of events	454	393
Median (in mos.)	4.7	6.9
Stratified HR (95% CI)	0.756 (0.660, 0.876)	
p-value	0.00007	
Objective response rate	**(n=530)**	**(n=531)**
ORR (95% CI)	11.1% (8.5, 13.8)	19.8% (16.4, 23.2)
p-value	0.0001	

The May 1998 FDA Guidance document also states that reliance on a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome and confirmation of the results in a second trial would be practically or ethically impossible.

VELOUR established that patients receiving aflibercept plus FOLFIRI experience a modest improvement in overall survival compared to FOLFIRI alone. Although it could be reasonably argued whether a second trial could ethically be conducted in the second-line setting (either with a similar population or in a population required to receive bevacizumab in the first-line setting) based on a median 1.44 month improvement in OS, a second trial in this setting would likely be practically impossible. In addition to VELOUR, results were publically presented at ASCO [J Clin Oncol 30, 2012 (suppl; abstr CRA3505)] of a study that investigated bevacizumab plus FOLFIRI in patients who progressed after receiving a bevacizumab-containing regimen in first-line. Although not confirmed by the Agency in the context of this BLA, the reported 1.4 month median improvement in OS following the use of bevacizumab plus FOLFIRI was similar to the effect observed in VELOUR. This reviewer is skeptical that either physicians or patients would be enthusiastic about initiating an additional second-line anti-VEGF trial in combination with FOLFIRI to confirm the benefit observed in VELOUR.

1.2 Magnitude of effect / Patient selection

This reviewer acknowledges the modest effect size on overall survival demonstrated in the VELOUR trial [HR 0.817 (0.714 to 0.935)] with a median difference in survival between arms of 1.44 months. Although modest, such improvements in OS have been the basis for approval of other drugs in oncology.

Physicians and patients will need to individually consider whether the modest improvement in OS is of sufficient magnitude to offset the increased toxicity when aflibercept is added to FOLFIRI (including an increased incidence of severe diarrhea).

Although the overall effect size was modest, the Kaplan-Meier curves continued to diverge after the medians were reached, indicating the *possibility* that a subset of patients may benefit to a greater degree from treatment with aflibercept. Unfortunately, biomarkers have not been identified that will allow for the selection of patients who will benefit from treatment (or perhaps more importantly, who will not benefit from treatment). The Office of Clinical Pharmacology (OCP) evaluated the effects of baseline VEGF levels on aflibercept response and found that although VEGF levels were potentially prognostic (in patients with previously treated mCRC), VEGF levels did not appear to select a population who would or would not benefit from treatment.

Given the modest effect size observed in VELOUR, this reviewer strongly encourages Sanofi-aventis to conduct additional research into identifying potential biomarkers that will allow for better patient selection for anti-VEGF therapy (i.e., to maximize benefit and to minimize harms in patients who will not benefit). At this time, however, based on the lack of a suitable

candidate biomarker, a specific PMC cannot be recommended to conduct a pivotal clinical trial for that biomarker.

1.3 Prior bevacizumab

The pivotal trial supporting this application enrolled only 28% of patients (per the CRFs) who received prior bevacizumab in combination with prior oxaliplatin-based treatment. In this reviewer's opinion, this raises some questions regarding the applicability of this trial to U.S. medical practice (i.e., bevacizumab is a common component of first-line mCRC regimens in the U.S.). Overall, the treatment effect in the prior bevacizumab subgroup, a stratification factor at randomization showed a HR of 0.86 with a 95% confidence interval that crossed 1.0 (0.676 to 1.1). The point estimate was of slightly lower magnitude compared to the effect in the overall population [HR 0.817 (95% CI: 0.714 to 0.935)]. Although the 95% CI for the prior bevacizumab subgroup crossed 1.0, the sample size of this subgroup was not necessarily powered to be able to demonstrate an improvement in OS.

Tests for interactions between outcomes and prior bevacizumab use were presented at ASCO [J Clin Oncol 30, 2012 (suppl; abstr 3505)] and in the Application. Sanofi-aventis calculated a p-value for interaction of 0.5668 for OS in an amendment submitted to the BLA on March 12, 2012 and concluded that there was no significant interaction based on a 10% significance level.

FDA approved bevacizumab in combination with an oxaliplatin-based regimen in 2006 based on the results of an ECOG trial that evaluated bevacizumab in combination with FOLFOX4 as a *second-line* treatment for metastatic colorectal cancer (Cohen et al. 356-61;Giantonio et al. 1539-44). In the ECOG trial, bevacizumab when added to FOLFOX4 increased median OS by 2.2 months compared to FOLFOX4 alone. Additionally, as described in bevacizumab product labeling, bevacizumab improved OS by a median of 4.7 months when added to the bolus-IFL regimen in the first-line setting. Of importance however, is that bolus-IFL is not commonly used in U.S. practice today compared to the standard FOLFOX and FOLFIRI regimens.

A separate trial of bevacizumab when added to FOLFOX4 or CapeOX in the *first-line* setting did not show a statistically significant benefit in OS, although the report of the trial indicated a modest 1.4 month median improvement in progression free survival (Saltz et al. 2013-19). Based on these results, this reviewer considers it reasonable to ask what is the benefit of anti-VEGF therapy in the *first line* setting, especially when administered with modern oxaliplatin-containing regimens and when anti-VEGF therapy is administered to patients in subsequent lines of therapy.

Given the lack of a consistently demonstrated OS effect when bevacizumab was investigated in the *first-line* setting in combination with FOLFOX, this reviewer considers it reasonable to approve aflibercept in the second-line setting in combination with FOLFIRI, even though less then one-third of the patients received prior bevacizumab. NCCN guidelines state that first-line therapy using FOLFOX or CapeOx for patients with mCRC can be administered with or without bevacizumab (http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf, accessed 12 Jul 2012).

This reviewer favors the inclusion of data describing the HR and 95% CI observed in the prior-bevacizumab treated subgroup in aflibercept product labeling without the inclusion of statements implying that the results in this subgroup were similar to the overall population. This reviewer does not consider the results of the interaction analyses to be sufficient to make any conclusions (i.e., these analyses do not constitute *substantial evidence* of an absence of an interaction) that the treatment effects were in-fact similar in the prior bevacizumab subgroup. Although described in the Statistical Analysis Plan, descriptions of these analyses were not included in the original VELOUR protocol. The prior-bevacizumab subgroup was also underpowered to make any definitive conclusions. Nevertheless, inclusion of the 95% CI will allow physicians to determine the strength of the data in this subgroup when determining whether to prescribe aflibercept to a patient previously treated with bevacizumab plus an oxaliplatin-containing regimen (i.e., the HR point estimate of the prior bevacizumab subgroup was in the range of the HR point estimate for the overall population; however, physicians can question whether the trial should have enrolled more patients who received prior bevacizumab).

See Section 1.1 above for considerations regarding a second trial (i.e., whether a second trial could be conducted in patients who received prior bevacizumab plus an oxaliplatin-containing regimen).

1.4 Was the optimal dose administered to patients in VELOUR?

One of the major issues identified by the Office of Clinical Pharmacology (OCP) was whether the optimal dose was administered to patients in VELOUR. The applicant selected the dose, in part, based on preclinical pharmacological data and *in-vivo* dissociation constant findings that suggested that maintaining a free/bound aflibercept ratio above 1.0 throughout the dosing interval would maximize binding of endogenous VEGF and maintain VEGF levels < 20 pg/mL (near the median value of 17 pg/mL in healthy subjects). Aflibercept doses > 2 mg/kg administered every other week resulted in a mean ratio of free/bound aflibercept > 1.0 in all monotherapy and combination phase 1 studies. The proposed dose of aflibercept of 4 mg/kg administered every other week was identified in phase 1 studies as safe and biologically active for development in subsequent studies.

The FDA Pharmacometric review found that in VELOUR, OS was related to free and VEGF-bound aflibercept exposure. Additionally, simulations performed by OCP suggested that a fixed dose of 300 mg (equivalent to a 4 mg/kg dose in a 75 kg patient) could result in a tighter distribution of AUC values with less variability in exposure in heavier and lighter patients.

This reviewer considers the optimal dosing regimen of aflibercept as unsettled. However, the only aflibercept-dosing regimen supported by substantial evidence of effectiveness was the regimen evaluated in VELOUR (4 mg/kg administered every other week). Although provocative, the exposure-response analyses were conducted using population PK data (with less than 100% ascertainment) and could not adjust for all imbalances in (known or unknown) baseline prognostic variables. Additionally, analyses of data that included patients who underwent dose delays/reductions may have selected for a worse prognosis group with lower levels of free aflibercept. Nevertheless, this reviewer considered the general spirit of the OCP recommendation to be reasonable in that Sanofi-aventis should consider further investigations

into determining the optimal dosing strategies for the administration of aflibercept, including determining whether strategies (for example, higher doses to lower weight patients) to individualize dosing could improve the beneficial effects of anti-VEGF therapy compared to the established dosing regimen of 4 mg/kg every other week.

2. Background

2.1 Disease and therapy related issues

Sanofi-aventis requested marketing authorization for the use of aflibercept in combination with irinotecan-fluoropyrimidine-based chemotherapy for patients with metastatic colorectal cancer (mCRC) previously treated with an oxaliplatin-containing regimen. In general, because mCRC is an incurable disease [with the notable exception of patients who have oligometastatic disease (usually hepatic)], the goal of treatment for these patients is to prolong life and/or improve quality of life (refer to the clinical review for details regarding the epidemiology of mCRC).

Table 2 lists regimens described by the NCCN (http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf, accessed 12 Jul 2012) for the first- and second-line treatment of patients with mCRC. Inclusion of these regimens in this review does not indicate endorsement by this reviewer or the Agency; however, the table lists regimens offered to patients in the United States.

Table 2 Regimens used to Treat mCRC

Initial therapy	Therapy after progression
FOLFOX or CapeOX ± bevacizumab *or* FOLFOX ± panitumumab (only if KRAS WT)	FOLFIRI *or* irinotecan *or* FOLFIRI + cetuximab or panitumumab (only if KRAS WT) *or* irinotecan + cetuximab or panitumumab (only if KRAS WT)
FOLFIRI + bevacizumab *or* FOLFIRI ± cetuximab or panitumumab (only if KRAS WT)	FOLFOX or CapeOX *or* irinotecan + cetuximab or panitumumab (only if KRAS WT)
	If not able to tolerate combination, single agent cetuximab or panitumumab (only if KRAS WT)
5FU/LA ± bevacizumab *or* capecitabine ± bevacizumab	FOLFOX *or* CapeOX *or* FOLFIRI *or* irinotecan ± oxaliplatin
FOLFOXIRI	Single agent cetuximab or panitumumab (only if KRAS WT) ± irinotecan.

Currently, the only anti-VEGF therapy approved for patients with mCRC is bevacizumab. However, multiple small molecule tyrosine kinase inhibitors approved in other cancers have anti-VEGF properties. Bevacizumab is indicated for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil–based chemotherapy. The approvals for mCRC were based on the results of one study in the first-line setting in combination with bolus-IFL and one study in the second-line

setting in combination with FOLFOX-4. As previously stated in this review, a study of bevacizumab plus either FOLFOX-4 or CapeOx did not establish an effect on OS in the *first-line* setting when bevacizumab was combined with these regimens.

Drugs that target the VEGF pathway cause a characteristic pattern of adverse events that include hypertension, proteinuria, thromboembolic events, hemorrhage, and reversible posterior leukoencephalopathy (RPLS). A boxed warning for bevacizumab describes gastrointestinal perforations, surgery and wound healing complications, and hemorrhage. The Warnings and Precautions section of the bevacizumab label describes non-gastrointestinal fistula formation, arterial thromboembolic events, hypertension, reversible posterior leukoencephalopathy syndrome (RPLS), and infusion reactions.

2.2 Regulatory history

The following summarizes the pertinent regulatory history and meetings held in relation to this BLA. Meetings held to discuss clinical trials pertinent to other indications will not be summarized below (Refer to Section 2.6.3 of the clinical review for details regarding the aflibercept development program).

