

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125418Orig1s000

OTHER REVIEW(S)

PMR/PMC

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

BLA # 125418
Product Name: Aflibercept (Zaltrap®)

PMC Description: Submission of complete study report and datasets from the pediatric Study COG-AVDL0714 (NCT00622414).

PMC Schedule Milestones:	Final Protocol Submission:	NA
	Study/Trial Completion:	NA
	Final Report Submission:	08/01/2013
	Other:	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

COG-AVDL0714 was a Phase 1 study of aflibercept in children with refractory solid tumors conducted by the Children's Oncology Group under NCI IND 100137 for aflibercept that has been completed in August 2011. This trial concluded that the MTD in the pediatric population was below the optimal biological dose.

Aflibercept is being approved for the treatment of patients with metastatic colorectal carcinoma that had progressed or is refractory to an oxaliplatin-containing first-line treatment. This indication is not relevant for the pediatric population; however, the inclusion of pediatric data in the label may inform pediatric oncologist of the risks of the off-label use of aflibercept in the pediatric population.

2. Describe the particular review issue and the goal of the study/clinical trial.

The main objectives of COG-AVDL0714 were to establish the MTD and to study the safety of aflibercept in the pediatric population. The MTD of aflibercept in children was determined to be 2.5 mg/kg when administered every two weeks, below the optimal biologic dose established throughout the aflibercept development at 4 mg/kg (the dose necessary to maintain a free-bounded aflibercept ratio of 1:1 during the 14-day dosing interval). Major safety concerns in the pediatric population were related to class effects such as hemorrhage.

According to the SEER report (2004-2008), 0.1% of all colorectal carcinomas are diagnosed under the age of 20 (fewer than 100 cases annually in the U.S.). Inclusion of the pediatric data in the label would inform pediatric oncologist of the risks of aflibercept in the pediatric population for the treatment of metastatic colorectal carcinoma and any off-label uses.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This trial has already being conducted. The PMC is requesting the submission of the complete study report and datasets.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 125418/Zaltrap

PMR/PMC Description: Addition of conductivity testing to release specification for Drug Product after qualification of the test method and sufficient data become available to set an acceptance criterion.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>11/DD/2012</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The Drug Product release specification approved under the BLA is sufficient to ensure adequate quality and safety (b) (4) for the initial marketed product. The addition of conductivity testing will support consistency of Drug Product formulation throughout continued manufacture.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The current Zaltrap Drug Product release specification includes methods for evaluating Drug Product formulation, and validation studies for Drug Product formulation have been performed; however the methods currently used for formulation assessment will only provide evaluation of a portion of the formulation components. The addition of conductivity testing will provide monitoring of the consistent addition of the remaining formulation components.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Qualification of the analytical conductivity method and statistical analysis of release data acquired using the new method

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 125418/Zaltrap

PMR/PMC Description: Reassessment of release and shelf-life specifications for Drug Product after manufacture of a sufficient number of commercial lots to allow for better statistical analysis

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The Drug Product release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety (b)(4) for the initial marketed product. Increased manufacturing and testing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Zaltrap Drug Product release and shelf-life specifications are based on clinical and manufacturing experience during the BLA review; however, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been tested and released.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Statistical analysis of release data acquired following manufacture of additional commercial lots

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 125418/Zaltrap

PMR/PMC Description: Reassessment of release and shelf-life specifications for Drug Substance after manufacture of a sufficient number of commercial lots to allow for better statistical analysis

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: MM/DD/YYYY
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The Drug Substance release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety (b) (4) for the initial marketed product. Increased manufacturing and testing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Aflibercept oncology Drug Substance release and shelf-life specifications are based on clinical and manufacturing experience during the BLA review; however, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been tested and released.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Statistical analysis of release data acquired following manufacture of additional commercial lots

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 125418

Product Name: Zaltrap

PMR/PMC Description: *To conduct a study to evaluate impact of worst case (b) (4) using a validated container closure integrity test. The study protocol and data should be submitted as a CBE-30 supplement.*