15 Dec 2005 (EOP1, non-clinical meeting): Regeneron requested this meeting to obtain advice regarding the design and duration of proposed pivotal toxicology studies. (b) (4) FDA stated that the duration of the required non-clinical studies was, in part, dependent upon the findings of clinical and non-clinical findings. FDA stated that, in general, 6 month studies were considered adequate for chronic toxicity studies of biotechnology products. FDA agreed with plans for embryofetal development studies and pharmacology studies for wound healing and thrombosis; however, FDA questioned the need for a proposed cardiovascular safety study because the changes in cardiovascular function (e.g., hypertension) were considered as a class effect. *Reviewer note: These recommendations were made prior to the promulgation of the ICH S9 Guidance document.*

16 May, 2006 (Type B, EOP1 CMC meeting): FDA and Regeneron met to discuss CMC development plans for aflibercept.

FDA stated that

- Regeneron provided insufficient information for FDA to agree with Regeneron's plans (b) (4)
- The DP process validation plans submitted in the meeting package appeared acceptable.
- Regeneron will not be able to use a binding/ELISA assay as the sole potency release assay (at the time of the meeting). FDA stated that a pivotal study will require a validated bioassay which was not developed at the time of the meeting.

- Proposed studies to evaluate antibody dependent cell-mediated cytotoxicity and complement-dependent cell lysis appeared acceptable.

16 Jul 2007 (Type B, pre-Phase 3 meeting): Regeneron/Sanofi-aventis scheduled a teleconference to discuss development and registration plans for the use of aflibercept in combination with FOLFIRI for the second-line treatment of patients with metastatic colorectal cancer (mCRC). The IND sponsor cancelled the meeting based on draft responses sent to the Agency on July 13, 2007. FDA stated in the preliminary draft comments that the proposed trial design (multi-national, randomized, placebo-controlled) with a primary endpoint of overall survival was acceptable; however FDA disagreed with the proposed statistical analysis plan (b) (4) Specifically, FDA did not agree that the proposed PFS effect size (b) (4) would be reasonably likely to predict clinical benefit.

Additionally, the draft responses contained the following statements (modified for the purposes of this review for brevity):

- The proposed PK assessment plan appeared acceptable; however, FDA recommended submission of PK summary results in a pre-BLA meeting with justification for assessing only a subset of patients for anti-product immune responses.
- Regeneron will need to develop an assay capable of detecting neutralizing antibodies.
- FDA stated that for the results to be generalizable, VELOUR would need to enroll a sufficient number of patients who received prior bevacizumab in combination with chemotherapy.

11 Oct 2007 (Type C, CMC meeting): Regeneron requested this meeting as a follow-up to a previous 16 May 2006 EOP1 CMC meeting. (b) (4) FDA agreed with the proposed (b) (4) drug product (DP) lot release and stability testing. FDA stated that Regeneron will need to provide data in a BLA that the VEGFR1 bioassay reflects and provides control for the ability of VEGF-trap to inhibit the binding of VEGF to VEGR2. Regeneron agreed to analyze stressed samples to demonstrate VEGFR2 activity and perform additional studies suggested by the Agency.

Additionally, the meeting minutes contained the following statements (modified for the purposes of this review for brevity):

- FDA did not agree with the proposal (b) (4)
- FDA requested that Regeneron establish acceptance criteria (b) (4)

- FDA stated that Regeneron's proposed approach [redacted] (b) (4) appeared reasonable.
- FDA recommended stability studies be conducted using temperatures higher than 25 degrees Celsius to mimic potential short-term product exposure to higher temperatures. FDA stated that no specific study was required, but recommended that Regeneron consider the type and extent of temperature excursions that might be encountered during commercial shipping of product.
- The proposed studies for viral clearance appeared reasonable.
- FDA requested that Regeneron clarify how much lot release and stability data would be included in a BLA submission in regards to proposed 4 and 8 mL presentations.
- FDA recommended that Regeneron measure anti-aflibercept antibody levels from all patients at pre-dose on Day 1 of each cycle in addition to baseline, 30, and 90 days after the last dose of aflibercept or placebo. FDA stated that Regeneron's proposal to assess immunogenicity every other cycle during the (phase 3) NSCLC, pancreatic cancer, and mCRC studies was acceptable.
- FDA did not agree with Regeneron's proposal [redacted] (b) (4)

14 Aug 2008 (FDA letter to Regeneron): FDA sent a letter to Regeneron that provided comments regarding a proposed clinical protocol (TES10642) designed to assess the effect of aflibercept on QTc intervals. In addition to the proposed analysis, FDA requested that Regeneron perform an analysis on QTcF differences between drug and placebo at each time-point.

29 Sep 2008 (FDA letter to Regeneron): FDA sent a letter to Regeneron in relation to the pivotal trial in mCRC (VELOUR). The letter requested that CRFs capture information regarding prior cardiovascular events and thromboembolic events. FDA requested submission of the IDMC charter. FDA again cautioned Regeneron that a PFS HR of [redacted] (b) (4) translating into a median [redacted] (b) (4) improvement in PFS was not a finding that would be reasonably likely to predict an improvement in overall survival.

8 Dec 2009 (FDA letter to Regeneron): FDA provided feedback on Regeneron's plan regarding anti-aflibercept antibody assay development and validation. FDA requested that Regeneron include a report on the assessment of interference by serum components, assess the stability of critical reagents, and that the BLA should contain assay protocols used to assess immunogenicity.

22 Apr 2009 (FDA letter to Regeneron): FDA expressed concern that one element of the IDMC charter may jeopardize the IDMC's ability to maintain independence from Regeneron. FDA stated that the Agency may require submission of all records of internal meetings and communications between the IDMC and Regeneron.

28 Jun 2010 (FDA letter to Regeneron): FDA provided feedback regarding a DDI assessment and stated that further investigations of interactions between aflibercept and the components of FOLFIRI appeared unnecessary.

30 Jul 2010 (FDA letter to Regeneron): FDA referred to Regeneron's June 14, 2010 submission requesting FDA responses to questions regarding a subsequent marketing authorization. FDA stated in the letter that a (revised) proposed PFS HR of (b) (4) translated into a median (b) (4) prolongation in PFS; and that this magnitude of effect was unlikely to predict clinical benefit. However, FDA stated that that the Agency would be open to further discussion if the effect on PFS was of overwhelming magnitude and supported by a strong trend in improved OS. (b) (4)

20 Sep 2010 (FDA letter to Regeneron): FDA provided comments to Regeneron regarding the Statistical Analysis Plan (SAP) of the VELOUR trial. FDA again reiterated previous comments regarding the magnitude of PFS as being too small to be able to predict clinical benefit.

12 May 2011 (Type B, pre-BLA, CMC meeting): During the meeting, FDA specified that Regeneron should test worst-case shipping scenarios. Regeneron stated that this will be addressed using data from freeze/thaw cycling studies.

FDA stated that all potential sterility and temperature studies should be addressed at the time of the BLA submission. FDA stated that the concurrent validation strategy for drug product (b) (4) was acceptable; however, the validation protocol would be a review issue during the BLA submission and that the protocol should define acceptable release specification levels. FDA provided comments regarding the proposed Table of Contents of Module 3 (quality) of the BLA. FDA stated that the DS section of the BLA should include the following:

- Monitoring of bioburden and endotoxin levels at critical manufacturing steps using validated bioburden and endotoxin tests.
- Data from three successful consecutive product (b) (4) hold time validation runs at manufacturing scales.
- Bioburden and endotoxin limits regarding bioburden and endotoxin levels before and after the maximum hold time.
- (b) (4) and storage validation.
- Bioburden and endotoxin data obtained during manufacture of the three conformance lots.
- Data summaries of shipping validation studies.
- Drug substance bioburden and endotoxin release specifications.
- Data summaries from method suitability studies for bioburden and endotoxin levels.

FDA stated that the DP section of the BLA should include the following:

- Validation data summaries (b) (4)

- Tests methods and validation data for the container closure integrity test.
- Study protocols (b) (4)
- Descriptions of routine environmental monitoring program, equipment requalification program, and (b) (4) procedures.
- Study protocols and data summaries for shipping validation.
- Data summaries from method suitability studies for bioburden, sterility, and endotoxin testing.

Actions items for the meeting included the following:

- Regeneron will perform (b) (4)
- Regeneron will submit validation data (b) (4)
- Regeneron will perform additional accelerated stability studies (b) (4)

07 Jul 2011 (Type B, pre-BLA meeting): FDA, Regeneron, and Sanofi-aventis met to discuss a proposed BLA submission based on the results of the VELOUR trial that enrolled patients with mCRC. Regeneron provided summary results in that the trial met the primary endpoint of an improvement in OS: stratified HR 0.817, 95.34% CI: 0.713 to 0.934, p = 0.0032. FDA recommended that Regeneron submit the application in a supplement to the original BLA (macular degeneration indication); however, Regeneron could propose a new trade name. During the meeting, the sponsor requested consideration regarding whether the application could be submitted under a separate BLA number (STN). FDA requested that Regeneron submit the proposal and a rationale regarding why the product should be considered as a stand-alone BLA and that the Agency would discuss the issue internally. *Comment: Subsequent to the meeting, it was determined that Sanofi-aventis would submit the BLA for the oncology indication with Regeneron holding the License for the ocular indication; thus, a separate BLA number was issued for the Sanofi-aventis application.*

FDA agreed with Regeneron's proposal regarding the Integrated Summary of Safety. Specifically FDA agreed with the plan to exclude certain smaller studies [PDY6655, PDY6656, TCD10173, TED6113, and TED6114 - see clinical review for details] from the integrated datasets provided that Regeneron submit stand alone datasets and study reports from these studies. FDA also requested that Regeneron submit analyses of adverse events of special interest (RPLS in particular) across all studies including NCI studies not conducted under the Regeneron IND. FDA agreed with Regeneron's plan to submit datasets in SDTM and analysis formats.

28 Oct 2011: Sanofi-aventis submitted original BLA (b) (4) for aflibercept (b) (4) Subsequently, Sanofi-aventis requested withdrawal of the application on **19 Dec 2011** following a telephone conference with the Agency in regards to CMC deficiencies (see 20 Dec 2011 letter below).

20 Dec 2011 (FDA letter to Sanofi-aventis): FDA sent a letter to Sanofi-aventis acknowledging the withdrawal of the application. The letter contained written comments regarding information necessary to ensure a complete application for filing purposes. Specifically, during the review of the BLA, FDA noted numerous inconsistencies (b) (4) FDA provided a list of multiple items that required either correction or resolution in order for the application to be filed.

02 Feb 2012: Sanofi-aventis submitted original application 125418.

The following table summarizes the purpose of amendments submitted to this BLA.

Table 3 Amendments to BLA 125418

Date of Submission	Purpose of Submission
02 Feb 2012	Original submission
02 Mar 2012	Response to FDA CMC information request (provide DP manufacturing schedule) and clinical information request (to provide contact information for all clinical sites that enrolled more than 15 subjects)
12 Mar 2012	Provided errata documents to correct p-values for interactions for subgroup analyses (based on ECOG and prior bevacizumab use)
22 Mar 2012	Provided a list of contract research organizations in preparation for FDA clinical inspections
30 Mar 2012	Response to FDA request for information including the approach used to determine the number of patients who had prior non-tumor therapies; a Master Check list for non-clinical studies (to identify studies unique to the mCRC indication); and to clarify whether the specific submission date was provided in each Letter of Authorization
03 Apr 2012	Response to FDA CMC information request and to update eCTD sections (3.2.S.4.3; 3.2.P.3.1; and 3.2.P.5.3)
09 Apr 2012	Response to information request to support clinical site inspections
11 Apr 0212	Formal response to an FDA request that U.S. license number 1752 was assigned to sanofi-aventis U.S. LLC
13 Apr 2012	Submission of a press release publically disclosing key results of a phase III trial in patients with metastatic androgen-independent prostate cancer. The trial did not meet the pre-specified criterion of an improvement in overall survival
18 Apr 2012	Response to FDA CMC information request to 25 items related to various aspects of the manufacture of aflibercept as Zaltrap (see CMC review)
24 Apr 2012	Request to determine whether, if licensed, Sanofi-aventis will receive a 12-year exclusivity period pursuant to PHSA section 351(k)(7). Sanofi-aventis provided a rationale intended for review by the Office of Chief Counsel
27 Apr 2012	Response to FDA request for information to provide the number of patients treated in NCI-sponsored studies at the time of data cut-off
30 Apr 2012	Submission of CMC information that Sanofi-aventis agreed to provide in an amendment dated 03 Apr 2012. This information included qualification reports for compendial methods performed at a Sanofi-aventis site in Frankfurt and the analytical procedure and validation report for Polysorbate-20 (b) (4)

Date of Submission	Purpose of Submission
07 May 2012	Response to FDA clinical pharmacology information request to provide oxaliplatin PK data from study report BDY-INT3010-EN-E01 and to provide cisplatin PK data from study report XRP6976E-1001
08 May 2012	Updated financial disclosure information that included a change in the status of an investigator
10 May 2012	Response to FDA CMC information request to 15 items related to various aspects of the manufacture of aflibercept as Zaltrap (see CMC review)
25 May 2012	Submission of 120 day safety update
30 May 2012	Formal response to an FDA request to submit revised labeling information that included some formatting and editorial changes
1 Jun 2012	Response to FDA CMC information request to 23 items related to various aspects of the manufacture of aflibercept as Zaltrap (see CMC review)
1 Jun 2012	Submission acknowledging the OSI inspection findings for Dr. Van Hazel in Australia and the submission of sensitivity analyses excluding the data from this site
4 Jun 2012	Provided the results from a completed microbiology study to support the storage time of diluted Zaltrap DP
8 Jun 2012	Response to FDA CMC information request to 10 items related to various aspects of the manufacture of aflibercept as Zaltrap (see CMC review)
18 Jun 2012	Response to FDA CMC information request to 7 items related to various aspects of the manufacture of aflibercept as Zaltrap (see CMC review)
22 Jun 2012	Response to FDA CMC information request to 5 items related to various aspects of the manufacture of aflibercept as Zaltrap (see CMC review)
27 Jun 2012	Response to FDA CMC information request to provide an attached draft SOP on allocation of particular DS batch lots for specific programs (i.e., either Eylea or Zaltrap)
29 Jun 2012	Response to FDA CMC information request to 6 items related to various aspects of the manufacture of aflibercept as Zaltrap (see CMC review)

3. CMC

Overall the CMC review team (Dr. Kennett, primary reviewer) determined that the manufacture of Zaltrap was well controlled and the product was both pure and potent. The product quality microbiology review team (Dr. Kalavati Suvarna, primary reviewer) also found that the BLA, as amended, should be approved from a CMC microbiology product quality perspective pending labeling agreement and with the post-marketing commitments described below.

Aflibercept (trade-name Zaltrap; code-name VEGF trap or AVE0005) is a recombinant fusion protein of human VEGFR1 Ig domain 2, human VEGFR2 Ig domain 3, and human IgG1 Fc. As documented in the CMC review, each polypeptide contains (b) (4) . The theoretical (unglycosylated) molecular weight is 96.9 kD, and the experimental molecular weight is 115 kD.

Zaltrap is intended to be administered as an injection and manufactured (DP) at a concentration of 25 mg/mL and filled in either 5 mL or 10 mL glass vials (total of 100 or 200

mg aflibercept in each vial, respectively). CMC reviewers defined potency as IC_{50} of the sample relative to IC_{50} of the reference standard in a proprietary VEGF-stimulated reporter gene assay and an a ELISA-based binding assay. The dating period for the drug product vials is 36 months when stored at 2-8ºC.

CMC issues were challenging to resolve as it related to the approval of this BLA. As described in the regulatory history section of this review, Sanofi-aventis submitted original BLA (b) (4) on 28 Oct 2011 for aflibercept (b) (4). Sanofi-aventis requested withdrawal of the application on 19 Dec 2011 following a telephone conference with the Agency (b) (4). Table 3 above also shows that FDA sent multiple information requests to Sanofi-aventis in order to resolve issues in the application so that DMA could ensure that Zaltrap was both pure and potent.

Inspections were waived by the Agency for this review. (b) (4) FDA conducted a cGMP inspection (b) (4) classifying the site as NAI. FDA previously classified the (b) (4) facility as VAI (b) (4). FDA waived the inspection of the DP manufacturing site (Sanofi-Aventis Deutshland GmbH) based on compliance history, current GMP status, and previous inspections. The CMC review also stated that other facilities involved in the manufacture of aflibercept as Zaltrap have previously been inspected and are in compliance with 21 CFR 210, 211, and 600.

Table 4, copied from the CMC review shows the consultant status for CMC-related reviews. Refer to the detailed CMC review for a discussion of the issues related to this application. Additionally, refer to summary/CDTL reviews for aflibercept as Eylea (b) (4)

Table 4 Consultant Status for CMC Review

Consultants / CMC Reviews	Recommendation	Date	Reviewer
Environmental assessment	Approval	23 Feb 2012	Sarah Kennett
OBP Carton and Vial Labeling	Comments to applicant sent; most requirements met	27 Jun 2012	Kimberly Rains
BMAB and DMA - memo for DS review	Waived	10 May 2012	Michelle Clark-Stuart Sarah Kennett
BMAB – memo for DP review	Waived	03 July 2012	Kalavati Suvarna Sarah Kennett

CMC review staff identified no unresolved CMC issues precluding approval; however, CMC reviewers recommend the following commitments related to the manufacture of aflibercept as Zaltrap:

- Add conductivity testing to the drug product (DP) release specification.
- To re-evaluate the release and shelf-life specifications for the aflibercept drug product after 30 commercial manufacturing runs using the current specifications methods.
- To re-evaluate the release and shelf-life specifications for the aflibercept drug substance after 30 commercial manufacturing runs using the current specifications methods.
- To conduct a study to evaluate impact of worst case [redacted] (b) (4) using a validated container closure integrity test. The study protocol and data should be submitted as a CBE-30 supplement.
- 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.
- [redacted] (b) (4) The [redacted] (b) (4) bioburden data from [redacted] (b) (4) batches manufactured using the commercial process [redacted] (b) (4) should be submitted as a CBE-0 supplement.
- 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 U.S. Distribution Center. The protocol and data from the shipping qualification study should be submitted as a CBE-0 supplement.

4. Nonclinical Pharmacology/Toxicology

Dr. Putman completed his review and recommended approval of this application from a pharmacology/toxicology perspective. Non-clinical review staff did not recommend any additional pharmacology/toxicology post-marketing commitments or requirements. In the BLA, Sanofi-aventis submitted the results from non-clinical studies used to support the approval of aflibercept as Eylea [treatment of neo-vascular (wet) age-related macular degeneration].

The non-clinical review summarized the following results of animal studies:

- Primary pharmacology studies confirmed the mechanism of action as described in product labeling and that aflibercept showed anti-tumor activity in non-clinical studies.
- In cynomolgus monkeys, a single 5 mg IV dose of VEGF-trap displayed a multi-compartment PK serum profile with a half-life of 98 hours (+/- 31 hours).
- Distribution of VEGF-trap in normal Sprague-Dawley female rats was primarily limited to the circulation.
- Delayed wound healing was observed in safety pharmacology studies conducted in rabbits.
- A 6-month IV toxicology study conducted in cynomolgus monkeys (most relevant species) did not identify a no-observed adverse effect level (NOAEL) and that the low-observed

adverse effect level (LOAEL) was the lowest dose tested (3 mg/kg). Toxicities observed included hunching, nose bleeding, sneezing, reduced activity, and reduced appetite. Investigators euthanized one monkey prior to the end of the study due to anemia and nasal bleeding. Radiological abnormalities observed at all dose levels in included kyphosis, degenerative joint disease, and periosteal reactions. Test-article associated changes were reported for menses and sperm motility. Test-article related changes were also observed in multiple organs including bones, nasal cavities, adrenal glands, brain (choroid plexus), liver, kidneys, ovaries, and digestive system.

- Investigators did not determine a NOAEL in a separate study of young skeletally immature cynomolgus monkeys. The lowest dose tested (0.5 mg/kg) induced adverse effects including histopathological degeneration/regeneration of the respiratory epithelium and olfactory epithelium. Histopathological changes in the bone (including growth plate maturation), nasal cavity, and other organs were observed at doses ≥ 3 mg/kg (refer to non-clinical review for details).
- The Applicant did not submit genetic toxicology studies or carcinogenicity studies for this biological drug.
- In an intravenous embryo-fetal toxicity study conducted in rabbits, the NOAEL was 3 mg/kg and a developmental NOAEL was not identified. The study identified decreased uterine weight at 60 mg/kg; this was assumed secondary to fetotoxic effects. Abortions and increased post-implantation loss were also observed at this dose, as were external, visceral, and skeletal malformations.

5. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacology reviewers (Dr. Ruby Leong and Dr. Kevin Krudys) stated in the OCP review that BLA 125418 is acceptable from a clinical pharmacology perspective provided that the Applicant and the Agency agree on final labeling. OCP recommended no PMCs or PMRs.

5.1 General clinical pharmacology/biopharmaceutics considerations

Aflibercept binds to VEGF-A, placenta growth factor, and VEGF-B. This ligand binding inhibited VEGFR1 and VEGFR2 activation with downstream effects on endothelial cell proliferation and new blood vessel formation. Aflibercept binds to endogenous VEGF-A at an equilibrium dissociation constant K_D of 0.5 pM for VEGF-A_{165} and 0.36 pM for VEGF-A_{121}; to human PlGF at K_D of 39 pM for PlGF-2; and to endogenous VEGF-B at K_D of 1.92 pM to form a stable inert complex.

To support the BLA, Sanofi-aventis submitted results from 19 studies (see Table 1 of the OCP review) containing PK or immunogenicity data including two pharmacodynamics studies conducted in healthy volunteers and three phase 3 registration trials (mCRC, pancreatic cancer, and NSCLC).

5.1.1 Dose selection

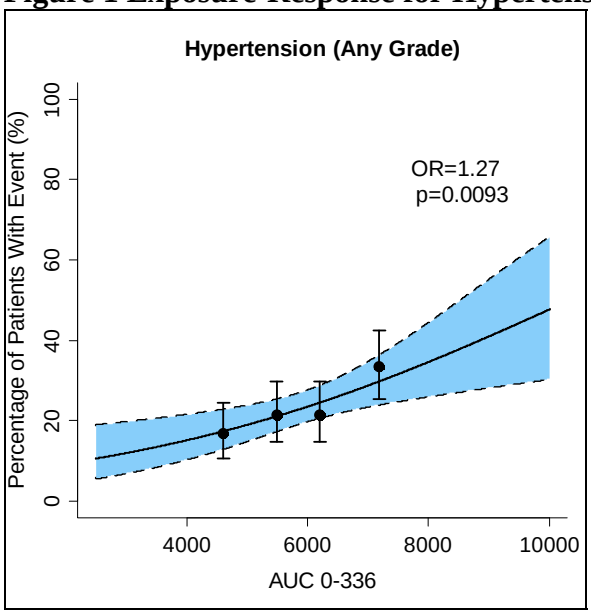
The Applicant selected the dose, in part, based on preclinical pharmacological data and *in vivo* dissociation constant findings that suggested that maintaining a free/bound aflibercept ratio above 1.0 throughout the dosing interval would maximize binding of endogenous VEGF and

maintain VEGF levels < 20 pg/mL (near the median value of 17 pg/mL in healthy subjects). Aflibercept doses > 2 mg/kg administered every other week resulted in a mean ratio of free/bound aflibercept >1.0 in all monotherapy and combination phase 1 studies. The proposed dose of aflibercept of 4 mg/kg administered every other week was identified in phase 1 studies as safe and biologically active for development in subsequent studies.

The FDA Pharmacometric review found that in VELOUR, OS was related to free and VEGF-bound aflibercept exposure. In a multivariate Cox proportional regression analysis using model-derived free aflibercept steady state AUC, the PM reviewer found that an increase of 1000 µg·h/mL was associated with a 21% decrease in the survival hazard ratio (HR). The incidence of hemorrhage and hypertension during the first two cycles also was found to be related to exposure of free aflibercept. The odds of experiencing hypertension increased by 27% for an increase in $AUC_{0\text{-}336h}$ of 1,000 µg·h/mL.