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 09/30/2012
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The applicant provided validation study results for a container closure integrity test using the red dye method. This method will be used in stability studies. However, the study did not consider the impact of different (b) (4). The study protocol for validation of the container closure integrity test and data should be submitted as a CBE-30 supplement by September 30, 2012.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Not applicable

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
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- Other
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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Not applicable

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
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- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
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- Other
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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # STN 125418

Product Name: Zaltrap

PMR/PMC Description:

(b) (4)

The (b) (4) bioburden data from (b) (4) batches manufactured using the commercial process (b) (4) should be submitted as a CBE-0 supplement.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The bioburden limit (b) (4) is high. The source of bioburden at this step was identified (b) (4).
Data from (b) (4) batches (b) (4) should be submitted in a CBE-0 supplement (timeline to be determined by applicant).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Not applicable

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 125418
Product Name: Zaltrap

PMR/PMC Description: *To conduct a shipping qualification study to assess the ability of the commercial shipper to maintain temperature during three shipments of minimum loads from Frankfurt to the US Distribution Center. The protocol and data from the shipping qualification study should be submitted as a CBE-0 supplement.*

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 11/30/2012
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The shipping studies submitted in the BLA did not assess the ability of the commercial shipper to maintain temperature during the shipment of minimum loads. The protocol for a shipping qualification study to address this issue and data from the shipping qualification study should be submitted as a CBE-0 supplement by November 30, 2012.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: July 20, 2012

To: Patricia Keegan, MD
Director
Division of Oncology Products 2 (DOP 2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Patient Package Insert
(PPI)

Drug Name (established name): ZALTRAP (afibercept)

Dosage Form and Route: Injection

Application Type/Number: BLA 125418

Applicant: sanofi-aventis U.S. LLC

1 INTRODUCTION

On February 3, 2012, sanofi-aventis U.S. LLC submitted for the Agency's review an Original Biologics License Application (BLA) 125418 for ZALTRAP (aflibercept) Injection. The proposed indication is as follows: ZALTRAP, in combination with a FOLFIRI chemotherapy regimen, for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen. On March 28, 2012, the Division of Oncology Products 2 (DOP 2) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for ZALTRAP (aflibercept) Injection.

This review is written in response to a request by DOP 2 for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for ZALTRAP (aflibercept) Injection.

2 MATERIAL REVIEWED

- Draft ZALTRAP (aflibercept) Injection Patient Information (PPI) received on February 3, 2012.
- Draft ZALTRAP (aflibercept) Injection Prescribing Information (PI) received on February 3, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on July 12, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. (b)(4)

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHARON R MILLS
07/20/2012

LASHAWN M GRIFFITHS
07/20/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: July 11, 2012

To: Melanie Pierce, Regulatory Project Manager
Division of Oncology Products 2 (DOP-2)
Office of Hematology Oncology Drug Products

From: Carole Broadnax, PharmD, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Subject: BLA 125418/0
Zaltrap (aflibercept) Concentrate for intravenous infusion
OPDP Labeling Comments

OPDP/DPDP has reviewed the proposed labeling (Package Insert (PI) and carton/container) as requested in your consult dated February 27, 2012.

DPDP's comments are based on the substantially complete version of the proposed PI titled, "FDA proposed revisions During 7 2 2012.doc," sent via electronic mail to OPDP (Carole Broadnax) from DOP 2 (Melanie Pierce) on July 3, 2012. OPDP's comments are provided directly in the attached document. Please note that for the PI, OPDP hid DOP 2's deletions, comments, and formatting changes so that OPDP comments are easier to read.

The proposed carton and container labeling used in this review may be found in the original application (folder 0017) dated May 31, 2012, at EDR location: \\Cbsap58\M\leCTD_Submissions\STN125418. OPDP does not have comments on the carton and container labeling at this time.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at (301) 796-0575 or Carole.Broadnax@fda.hhs.gov.