Figure 1, copied from the review by Dr. Krudys, shows the exposure-response relationship for hypertension in VELOUR. The pattern (with a slight decrease in the number of patients with an event in the third quartile) was replicated for hemorrhage, except for a smaller absolute increase in number of events in the forth quartile. *Comment: Patients at higher weights with increased exposure were also likely at higher risk for development of hypertension due to factors external to the trial. Additionally, exposure-safety relationships were not identified for dysphonia, venous thromboembolic events, renal failure, diarrhea, stomatitis or ulceration, and infections and infestations.*

Figure 1 Exposure-Response for Hypertension (VELOUR)



Comment: Although provocative, the analyses of efficacy by free aflibercept AUC were based on population PK data (with less than 100% ascertainment) and could not adjust for all imbalances in baseline confounding factors and thus should be considered exploratory. Additionally, analyses of data that included patients who underwent dose delays/reductions may have selected for a worse prognosis group of patients with lower levels of free aflibercept.

As previously stated, OCP found that weight-based dosing resulted in a strong relationship between body weight and free aflibercept exposure. OCP performed exploratory simulations suggesting that a fixed dose of 300 mg (equivalent to a 4 mg/kg dose in a 75 kg patient) could result in a tighter distribution of AUC values with less variability in exposure in heavier and lighter patients.

Based on these findings, the Pharmacometrics review recommended that for future development of aflibercept, the Applicant should consider the following to optimize dosing:

- Using a fixed dose of aflibercept.
- Individualize dosing by identifying a subset of patients who will benefit from an increase in aflibercept exposure. One possibility is to allow for an increase in aflibercept dose in patients who tolerate the starting dose. Another strategy may be to measure free aflibercept concentrations and increase the dose in those patients with low exposure.

Comment: Because of the exploratory nature of the E-R analyses, this reviewer does not recommend that the label be revised to alter the dosing regimen from the established dosing regimen studied in the VELOUR trial (for example, U.S. patients frequently weigh more than 75 kg and may benefit less with fixed dosing). Nevertheless, this reviewer considers the general spirit of the OCP recommendation to be reasonable in that Sanofi-aventis should consider further investigations into determining the optimal dosing strategies for the administration of aflibercept, including determining whether strategies (for example, higher doses to lower weight patients) to individualize dosing could improve the beneficial effects of anti-VEGF therapy.

5.1.2 Pharmacokinetics

Following the intravenous administration of aflibercept, free aflibercept appeared to exhibit linear PKs at doses ranging from 2 to 9 mg/kg. The mean elimination half-life following the dose of 4 mg/kg every other week was approximately 6 days (range 4-7 days). OCP found that steady state of free aflibercept was reached by the second dose. OCP found the half-life of VEGF-bound aflibercept to be approximately 15 days based on population PK analyses of data from 1,378 patients who received 2 to 9 mg/kg aflibercept every two weeks or every three weeks. OCP estimated the time to reach steady state concentrations of VEGF-bound aflibercept to be approximately 70 days, corresponding to the sixth dose. Healthy volunteer subjects experienced modestly higher free aflibercept exposure compared to patients with cancer.

The OCP review summarized the following additional findings:

- The volume of distribution (V_{ss} = 7.8 L) at steady state was slightly greater than the blood volume.
- In addition to VEGF-targeted drug disposition, free aflibercept is most likely eliminated through proteolysis.
- Aflibercept exhibited minimal drug accumulation, with an accumulation ratio of approximately 1.3 following administration of 4 mg/kg every 2 weeks.

- Inter-individual variability (CV%) in CL and V_{ss} ranged from approximately 20% to 40% in Phase 1 studies. In VELOUR, the variability in CL, V_{ss}, Cmax, and AUC0-336h, were 33%, 14%, 19%, and 20%, respectively.

5.2 Drug-drug interactions

OCP concluded that, based on cross-study comparisons and population PK analyses, no meaningful pharmacokinetic drug interactions were observed between aflibercept and various chemotherapy drugs including irinotecan/SN-38, 5-FU, oxaliplatin, cisplatin, docetaxel, gemcitabine, erlotinib, or pemetrexed.

5.3 Immunogenicity

Determination of the true incidence of immunogenicity was complicated because multiple patients who received placebo tested positive for anti-product antibodies (APA). The APA assay detected APAs across fifteen studies in 72 out of 1,706 patients (4.2%) receiving IV aflibercept (19 positive at baseline) and in 41 out of 1,156 patients (3.5%) receiving placebo (22 positive at baseline). The anti-neutralizing antibody assay detected neutralizing antibodies in 17 of 48 aflibercept-treated patients (out of the 72 patients with APAs who had sufficient samples for further resting) and 2 out 40 patients who received placebo. Limited data precluded an assessment of the effects of neutralizing antibodies on efficacy or safety.

5.4 Demographic interactions/special populations

OCP concluded that age, race, gender, or renal/hepatic impairment did not have a clinically meaningful effect on the exposure of free aflibercept (based on analyses of population PK data). Dedicated renal and hepatic studies were not conducted for this therapeutic biologic protein. Patients weighing ≥ 100 kg appeared to have increased drug exposure (30%) compared to patients weighing < 100 kg. The clinical reviewer performed an analysis of safety (by BMI) and showed that, in general, patients with higher BMI (i.e., ≥ 30) did not appear to experience increased adverse events following aflibercept exposure compared to patients with lower BMI (see safety section below).

5.5 Thorough QT study or other QT assessment

The QT interdisciplinary review team (QT-IRT) analyzed data from Study TES10897 entitled, "A randomized, double-blind, placebo-controlled study comparing aflibercept versus placebo on the QTc interval in cancer patients treated with docetaxel." The QT-IRT reviewed the protocol under the IND prior to the conduct of the study. TES10897 was a randomized (1:1), double-blind, parallel design study where patients received either aflibercept (6 mg/kg every three weeks) plus docetaxel or placebo plus docetaxel for at least three cycles. QT-IRT determined that the 6 mg/kg dose was acceptable and was expected to exceed free peak aflibercept at the 4 mg/kg dose administered to patients with mCRC. A total of 87 patients with metastatic cancer entered the study and 14 completed the entire study. Patients generally discontinued early due to disease progression or adverse events.

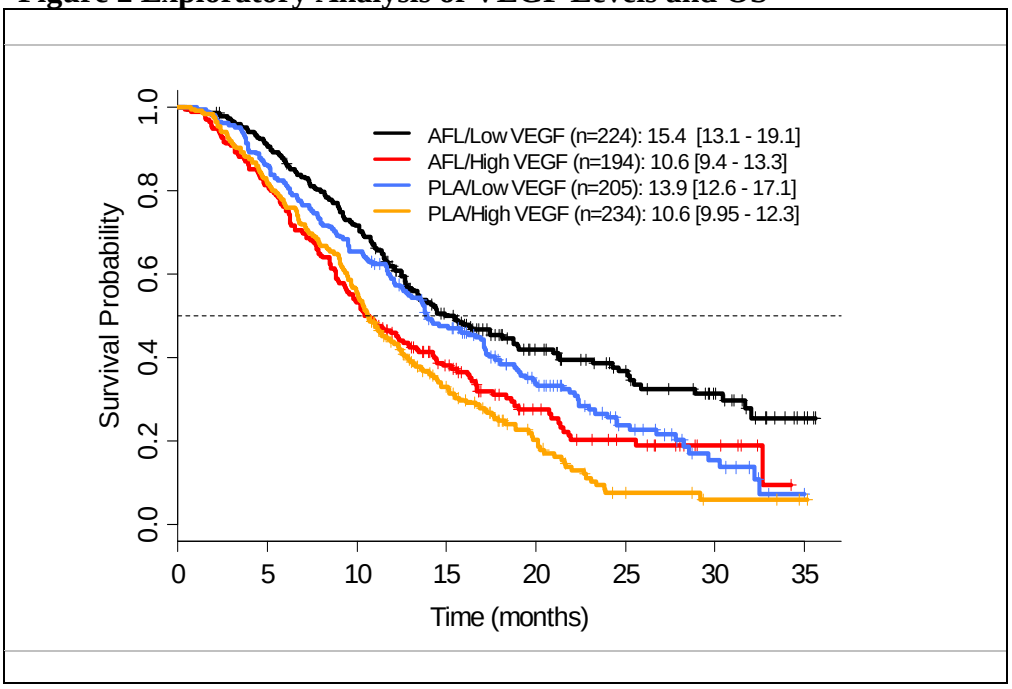
QT-IRT determined that no large change (>20 ms) in QTc interval occurred in patients receiving aflibercept in TES10897. QT-IRT found that the largest upper bound of the 2-sided 90% CI for the mean difference between aflibercept and placebo was 15.7 ms on Cycle 3 (2

hours post-dose). QT-IRT stated that study design limitations precluded assessments of small increases in mean QTc intervals (i.e., < 10 ms).

5.6 Biomarker assessments

Based on the modest magnitude of the clinical benefit observed in VELOUR (see Section 7 below), FDA review staff (clinical and OCP) recognized the potential importance of being able to select patients who would benefit from anti-VEGF therapy (in order to maximize benefit for these patients while sparing patients who would not benefit from the toxicities of therapy). OCP performed an exploratory analysis of OS (Figure 2, copied from the review by Dr. Krudys) in patients with low and high VEGF levels (cut-off selected was 42 pg/mL). Unfortunately, while possibly prognostic (patients with low VEGF levels did better irrespective of whether they received placebo or aflibercept compared to those with high VEGF levels), the marker was not able to differentiate patients who would or would not benefit from aflibercept (patients who received aflibercept fared modestly better than placebo in both the low VEGF and high VEGF comparisons).

Figure 2 Exploratory Analysis of VEGF Levels and OS



6. Clinical Microbiology

This section is not applicable to this review.

7. Clinical/Statistical- Efficacy

As stated in Section 1, this application was supported by the results of one well conducted clinical trial, EFC10262, "VELOUR." VELOUR was a prospective, multicenter, multi-national, randomized (1:1), double-blind, parallel-arm study of aflibercept versus placebo in patients with mCRC treated with FOLFIRI.

Dr. Zhang (statistical reviewer) concluded in her review that the results of the study (VELOUR) demonstrated that patients treated with aflibercept plus FOLFIRI had longer median OS than those treated with placebo plus FOLFIRI. Dr. Zhang found the data submitted in this application to be of high quality and well documented and she was able to reproduce the Applicant's results with reasonable effort.

Dr. Casak concluded that the EFC10262/VELOUR study demonstrated a clinically and statistically significant improvement of OS in patients treated with aflibercept and FOLFIRI over patients treated with placebo and FOLFIRI (stratified hazard ratio: 0.817, 95.34% CI: 0.713 to 0.937; p = 0.0032, equivalent to an 18.3% reduction in the risk of death). These results were supported by improvements in PFS and response rate in patients treated with aflibercept/FOLFIRI, as well as subgroup and sensitivity analyses.

7.1 Background of clinical program

Refer to Section 2.2 above.

7.2 Design of efficacy studies

As previously stated VELOUR was a multi-national, randomized (1:1), double-blind study.

7.2.1 Primary endpoint

The primary endpoint of VELOUR was overall survival (OS), defined as the time from randomization to the date of death due to any cause. *Comment: As stated in the May 2007 FDA Guidance Document regarding endpoints for cancer drugs (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf; accessed on 12 Jul 2012), survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. An effect on OS is considered regulatory evidence of clinical benefit used by the Agency to substantiate regular approval of a drug.*

7.2.2 Secondary endpoints

The second endpoint tested was progression free survival (PFS). The protocol defined PFS as the time interval from the date of randomization to the date of first observation of disease progression or the date of death due to any cause.

Technically, PFS could be considered as a co-primary endpoint as the alpha was split between PFS and OS with a two sided alpha of 0.0001 set for PFS and 0.0499 set for OS. The final PFS analysis was based on the assessment by an independent radiology review (IRC) and was performed (as planned) at the time of the second interim OS analysis. Investigators' assessments, however, were used for patients who died before an April 2008 amendment (that established the IRC) or who declined consent for the IRC review.