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CAROLE C BROADNAX
07/11/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 6, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; **Proposed** PMC/PMR language

Dr. Fernandes,

Please see FDA's post-marketing commitment proposals for Zaltrap (aflibercept) application 125147/0:

POST-MARKETING COMMITMENTS:

CLINICAL:

Pediatric Assessments:

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

Final Protocol Submission:	XX/XX/XXXX
Trial Completion Date:	XX/XX/XXXX
Final Report Submission	08/01/2013

CHEMISTRY MANUFACTURING AND CONTROLS:

Conductivity Specification:

2. To add conductivity testing to the DP release specification. The analytical method protocol, qualification report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be provided in a CBE by November [sanofi, provide date]

Final Protocol Submission:	XX/XX/XXXX
Trial Completion Date:	XX/XX/XXXX
Final Report Submission	11/XX/2012

Reassessment of Drug Product Specifications:

- 3. To re-evaluate the release and shelf-life specifications for aflibercept drug product after 30 commercial manufacturing runs tested using the current specification methods. The revisions to the quality control system, the corresponding data, and the analysis and statistical plan used to evaluate the specifications and any changes to specifications will be provided in a PAS by [sanofi, provide date]

Final Protocol Submission: XX/XX/XXXX
Trial Completion Date: XX/XX/XXXX
Final Report Submission XX/XX/XXXX

Reassessment of Drug Substance Specifications:

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

Final Protocol Submission: XX/XX/XXXX
Trial Completion Date: XX/XX/XXXX
Final Report Submission XX/XX/XXXX

FACILITIES:

Container/Closure Assessments:

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

The timetable you submitted on XX/XX/XXXX states that you will conduct this study according to the following schedule:

Final Protocol Submission: XX/XX/XXXX
Trial Completion Date: XX/XX/XXXX
Final Report Submission 09/30/2012

Dye Interference Assessment:

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

Final Protocol Submission: XX/XX/XXXX
Trial Completion Date: XX/XX/XXXX
Final Report Submission 09/30/2012

Pre-filtration Assessment:

7.

(b) (4)
The (b) (4) bioburden data from (b) (4) batches manufactured using the commercial process (b) (4) should be submitted as a CBE-0 supplement.

Final Protocol Submission:	XX/XX/XXXX
Trial Completion Date:	XX/XX/XXXX
Final Report Submission	XX/XX/XXXX

Shipping Qualification Study:

8. To conduct a shipping qualification study to assess the ability of the commercial shipper to maintain temperature during three shipments of minimum loads from Frankfurt to the US Distribution Center. The protocol and data from the shipping qualification study should be submitted as a CBE-0 supplement.

Final Protocol Submission:	XX/XX/XXXX
Trial Completion Date:	XX/XX/XXXX
Final Report Submission	11/30/2012

If you have any questions, please call me at 301-796-1273.

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

/s/

MELANIE B PIERCE
07/06/2012



Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9858

Maternal Health Team Review

Date: July 6, 2012 **Date Consulted:** February 27, 2012

From: Tammie Howard, RN, MSN
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Melissa Tassinari, PhD
Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

To: Division of Oncology Products 2 (DOP2)

Drug: Zaltrap (aflibercept) BLA 125418

Subject: New BLA Application

Sponsor: Sanofi-Aventis, US, LLC

Materials Reviewed: Zaltrap product labeling

Consult Question: Please review label and provide recommendations.

INTRODUCTION

On February 3, 2012, Sanofi-Aventis, U.S. Inc. (Sanofi-Aventis) submitted an Original Biologics License Application (BLA) 125418 to the Division of Oncology Drug Products 2 (DOP2) for aflibercept concentrate solution for infusion. The sponsor's proposed indication is for use in combination with irinotecan-fluoropyrimidine-based chemotherapy for patients with metastatic colorectal cancer (MCRC) previously treated with an oxaliplatin-containing regimen. Aflibercept is a recombinant fusion protein that blocks the activation of vascular endothelin growth factor (VEGF) receptors and proliferation of endothelin cells, inhibiting the growth of new vessels supplying tumors with oxygen and nutrients¹. The sponsor was granted priority review status with a PDUFA goal date of August 4, 2012. On February 27, 2012, the Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) was consulted by DOP2 to review product labeling and provide recommendations.