Sanofi-aventis evaluated response rate (complete plus partial responses) based on RESIST after both the OS and PFS analyses were statistically significant.

7.2.3 Eligibility criteria

The following describes the major eligibility criteria for VELOUR (refer to the clinical review for full details and additional criteria): mCRC not amenable to curative treatment; cancer progressed during or following prior oxaliplatin-based therapy; one prior regimen in the metastatic setting (unless relapsed within 6 months of completion of adjuvant oxaliplatin); ECOG ≤ 2; and age ≥ 18 years. Patients were excluded for the following: brain metastases; prior ≥ Grade 3 GI bleeding or severe GI disease (see clinical review); DVT within 4 weeks; significant cardiac disease within 6 months; severe or chronic medical conditions that could impair the ability of the patient to participate in the study or to interfere with interpretation of study results; UPCR > 1.0 on morning urinalysis; uncontrolled hypertension; underlying coagulopathy; known dihydropyrimidine dehydrogenase deficiency; inadequate bone marrow function; and known Gilbert's syndrome.

7.2.4 General study design/treatment plan

- The protocol specified randomization (1:1) of patients to treatment in one of the following arms:
  - FOLFIRI (irinotecan 180 mg/m^2 over 90 minutes and leucovorin (dl racemic) 400 mg/m^2 over 2 hours at the same time on day 1, followed by 5 FU 400 mg/m^2 bolus, followed by 5-FU 2,400 mg/m^2 continuously over 46 hours) every other week. All drugs were administered intravenously.
  - Aflibercept (4 mg/kg every other week) plus FOLFIRI
- Prior to each treatment, investigators performed clinical examinations, assessed for adverse events, and assessed laboratory parameters (hematology, biochemistry, coagulation, and urinalyses).
- Tumor imaging to assess for progression occurred every six weeks; imaging continued if patients discontinued therapy prior to disease progression.
- After progression, patients were followed every two months until death or until the end of the study.
- The protocol contained rules to reduce the doses of irinotecan or 5FU depending on the specific toxicity (see clinical review).
- The protocol allowed one dose reduction for aflibercept to 2 mg/kg (e.g., for hypertension and proteinuria).

7.2.5 Statistical design and analysis issues

Randomization/Stratification Factors

Patients were assigned to treatment arms using an interactive voice response system (IVRS) with permuted-block randomization stratified by prior therapy with bevacizumab (yes vs. no) and ECOG performance status (0 vs. 1 vs. 2).

Although the Statistical Analysis Plan (SAP) described testing stratification factors for interactions, the only tests described in the Multiplicity Issues section of the SAP were the final tests for OS, PFS, and ORR. *Comment, this reviewer considers these p-values to be the only interpretable p-values for the purposes of labeling and promotion.*

Determination of Sample Size
VELOUR was designed with 90% power to detect a 20% reduction in the risk of death with a median expected OS of 13.75 months in the experimental arm and 11 months in the control arm at a two-sided significance level of 0.0499. Assuming exponential survival, the final analysis was planned after 863 deaths. A total of 1,200 patients were projected for enrollment assuming an accrual period of 30 months followed by 9 months of follow-up. The above calculations took into account two interim analyses for efficacy (after 36.5% and 65% of projected events) and one for futility that was to occur at the time of the first efficacy analysis. The protocol stipulated a group sequential approach using the O'Brien-Fleming method to control the overall alpha at 0.0499. The first interim analysis was requested by the DMC after the initial protocol was written but before the blind was broken. As previously stated, PFS was to be tested at an alpha of 0.0001 at the time of the interim analysis for OS.

Analyses
The primary analysis compared OS between the two treatment arms in the ITT population using the log-rank test stratified by the stratification factors specified at the time of randomization (prior bevacizumab and ECOG performance status). The HRs and confidence intervals were obtained using a stratified Cox proportional hazards model. Technically, the protocol specified CIs for OS and PFS were designated as 95.34% and 99.99% CIs, respectively. However, for labeling consistency and ease-of-interpretation (among clinicians), all CIs were reported as 95% CIs in the FDA reviews.

Refer to statistical and clinical reviews for methods used to perform additional sensitivity and subgroup analyses.

Protocol Amendments
Table 5, excerpted from the clinical review, shows that the amendments to the protocol were unlikely to have resulted in a qualitative difference in the clinical trial results. The early analysis of OS was specified by the DMC prior to un-blinding of data.

Table 5 Amendments to the VELOUR Protocol

Amendment	Date	Major changes
Amendment 1	3 Aug 2007	– Changed performance status stratification factor from PS 0-1 versus 2 to 0 versus 1 versus 2 – Deleted biased coin dynamic allocation method – Added response rate as a secondary endpoint
Amendment 2	23 Apr 2008	– Added prior bevacizumab as a stratification factor – Changed the immunogenicity evaluation – Added a third party review of radiographs
Amendment 3	16 Nov 2009	– Added an early efficacy analysis when 36.5% of the planned OS events occurred, following a DMC request – Specified that the final PFS analysis will be based on the IRC assessment – Specified that the evaluable patient population was based on randomization and not treatment actually received

Amendment	Date	Major changes
Amendment 4	11 Feb 2010	– Following the DMC meeting after 880 patients completed at least 1 cycle, addition of a recommendation to administer G-CSF upon occurrence of ≥ Grade 3 neutropenia and prophylactic administration of G-CSF for subsequent cycles
Amendment 5	27 Apr 2011	– Extension of study participation beyond the cut-off date for the primary analysis of overall survival

7.3 Summary results

7.3.1 Demographics

Demographics appeared balanced in the two study arms. Table 6, excerpted from two tables in the clinical review, shows that 59% of patients were Men and the majority of patients were White. Median age in both arms was 61 years. Approximately one-quarter of patients had liver only involvement. Not shown below is that all patients received prior chemotherapy and over 80% of patients received prior anti-cancer surgery. A total of 10% of patients in both arms received chemotherapy only in the adjuvant setting.

Table 6 Demographics and Disease Characteristics (VELOUR)

	Placebo (n, %) N=614	Aflibercept (n, %) N=612
Gender		
Male	353 (58)	365 (60)
Female	261 (42)	247 (40)
Race		
White	523 (85)	548 (90)
Asian	51 (8)	35 (6)
Black	27 (4)	16 (3)
Other	13 (2)	13 (2)
Age (years)		
Range	19-86	21-82
Mean (SD)	60.16 (10.8)	59.46 (10.5)
Median	61	61
65 years and older	238 (39)	205 (33)
75 years and older	39 (6)	33 (5)
Tumor site		
Colon	302 (49)	289 (47)
Rectum	174 (28)	197 (32)
Recto-sigmoid	136 (22)	123 (20)
Other site	2 (<1)	3 (<1)
Metastatic organ involvement		
Liver	431 (70)	459 (75)
Lung	277 (45)	271 (44)
Lymph nodes	181 (30)	173 (28)
Peritoneum	88 (14)	68 (11)
Liver metastasis only	146 (24)	153 (25)

Table 7, copied from the clinical review, shows that the overwhelming majority of patients were ECOG PS 0 or 1. Approximately 30% of patients were included in the "prior bevacizumab" group; however, per the CRFs, approximately, 29% and 28% in the placebo/FOLFIRI and aflibercept/FOLFIRI arms, respectively received bevacizumab. The Applicant stated that one reason for this discrepancy was that some patients were still in follow-up on another trial where they were previously assigned to blinded bevacizumab or placebo. These patients were assigned to the "prior bevacizumab" stratum; however, upon un-blinding, the CRF was updated to indicate the patient's correct status.

Table 7 ITT Population by Stratification According to IVRS (VELOUR)

	Placebo (n, %) N=614	Aflibercept (n, %) N=612
ECOG PS		
0	350 (57)	349 (57)
1	250 (41)	250 (41)
2	14 (2)	13 (2)
Prior bevacizumab		
Yes	187 (30)	186 (30)
No	427 (70)	426 (70)

Dr. Zhang performed sensitivity analyses of OS using stratum defined by the CRFs and performing an unstratified LR test. The results of these analyses confirmed the results of the primary analysis using strata defined by the IVRS.

7.3.2 Disposition

The first patient was enrolled in VELOUR on November 19, 2007 and the last patient was enrolled on March 16, 2010. A total of 1,226 patients were randomized: 614 patients to placebo and 612 patients to aflibercept. Five patients in each arm were not treated. At the time of data cut-off, 598 patients (97%) in the placebo arm and 593 patients (97%) in the aflibercept arm discontinued study treatment.

Table 8, copied from the clinical review, shows patient disposition in the VELOUR trial. Discontinuation due to adverse events differed according to what data set was analyzed [i.e., disposition dataset versus adverse event dataset (see Section 8 below)]. Loss of follow-up occurred infrequently during VELOUR.

Table 8 Disposition (VELOUR)

	Placebo (n, %) N=614	Aflibercept (n, %) N=612
Randomized and treated	609 (99)	607 (99)
Discontinued study treatment	598 (97)	593 (97)
Reasons for treatment discontinuation (including patients randomized but not treated)		
Adverse event	74 (12)	163 (27)
Disease progression	437 (71)	305 (50)
Lost to follow-up	2 (0.3)	0
Poor compliance	4 (0.6)	4 (0.6)
Other	86 (14)	126 (21)

7.3.3 OS analyses

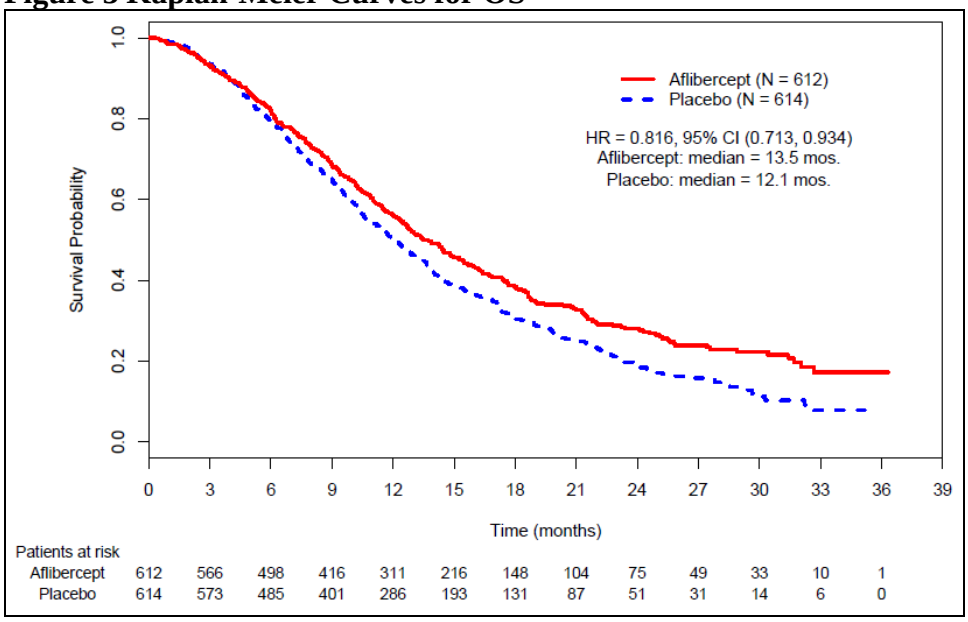
Table 9, copied from the statistical review shows that OS was modestly prolonged in patients randomized to receive aflibercept. Median OS was 12.1 months on placebo and 13.5 months on aflibercept with a corresponding stratified HR of 0.82 (95% CI: 0.71, 0.93). The table also shows three sensitivity analyses that confirmed the robustness of the results of the primary analysis (refer to Section 11.4 of this review regarding issues related to Site 036007).