BACKGROUND

Vascular Endothelin Growth Factor (VEGF) and VEGF Inhibitors

Vascular endothelial growth factor (VEGF) is a family of signal proteins that function in a pathway responsible for stimulation and regulation of embryonic circulatory system formation (vasculogenesis) and formation of new blood vessels (angiogenesis). There are five VEGF family members in mammals, VEGFA, B, C, D and placenta growth factor (PLGF), which are normally part of the system that creates new blood vessels during embryonic development, after injury, muscle following exercise, and collateral circulation to bypass blocked vessels. VEGF proteins bind to one of three VEGF receptors (VEGFR 1-3) to initiate the pathway. Over expression of VEGF can contribute to disease such as cancer and retinal vascular disease of the eye. In oncologic disease, tumors can express VEGF, resulting in growth of vessels providing blood supply and allowing tumor growth. Drugs that inhibit the VEGF pathway, such as aflibercept, appear to control or slow the disease process.^{2,3,4,5}

Aflibercept

Aflibercept is a recombinant fusion protein that consist of VEGF-binding portions from extracellular human VEGF Receptors 1 and 2, which are fused to the Fc portion of human immunoglobulin. Aflibercept acts as a decoy receptor, binding VEGF-A with higher affinity than native receptors, blocking receptor mediated signaling. Growth of new vessels supplying tumors is inhibited as a result of the action of aflibercept⁶. Aflibercept was approved in the United States, as Eylea injection (Regeneron Pharmaceuticals, Inc.), for intra-vitreous treatment of patients with neovascular (wet) age-related macular degeneration (AMD) on November 18, 2011. Regeneron is an alliance partner of Sanofi-Aventis in the development of aflibercept for cancer treatment, and Sanofi-Aventis seeks approval of the currently submitted stand alone BLA.

¹ Zaltrap (aflibercept) proposed product labeling.

² Website: http://en.wikipedia.org/wiki/Vascular_endothelial_growth_factor

³ Olsson AK, Dimberg A, Kreuger J, Claesson-Welsh L. VEGF receptor signalling — in control of vascular function. *Nature Reviews Molecular Cell Biology*. 2006;7:359-371.

⁴ Holash et al. VEGF-Trap: A VEGF blocker with potent antitumor effects. *Proceedings of the national academy of sciences*. 2002;99(17):11393-11398.

⁵ Fraser HM, Morris KD, Wiegand SJ, Wilson H. Inhibition of vascular endothelial growth factor during the postovulatory period prevents pregnancy in the marmoset. *Contraception*. 2012;82:572-578.

⁶ Zaltrap (aflibercept) proposed product labeling.

Aflibercept: Pregnancy, Lactation and Fertility

There are no available human data regarding aflibercept intravenous infusion in pregnancy. Aflibercept was studied in pregnant rabbits at doses of 3 mg/kg and above given every 3 days during the period of organogenesis. In rabbits, systemic exposure (AUC) with a 3 mg/kg dose was approximately 30% of the AUC at the recommended human therapeutic dose. At these doses adverse effects included increased incidences of postimplantation loss and external (anasarca, umbilical hernia, diaphragmatic hernia and gastroschisis, cleft palate, ectrodactyly, and atresia), visceral (heart, great vessels, and arteries), and skeletal fetal malformations (fused vertebrae, sternebrae, and ribs; supernumary arches and ribs, and incomplete ossification). The incidence and severity of fetal anomalies increased with increasing exposure.

There are no available human or animal data regarding effects of aflibercept use during lactation.

In a 6-month repeat-dose toxicology study in sexually mature monkeys, at doses of 3 mg/kg and above, aflibercept inhibited ovarian function and follicular development in females and alterations in sperm morphology and decreased sperm motility was observed in males. Reversibility of these effects were noted within 18 weeks after cessation of treatment. Systemic exposure (AUC) with a 3 mg/kg dose in monkeys was approximately 60% of the AUC at the recommended human therapeutic dose.