Table 9 OS Analyses (VELOUR)

	Placebo (n=614)	Aflibercept (n=612)
Primary analysis (IVRS)		
# of events	460	403
Median (in mos.)	12.1	13.5
Stratified HR (95% CI)	0.816 (0.713, 0.934)	
p-value	0.0032	
CRF Stratification		
Stratified HR (95% CI)	0.807 (0.705, 0.923)	
p-value	0.0018	
Unstratified analysis		
HR (95% CI)	0.809 (0.707, 0.924)	
p-value	0.0019	
Excluding Site 036007	**(n=606)**	**(n=597)**
Stratified HR (95% CI)	0.822 (0.717, 0.941)	
p-value	0.0047	

Figure 3, copied from the statistical review, shows the Kaplan-Meier curves for OS from VELOUR. The curves appear to separate between three and six months and continue to separate after the medians.

Figure 3 Kaplan-Meier Curves for OS



Subgroup analyses of OS also confirmed the robustness of the overall results. The HR for OS was less than one [although the CIs for these subgroups frequently crossed one (refer to the statistical review for details] for most subgroups evaluated including ECOG strata, prior bevacizumab strata, age categories, gender categories, race categories, geographic categories, and baseline disease characteristics categories. Only "primary tumor location other" (HR 1.04) and ECOG PS 2 (n=27) (HR 0.978) were approaching or greater than 1.0.

Overall, the treatment effect in the prior bevacizumab subgroup, a stratification factor at randomization was HR of 0.86 with a 95% confidence interval that crossed 1.0 (0.676 to 1.1). This was of slightly lower magnitude compared to the effect in the overall population [HR 0.817 (95% CI: 0.714 to 0.935)]. Although the 95% CI for the prior bevacizumab subgroup crossed 1.0, the sample size of this subgroup was not necessarily powered to be able to demonstrate an improvement in OS in this subgroup.

Tests for interactions between outcomes and prior bevacizumab use were presented in the Application. Sanofi-aventis calculated a p-value for interaction of 0.5668 for OS in an amendment submitted to the BLA on March 12, 2012 and concluded that there was no significant interaction based on a 10% significance level (refer to Section 1 above for interpretation of this data).

7.3.4 Secondary endpoints

Median PFS was modestly prolonged in patients randomized to the aflibercept arm. Median PFS was 4.7 months on placebo and 6.9 months on aflibercept with a corresponding stratified HR of 0.76 (95% CI: 0.66, 0.88). The two-sided p-value for the stratified log-rank test was 0.00007, which was < 0.0001 and supported that the PFS effect was statistically significant. In general, sensitivity analyses of PFS (e.g., different rules for censoring) confirmed the results of the primary PFS analyses. Refer to the statistical review for the KM curves.

The Applicant excluded 165 patients (13%) from the evaluation of objective response rate (ORR), although these patients were evaluated for time to event endpoints. The number of patients excluded from the evaluable patient population (EP) were similar between arms with absence of target lesions the most frequent reason for exclusion. Table 10, copied from the statistical review, shows that more patients responded in the aflibercept arm than in the placebo arm.

Table 10 Objective Response Rate (VELOUR)

	Placebo (n=530)	Aflibercept (n=531)
CR	2 (0.4%)	0
PR	57 (10.8%)	105 (19.8%)
SD	344 (64.9%)	350 (65.9%)
PD	114 (21.5%)	55 (10.4%)
NE	13 (2.5%)	21 (4.0%)
ORR (95% CI)	11.1% (8.5, 13.8)	19.8% (16.4, 23.2)
p-value	0.0001	

8. Safety

8.1 Adequacy of database, major safety findings

Overall, the clinical reviewer analyzed data from the integrated dataset from a total of 2,073 patients exposed to aflibercept in various clinical trials. The number of patients for the safety review was considered adequate for the purposes of the BLA submission.

The clinical reviewer performed the primary safety analyses using data from Trial EFC10262 (VELOUR). A total of 611 patients with mCRC received aflibercept during the pivotal trial at the same dose and schedule (and in combination with FOLFIRI) as that proposed in the package insert. Dr. Casak also conducted analyses of data from two additional large randomized trials in patients with metastatic cancer: VITAL (NSCLC; n = 452 patients exposed to aflibercept); and VANILLA (pancreatic cancer; n = 270 patients exposed to aflibercept). Safety data were also reviewed from additional phase 1 and 2 trials and data from NCI trials submitted to the BLA but conducted under a separate IND (Table 40 of the clinical review contains a listing of trials reviewed).

Patients enrolled in VELOUR received a median of 9 cycles of aflibercept plus FOLFIRI. Patients in the placebo arm received a median of 8 cycles of placebo plus FOLFIRI. *Comment: this difference was likely explained by the difference in PFS.* The clinical review also found aflibercept/placebo dose modifications (dose delays and dose modifications) to occur more frequently in the aflibercept arm (78% and 17%, respectively) compared to the placebo arm (60% and 5%, respectively). The relative dose intensity of both irinotecan and 5-FU were higher in the placebo arm compared to the aflibercept arm: irinotecan relative dose intensity was 0.91 and 0.84 in the placebo and aflibercept arms, respectively; 5-FU relative dose intensity was 0.91 and 0.83 in the placebo and aflibercept arms, respectively.

In general, toxicities caused by aflibercept could be classified into two major classes: toxicities caused by VEGF inhibition (e.g., hypertension, hemorrhage, proteinuria), and increased incidence of toxicities known to be caused by FOLFIRI [e.g., increase in incidence of diarrhea, neutropenia, and palmar-plantar erythrodysesthesia compared to patients receiving FOLFIRI alone)].

Adverse events frequently caused patients to discontinue treatment with aflibercept/FOLFIRI. At least 27% of patients discontinued treatment due to an adverse event (the incidence was 41% in a different dataset, although an assessment of the true incidence was complicated due to the occurrence of adverse events in the setting of disease progression). Adverse events leading to discontinuation included hypertension, diarrhea, fatigue/asthenia, pulmonary embolism, and proteinuria.

Severe toxicities frequently occur in patients with advanced cancer receiving cytotoxic chemotherapy. As found in the clinical review, Grade 3-4 adverse events occurred more frequently in patients assigned to the aflibercept arm (84%) compared to the placebo arm (63%). The most common Grade 3 and 4 adverse events occurring in the aflibercept arm were neutropenia (25%), diarrhea (19%), hypertension (19%), fatigue (13%), and stomatitis (13%). Although severe, most of these toxicities were Grade 3 as opposed to Grade 4. Additionally, these toxicities are well understood in the practice of oncology and are reversible in most patients. It is standard practice to monitor for these adverse reactions, institute treatment as necessary, and to dose modify therapy or discontinue therapy if necessary.

8.2 Deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

8.2.1 Deaths

The clinical reviewer conducted the analysis of deaths that occurred from the start of treatment up to 30 days after the last dose of aflibercept. Disease progression/malignancy caused the most deaths during follow-up of the randomized phase 3 trials. Potential treatment-related deaths are summarized in Table 11 copied from the clinical review.

Table 11 Deaths Occurring during Treatment and up to 30-Days after the Last Dose of Study Drugs (VELOUR)

PT	(n) Placebo n=605	(n) Aflibercept n=611
Disease progression	13	11
Death	1	2
Dehydration	0	2
Intestinal obstruction	1	1
Sepsis	1	1
Acute respiratory failure	0	1
Duodenal ulcer hemorrhage	0	1
Gastrointestinal inflammation	0	1
Hypovolemic shock	0	1
Ileal perforation	0	1

PT	(n) Placebo n=605	(n) Aflibercept n=611
Large intestinal obstruction	0	1
Metabolic encephalopathy	0	1
Neutropenic sepsis	0	1
Pneumonia aspiration	0	1
Pulmonary embolism	0	1
Rectal abscess	0	1
Septic shock	0	1
Ileus	1	0
Interstitial lung disease	1	0
Lobar pneumonia	1	0
Neutropenic infection	1	0
Sudden death	1	0
Total	**21**	**29**

As the table shows, attribution of many of the deaths was difficult. For example, large intestinal obstruction may have been caused by the underling malignancy even in the absence of therapy. After considering deaths classified as "other" in addition to those classified as "adverse event", the clinical reviewer found treatment-related deaths to be more frequent in patients exposed to aflibercept (6% versus 4%).

Although deaths within 30 days of therapy occurred more frequently in aflibercept treated-patients than placebo, the overall KM curves favored treatment with aflibercept. Nevertheless, therapy related fatalities of the gastrointestinal tract (i.e., perforation) can occur following anti-VEGF therapy; and these fatalities occurred more frequently following treatment with aflibercept in VELOUR.

8.2.2 SAEs and analyses of severe adverse events

The VELOUR protocol defined serious adverse events (SAE) as any untoward medical occurrence that, at any dose resulted in death; was life-threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; caused a congenital anomaly/birth defect; or was a medically important event. Non-fatal SAEs occurred more frequently among aflibercept-treated patients compared to patients who received placebo. Most non-fatal SAEs were NCI CTCAE Grade 3 or 4 in severity.

Table 12, copied from the clinical review, shows the most common non-fatal SAEs at the MedDRA preferred term level reported in the VELOUR trial. Most SAEs occurred at a similar frequency in both arms; however, serious dehydration and serious diarrhea occurred in more patients who received aflibercept compared to placebo. Overall the analyses of SAEs at the MedDRA HLT level were similar to the PT level, except for the neutropenia HLT (incidence rate 6% aflibercept arm versus 2% placebo arm).

Table 12 Non-Fatal SAEs (VELOUR)

PT	Placebo (n, %) n=605	Aflibercept (n, %) n=611
Diarrhea	14 (2)	44 (7)
Dehydration	7 (1)	23 (4)
Pulmonary embolism	12 (2)	18 (3)
Febrile neutropenia	6 (1)	19 (3)
Pyrexia	15 (2)	10 (2)
Abdominal pain	7 (1)	12 (2)
Neutropenia	4 (1)	11 (2)
Pneumonia	5 (1)	11 (2)
Vomiting	7 (1)	10 (2)
Hypertension	0	10 (2)
Intestinal obstruction	10 (2)	9 (1)

The clinical reviewer also evaluated non-fatal severe adverse events using NCI CTCAE. By convention, she assessed Grade 3 and 4 adverse events as severe (non-hematological Grade 4 adverse events are considered life-threatening). Table 13, excerpted from the clinical review, shows the most common severe events (three percent or greater among aflibercept-treated patients) by MedDRA preferred term. The largest differences in severe adverse events occurred for diarrhea, hypertension, fatigue, and stomatitis, although there were also notable differences (≥ 3% between arms) for neutropenia, dehydration, palmar-plantar erythrodysesthesia, and proteinuria. The per-patient incidence rate for the more common severe adverse events was similar when the data were analyzed at the HLT level, with the exception of fatigue (HLT asthenic conditions: 11% placebo, 18% aflibercept).

Table 13 Non-Fatal Grade 3-4 AEs (VELOUR)

PT	Placebo (%) n=605	Aflibercept (%) n=611
Neutropenia	22	25
Diarrhea	8	19
Hypertension	1	19
Fatigue	8	13
Stomatitis	5	13
Asthenia	3	5
Pulmonary embolism	3	4
Abdominal pain	2	4
Febrile neutropenia	2	4
Dehydration	1	4
Vomiting	3	3
Decreased appetite	2	3
Weight decreased	1	3
Palmar-plantar erythrodysesthesia syndrome	0	3
Proteinuria	0	3

Although not shown in the table (refer to the clinical review), when grouped by HLT, (terms containing "hemorrhage" or "bleeding"), 7 patients in the placebo arm (1%) and 17 patients in the aflibercept arm (3%) experienced Grade 3-4 hemorrhage.

8.2.3 Drop-outs and discontinuations due to adverse events

Determination of the reasons for treatment discontinuation in VELOUR was difficult because the analyses of data using the adverse events data set differed markedly from the analyses of data using the disposition dataset. Using the adverse events dataset, a total of 41% of patients in the aflibercept arm permanently discontinued treatment. The discrepancies in the datasets regarding reasons for discontinuing aflibercept may have been caused, in part, by differences in the classification of adverse events occurring at the time of disease progression. Because the exact numbers could not be reliably estimated, the clinical review team recommended that the label only include information that could reliably be determined (i.e., the most frequent adverse reactions leading to permanent discontinuation in ≥1% of patients treated with ZALTRAP/FOLFIRI). The most common adverse events leading to discontinuation of study therapy included the following: asthenia/fatigue, infections, diarrhea, dehydration, hypertension, stomatitis, venous thromboembolic events, neutropenia, and proteinuria (see Table 14, copied from the clinical review).

Table 14 Most Frequent Adverse Events Causing Treatment Discontinuation (VELOUR)

PT	Placebo (n, %) n=605	Aflibercept (n, %) n=611
Hypertension	1 (<1)	29 (5)
Proteinuria	0	33 (5)
Pulmonary embolism	13 (2)	18 (3)
Diarrhea	7 (1)	21 (3)
Fatigue	6 (1)	18 (3)
Asthenia	2 (<1)	10 (2)
Stomatitis	1 (<1)	11 (2)

8.2.4 Common adverse events

In general, toxicities caused by aflibercept could be classified into two major classes: toxicities caused by VEGF inhibition (e.g., hypertension, hemorrhage, proteinuria), and increased incidence of toxicities known to be caused by FOLFIRI (e.g., increase in incidence of diarrhea, neutropenia, and palmar-plantar erythrodysesthesia compared to patients receiving FOLFIRI alone).

Table 15, with numbers excerpted from the clinical review, shows the adverse events that occurred in at least 5% of patients in the aflibercept arm and with at least a 2% higher incidence in the aflibercept arm compared to placebo. The following adverse events occurred with at least a *5%* difference between arms (difference in parentheses): hypertension (24%), dysphonia (22%), epistaxis (20%), weight decrease (18%), stomatitis (15%), headache (13%), diarrhea (11%), proteinuria (9%), fatigue (8%), palmar-plantar erythrodysesthesia (7%), and asthenia (5%).

The difference between arms for asthenic conditions was of greater magnitude in the HLT analysis (11% difference between arms).

Table 15 Common Adverse Events (VELOUR)

PT	Placebo (%) n=605	Aflibercept (%) n=611
Diarrhea	54	65
Stomatitis	32	47
Fatigue	37	45
Hypertension	10	34
Weight decrease	14	32
Decreased appetite	23	31
Epistaxis	7	27
Dysphonia	3	25
Neutropenia	22	25
Headache	9	22
Asthenia	12	17
Palmar-plantar erythrodysesthesia	4	11
Dyspnea	8	11
Proteinuria	1	10
Abdominal upper pain	7	10
Urinary tract infection	5	9
Edema peripheral	7	9
Skin hyperpigmentation	3	8
Oropharyngeal pain	3	7
Dysgeusia	5	7
Hemorrhoids	2	6
Rhinorrhea	2	6
Aphthous stomatitis	2	5
Dehydration	2	5
Nasopharyngitis	2	5
Proctalgia	2	5
Rectal hemorrhage	2	5

8.2.5 Laboratory tests

Aflibercept when combined with FOLFIRI caused an increased incidence rate of leukopenia, neutropenia, and thrombocytopenia. Shift tables in the clinical review confirmed the analyses of Grade 3 and 4 events and showed that severe neutropenia was more common following treatment with aflibercept. Severe thrombocytopenia was less common than severe neutropenia but occurred more frequently in patients treated with aflibercept plus FOLFIRI.

A slight increase in ALT and AST elevations were observed in patients who received aflibercept; however, there were no differences in severe ALT/AST elevations. Seven patients in each arm met laboratory criteria for Hy's law; however, underlying malignancy was present in some of these patients. One patient in the placebo arm experienced biopsy confirmed drug-induced hepatitis.

Patients exposed to aflibercept experienced more Grade 1 and 2 calcium (51% versus 41%), potassium (38% versus 33%), and magnesium (41% versus 35%) abnormalities than placebo, potentially caused by the increased incidence of diarrhea. Severe electrolyte abnormalities; however, were balanced between the two arms (see Table 92 of the clinical review).

8.3 Immunogenicity

See Section 5.3 above.

8.4 Special safety concerns

8.4.1 Drug-demographic Interactions

In general, as described in the clinical review, adverse events across gender occurred with similar frequency (acknowledging that these were analyses of non-random subgroups). Women experienced a higher incidence of urinary tract infections (17% versus 4%). Men experienced a higher incidence of decreased appetite, but nausea was more frequent in women (*it is unclear if this difference was caused by differences in reporting among investigators*). Grade 3 or greater weight reduction was similar among genders. Men experienced slightly more Grade 3 or 4 diarrhea than women (22% versus 16% with similar rates among placebo). Grade 3 or 4 neutropenia occurred more frequently among women in both the placebo and treatment arms.

Severe (Grade 3 or 4) gastrointestinal disorders occurred with a higher incidence in the ≥ 65 category than the < 65 category in the aflibercept arm (43% versus 36%). The most frequently reported event was diarrhea, which occurred in 24% of patients in the ≥ 65 category and 17% in the < 65 category.

Based on the issues related to drug exposure described in the clinical pharmacology review above, Dr. Casak performed analyses of safety based on body mass index (BMI). Table 16, using numbers found in Table 103 of the clinical review, shows that in general, there were minimal differences (with exceptions of neutropenia, diarrhea, and pulmonary embolism) in the proportion of patients experiencing severe adverse events by BMI status.

Table 16 Analysis of Grade 3 and 4 Adverse Events by BMI Status

PT	Differences in % Placebo vs. Aflibercept		
	Underweight/ Normal (n=260)	Overweight (n=233)	Obese (n=109)
Neutropenia	-1	4	11
Diarrhea	12	7	18
Hypertension	18	16	20
Fatigue	3	5	6
Stomatitis	9	7	8
Asthenia	5	1	0
Febrile neutropenia	4	2	2
Dehydration	3	1	4
Abdominal pain	1	4	1
Decreased appetite	1	3	2
Vomiting	0	-1	-2
Palmar-plantar erythrodysesthesia	3	3	0
Pulmonary embolism	0	1	4

8.4.2 120 day safety update

The clinical reviewer concluded that the results of the 120 day safety update were consistent with the results submitted in the original BLA. In the 120 day submission, Sanofi-aventis submitted the summary of study EFC10688 (AFFIRM), a randomized, phase 2 study in first-line mCRC evaluating the combination of mFOLFOX6 versus aflibercept/mFOLFOX6. As in the VELOUR study, the safety profile was typical of a drug targeting VEGF, and enhancement of the backbone regimen toxicity was observed, including stomatitis, diarrhea, palmar-plantar erythrodysesthesia, infections, and neutropenia. In this study, although patients in the aflibercept/mFOLFOX6 arm had an increased 12-month PFS [25.8% (95% CI 17.2% to 34.4%) versus 21.2% (95% CI 12.2% to 30.3%) in the mFOLFOX6 arm], this difference was not statistically significant, with a stratified HR of 1.003 (95% CI 0.73 to 1.36). The OS HR was 0.97 (95% CI 0.65 to 1.44).

8.4.3 Additional in-depth analyses of specific events

Cardiac/arterial:

The clinical reviewer found that aflibercept did not appear to increase the risk of cardiac dysfunction in VELOUR. Arterial thrombotic events occurred at a similar but slightly higher incidence rate in the aflibercept arm (2.6% versus 1.7%). The label includes a Warning based on arterial events due to the serious nature of these events.

Acute drug reactions

Acute drug reactions occurred at the same incidence rate in both arms (4% in the Sanofi-aventis analysis) with no Grade 4 (life-threatening) acute drug reactions. Table 17, copied from the clinical review, shows the incidence of acute drug reactions by preferred term.

Table 17 Acute Drug Reactions (VELOUR)

PT	Placebo (n, %) n=605	Aflibercept (n, %) n=611
Edema peripheral	44 (7)	52 (9)
Rash	35 (6)	41 (7)
Conjunctivitis	10 (2)	13 (2)
Hypersensitivity	15 (2)	11 (2)
Pruritus	12 (2)	11 (2)
Drug hypersensitivity	3 (<1)	4 (1)
Erythema	3 (<1)	7 (1)
Edema	1 (<1)	5 (1)
Urticaria	1 (<1)	7 (1)
Flushing	9 (1)	2 (<1)

Gastrointestinal perforation/wound healing/fistula

Adverse events in these categories are known to occur following treatment with anti-VEGF drugs. Fistula occurred in 9 patients who received aflibercept, 8 of whom had rectal or rectal sigmoid tumors. In VELOUR, three patients per arm experienced GI perforation with one fatality in the aflibercept arm.

Reversible posterior leukoencephalopathy syndrome (RPLS)
The clinical review contains an extensive discussion of RPLS. During aflibercept development, a total of 17 cases of RPLS were reported across Sanofi-aventis trials and NCI trials. No cases were reported in VELOUR. Dr. Casak found that RPLS occurred more frequently in women and that there was no prior history of hypertension in some of the patients. One clinical trial in the development program, investigating aflibercept in combination with pemetrexed and cisplatin, was closed to accrual after three women experienced RPLS.

8.5 Discussion of primary reviewer's comments and conclusions

The primary reviewer summarized that the addition of aflibercept to the FOLFIRI regimen in the VELOUR study increased FOLFIRI-related toxicity, and subjected patients to VEGF/R inhibition-related toxicities. More patients in the aflibercept arm experienced adverse events, toxicity-related deaths, dose modifications, and treatment-related withdrawals. However, the safety profile of aflibercept was generally consistent with the known safety profile of bevacizumab, a drug approved in the mCRC setting. *Comment: This reviewer agreed with the major conclusions in the clinical review. The incidence of adverse events in the clinical review was, in general, similar to those of the Applicant. Small differences in the incidence rates of certain adverse events were not clinically significant.*

8.6 Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed

There were no substantive differences in conclusions regarding safety between this CDTL and the review team.

9. Advisory Committee Meeting

The review team did not find that an ODAC needed to be convened for this BLA. The effect on OS was statistically robust, and although this was an original BLA, anti-VEGF therapies are well understood by the practice of oncology.

10. Pediatrics

In the sBLA submission, Sanofi-aventis requested a full waiver of the Pediatric Research and Equity Act requirement to assess the safety and effectiveness of aflibercept for the claimed indication in all pediatric age groups. In the application, Sanofi-aventis stated that "pediatric studies are neither clinically relevant nor practical in this case because the number of pediatric patients is so small and as noted in 2(a) of FDA guidance document, colorectal cancer is on the list of adult-related conditions that may qualify the drug for disease-specific waiver."

This CDTL reviewer agrees that a full waiver is appropriate as described in 21 CFR 314.55(c)(2)(ii) and Section 505B(a)(4)(A)(i) of the Act. Specifically 21 CFR 314.55(c)(2)(ii) states that an applicant can request a waiver if the "necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed." FDA guidance (draft FDA Guidance for Industry: How to Comply with the Pediatric Research and Equity Act dated September 2005) describes colorectal cancer as one of the

diseases that qualifies for a waiver based on the limited number of children diagnosed with the disease.

The PeRC PREA subcommittee met on 06 Jun 2012 and confirmed by email on June 25, 2012 that a full waiver can be granted for this application because studies are impossible or highly impractical.

Nevertheless, during the review, the clinical reviewer became aware of a completed pediatric phase 1 study completed by the Children's Oncology Group. Results from this trial were presented during the 2010 ASCO Annual Meeting [J Clin Oncol 28: 15s, 2010 (suppl; abstr 9530)]. The abstract stated that the recommended phase 2 dose was 2.5 mg/kg/dose every 14 days; this dose was lower than the adult dose. Because the lower dose may have efficacy implications, the clinical reviewer recommended that Sanofi-aventis agree to a PMC to obtain and submit the results of the COG study in order to determine whether the results from this study should be included in product labeling.

11. Other Relevant Regulatory Issues

11.1 Application Integrity Policy (AIP)

The Application contained a statement signed by Dr. Richard Gural of Sanofi-aventis that certified that Sanofi-aventis did not use and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

11.2 Financial disclosures

The clinical review listed investigators and sub-investigators who disclosed a financial interest as defined in 21 CFR 54.2(b) or 21 CFR 54.2(f) (b) (6)

11.3 GCP issues

Study reports submitted in the BLA included a statement that the trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

11.4 OSI audits

DOP2 requested OSI inspections for this application in order to support the initial approval of intravenous aflibercept in the oncology setting. After internal discussions with OSI, three clinical sites and the sponsor were inspected. DOP2 suggested inspection of the three clinical sites based on site-specific efficacy results, financial conflicts of interest, or numbers of patients enrolled at each site. OSI inspected the following three sites: Site #203001 (Dr. Radek Lakomy, Czech Republic); Site #203004 (Dr. Jana Prausova, Czech Republic); and Site

#643003 (Dr. Vladimir Moiseyenko, Russian Federation). OSI provided interim classifications of all three sites as NAI (no action indicated).

OSI submitted an interim classification of VAI (voluntary action indicated) for the Sanofi-aventis inspection (Bridgewater, New Jersey). The primary issue identified during the Sanofi-aventis inspection dealt with Sanofi's actions regarding one clinical site [Site 036007 (Dr. Van Hazel, Australia)]. This site enrolled six subjects that should have been excluded according to the protocol; additionally the investigator did not document AST levels at baseline in two subjects. Sanofi-aventis also identified 12 patients who received incorrect chemotherapy doses and four patients who did not receive scheduled treatment cycles. Sanofi-aventis attempted to secure compliance; however, despite non-compliance, the site was permitted to enroll 24 subjects.

Clinical and statistical reviewers conducted analyses of the overall results that excluded the data from the Australian site and determined that the results did not affect the overall study outcome. Tables 108 and 109 of the clinical review contain the results of Sanofi's sensitivity analyses of OS and PFS that excluded all patients enrolled at site 036007.

11.5 Other discipline consults

11.5.1 Maternal Health Team

MHT reviewed the application and stated in the review that there are no available human data regarding aflibercept use in pregnancy. Pregnant rabbits exposed to 30% of the AUC at the recommended human aflibercept dose experienced adverse effects including increased incidence of post-implantation loss. Additionally, fetal anomalies included external, visceral, and skeletal fetal malformations. Based on these findings, aflibercept was designated Pregnancy Category C (no adequate and well-controlled studies in pregnancy women but embryotoxicity and teratogenicity observed in rabbits). Specific MHT recommendations regarding product labeling where incorporated into the label sent to Sanofi-aventis on 06 Jul 2012. In general, recommendations were made to improve clarity, use appropriate regulatory language, and in Section 17, to more carefully describe the potential risks, and type of contraception to use.

11.5.2 DMEPA

DMEPA submitted a review to the BLA that provided recommendations for Sanofi-aventis if the established name stays as Zaltrap. DMEPA provided recommendations regarding container labels to ensure the label complies with 21 CFR 201.10(g)(2). Recommendations regarding carton labeling were also made to reduce the risk of medication errors. This reviewer does not object to the proposed DMEPA recommendations regarding the carton and container. Final labeling agreement is pending.

11.6 Exclusivity/Patent Issues

At this time, there is an outstanding issue regarding the exclusivity request that Sanofi-aventis submitted to the BLA on April 24, 2012. During the review of the application, FDA requested additional information in order to determine whether Zaltrap meets the exclusivity criteria described in 351(k)(7) of the BPCI Act.

11.7 Drug Name Review

DMEMA completed a proprietary name review on February 13, 2012. The review stated that OPDP determined that the proposed name Zaltrap was acceptable from a promotional perspective. Additionally, DMEPA determined that Zaltrap was acceptable from a safety perspective.

12. Labeling

As directed by the 21st Century Review process, FDA sent draft labeling recommendations to Sanofi-aventis on July 6, 2012. Labeling recommendations described below should not be considered final as labeling negotiations are ongoing.

In general, DOP2 revised all sections of the label for brevity and clarity. Command language was preferred as directed by the PLR. The remainder of this section of the review will only focus on high-level issues regarding the label submitted by Sanofi-aventis. Numbering below is consistent with the applicable sections in product labeling. This review will not comment on all sections (for example, if only minor edits were made to a section). This CDTL agreed with the recommendations made by the review teams that are described below.

1. Indication and Usage: FDA recommended revising the indication to clarify that aflibercept is indicated for patients with mCRC in combination with FOLFIRI who are resistant to or progressed after an oxaliplatin-containing regimen (b) (4)

2. Dosage and Administration: (b) (4) FDA deleted redundant information described in other sections. FDA requested that Sanofi-aventis provide data, if available, to support the duration of storage conditions at room temperature. FDA requested that Sanofi-aventis provide justification for the requirement to administer aflibercept through a 0.2 micron filter.

4. Contraindications: (b) (4) Sanofi-aventis did not provide data in the BLA to support the proposed contraindication.

5. Warnings and Precautions:

5.2. Gastrointestinal Perforation: (b) (4) FDA left intact the statement in this Section that compared the incidence of GI perforation across three randomized controlled trials.

5.6. Proteinuria: FDA recommended updating the information regarding thrombotic microangiopathy to describe the incidence across all Zaltrap studies.

FDA asked Sanofi-aventis, based on current medical practice and the available data in the submission whether 24 hour urine collections were necessary to either quantify proteinuria or diagnose nephritic syndrome or whether a Urine Protein-to-Creatinine Ratio measurement was sufficient.

5.9. (b) (4)

5.10. Wound Healing: FDA (b) (4) left intact the statement describing Grade 3 events (incidence of events of all severity was lower in the aflibercept arm in VELOUR).

5.11. Reversible Posterior Leukoencephalopathy Syndrome: FDA recommended inclusion of a denominator in this Section to quantify the risk. FDA included additional information regarding reversibility.

6. Adverse Reactions: FDA recommended deletion of (b) (4) as an adverse reaction (see Warnings above). (b) (4) FDA was able to confirm the adverse reactions leading to treatment discontinuation and left the statement describing these reactions intact. FDA recommended removal of adverse reactions occurring in ≤ 5% of aflibercept-treated patients but with a ≥ 2% treatment difference between arms because the events of substantial concern were described elsewhere in the label (b) (4)

6.2. Immunogenicity: FDA revised this label for consistency with other labels and to present the findings as determined by OCP.

8.1. Pregnancy: DOP2 review staff recommended removal of unnecessary statements (b) (4) and incorporated recommendations from MHT and DHOT.

8.5. Geriatric Use: FDA revised the data in this Section to summarize the data for patients ≥ 65 years of age rather than > 65 years (based on FDA practice). These changes did not result in any substantive changes regarding findings of safety or efficacy contained in this section.

8.6. Hepatic Impairment: FDA simplified this Section to summarize that aflibercept exposure in patients with mild to moderate hepatic impairment was similar to that observed in patients with normal hepatic function.

8.7. Renal Impairment: FDA simplified this Section to summarize that aflibercept exposure in patients with mild, moderate, or severe renal impairment was similar to that observed in patients with normal renal function.

11. Description: Information considered unnecessary to prescribers was removed from this section (b) (4)

12. Clinical Pharmacology: OCP recommended extensive revisions to these sections of the label. Please refer to OCP review for details and recommendations.

13. Nonclinical Toxicology: This section was edited for brevity and reorganized based on recommendations from DHOT.

14. Clinical Studies: FDA added additional demographic information regarding the VELOUR study. FDA recommended deletion of statements (b) (4) FDA favored presenting the data regarding the subgroups defined by stratification factors as hazard ratios with 95% confidence intervals.

15. Patient Counseling Information: This section was edited to ensure clear command language for prescribers.

Patient information: FDA recommended removal of this section because aflibercept will be administered in infusion centers and hospitals (rather than the typical scenario where a PPI is handed to the patient by their pharmacist). Standard practice in oncology dictates informed consent prior to anti-neoplastic drugs.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended regulatory action

This reviewer recommends regular approval of BLA 125418 based on substantial evidence from one adequate and well controlled trial demonstrating a modest effect on OS observed in VELOUR. This approval recommendation is contingent upon reaching agreement on labeling and PMCs.

13.2 Risk-benefit assessment

The recommendation for approval of this application is based on a modest effect on OS observed in VELOUR. According to the May 2007 FDA Guidance Document regarding endpoints for cancer drugs (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf; accessed on 12 Jul 2012), survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. An effect on OS is considered regulatory evidence of clinical benefit used by the Agency to substantiate regular approval of a drug.

In general, because mCRC is an incurable disease [with the notable exception of patients who have oligometastatic disease (usually hepatic)] the goal of treatment for these patients is to prolong life and/or improve quality of life. The VELOUR study established that patients who received aflibercept in combination with FOLFIRI lived a median 1.44 months longer than patients who received placebo in combination with FOLFIRI (HR 0.817, 95% CI 0.714, 0.935). Although modest, the Kaplan-Meier curves did continue to separate after the medians, *possibly* indicating that a subset of patients could be identified in the future who will preferentially respond to anti-VEGF therapy. The effect on OS was supported by statistically significant effects on PFS and ORR; these effects should be considered supportive of the robustness of the VELOUR results rather than considered as evidence of direct benefit.

Adverse events observed in the VELOUR trial were generally considered as expected for a drug that inhibits the VEGF pathway and in combination with drugs (i.e., FOLFIRI) with established toxicity profiles. Severe adverse events caused by anti-VEGF drugs including aflibercept include hemorrhage, GI perforation/fistula, hypertension, arterial thrombotic events, proteinuria, compromised wound healing, and RPLS. With the exception of hypertension and proteinuria, these events were infrequent. More frequent; however, were adverse events related to FOLFIRI (aflibercept increased the incidence rate of such events), especially diarrhea, dehydration, fatigue, stomatitis, and neutropenia. Such events are understood in the practice of oncology, usually reversible, and can be managed (with careful monitoring) with dose interruption, dose reductions, and supportive care.

In summary, the risk-benefit assessment is considered favorable in light of the overall survival effect observed in a patient population with incurable metastatic cancer. Nevertheless, physicians and patients will need to consider whether the modest improvement in OS is of sufficient benefit to offset the increased toxicity when aflibercept is added to FOLFIRI (including the increased incidence of severe diarrhea).

13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies

The review team did not identify any REMS as necessary prior to the marketing authorization of aflibercept. Aflibercept will be administered in infusion centers and hospitals, and aflibercept will be prescribed by oncologists who are trained in the diagnosis and management of serious toxicities caused by anti-neoplastic drugs. Standard practice in oncology dictates informed consent prior to anti-neoplastic drugs.

13.4 Recommendation for other postmarketing requirements and commitments

Final agreement regarding PMCs is pending at this time, including agreements on timelines. One PMC was recommended by the clinical reviewer and is described in the Pediatrics Section of this review.

The majority of PMCs were recommended by DMA and BMAB. Although not necessary pre-Approval, these PMCs will ensure that a pure, potent, and sterile product will be manufactured in the post-marketing setting. Refer to CMC review for specific details regarding these issues.

- Add conductivity testing to the drug product (DP) release specification.

- To re-evaluate the release and shelf-life specifications for the aflibercept drug product after 30 commercial manufacturing runs using the current specifications methods.
- To re-evaluate the release and shelf-life specifications for the aflibercept drug substance after 30 commercial manufacturing runs using the current specifications methods.
- To conduct a study to evaluate impact of worst case [redacted] (b) (4) using a validated container closure integrity test. The study protocol and data should be submitted as a CBE-30 supplement.
- 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.
- [redacted] (b) (4) The [redacted] (b) (4) bioburden data from [redacted] (b) (4) batches manufactured using the commercial process [redacted] (b) (4) should be submitted as a CBE-0 supplement.
- 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 U.S. Distribution Center. The protocol and data from the shipping qualification study should be submitted as a CBE-0 supplement.

Reference List

Cohen, M. H., et al. "FDA drug approval summary: bevacizumab plus FOLFOX4 as second-line treatment of colorectal cancer." Oncologist 12.3 (2007): 356-61.

Giantonio, B. J., et al. "Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200." Journal of clinical oncology : official journal of the American Society of Clinical Oncology 25.12 (2007): 1539-44.

Saltz, L. B., et al. "Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study." Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26.12 (2008): 2013-19.

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/s/

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07/13/2012