This review provides PMHS-MHT labeling recommendations regarding the highlights, pregnancy, lactation, and patient counseling sections of labeling.

REVIEW OF SUBMITTED MATERIAL

Sponsor's Submitted Proposed Zaltrap Labeling (Appendix A)

A series of labeling meetings were conducted during the review cycle. The PMHS-MHT reviewed the sponsor's proposed labeling, with non-clinical team draft revisions on June 26, 2012 and participated in the June 29, 2012 labeling meeting. The reviewed labeling excerpts from the June 26, 2012 version of the sponsor's proposed label are provided in **Appendix A** of this review.

DISCUSSION AND CONCLUSIONS

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. A section for Females and Males of Reproductive Potential may be added containing information regarding pregnancy planning, prevention and/or fertility issues. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

The PMHS-MHT discussed labeling recommendations with the review team during a labeling meeting on June 29, 2012. During the labeling meeting, MHT recommendations were edited per discussion with the review team. A summary of PMHS-MHT labeling recommendations appear by label section below,

followed by label excerpts. The label, including MHT edited recommendations, was sent to the sponsor on July 3, 2012. Further labeling revisions are pending final labeling discussions with the sponsor. **Appendix B** of this review provides a tracked-changes version of labeling that highlights the recommended PMHS-MHT revisions.

MHT Summary of Labeling Recommendations:

Highlights of Prescribing Information

Language regarding nursing mothers was revised to display preferred labeling language. Information regarding females and males of reproductive potential was added to align with the addition of this section in the full prescribing information.

Use in Specific Populations (8)

Pregnancy (8.1)

The Pregnancy section was restructured and sub-headers (Risk Summary, Animal Data) were added to provide an organized presentation of data. The first paragraph provides the appropriate regulatory language and a summary of risks, based on the available data (animal studies), followed by the available animal data. Information regarding male and female fertility was moved to section 8.8 Females and Males of Reproductive Potential.

Nursing Mothers (8.3)

The sentence (b) (4)
[REDACTED] was removed, leaving the appropriate regulatory language currently in use.

Females and Males of Reproductive Potential (8.8)

This section of labeling was added to house information regarding pregnancy planning, prevention and fertility. A statement of the risk is provided, based on animal data, followed by recommendations regarding use of highly effective contraception to mitigate the potential risk.

Non-clinical Toxicology (13)

[REDACTED] (b) (4)

Patient Counseling Information (17)

Patient Counseling Information provides detailed instructions for health care providers should to provide to patients regarding safe use of a drug. Information is presented in bulleted format, stating the risks and counseling to provide to patient regarding the risks. Language was revised to more carefully describe the potential risk, type of contraception and when to contact the health care provider. All information appearing in this section must align with the prior sections of the label.

MHT Labeling Recommendations (label excerpts):

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Based on animal data, ZALTRAP may cause fetal harm. (8.1)

- Nursing mother: Discontinue drug or nursing taking into account the importance of the drug to the mother. (8.3)
- Females and Males of Reproductive Potential: [REDACTED] (b) (4)

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with ZALTRAP in pregnant women. ZALTRAP was embryotoxic and teratogenic in rabbits at exposure levels lower than human exposures at the recommended dose, with increased incidences of external, visceral, and skeletal fetal malformations. ZALTRAP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Aflibercept produced embryo-fetal toxicity when administered every 3 days during organogenesis in pregnant rabbits at all intravenous doses tested, ≥ 3 mg/kg. Adverse embryo-fetal effects included increased incidences of postimplantation losses and external (anasarca, umbilical hernia, diaphragmatic hernia and gastroschisis, cleft palate, ectrodactyly, and atresia), visceral (heart, great vessels, and arteries), and skeletal fetal malformations (fused vertebrae, sternebrae, and ribs; supernumerary arches and ribs, and incomplete ossification). [REDACTED] (b) (4)

[REDACTED] The incidence and severity of fetal anomalies increased with increasing exposure.

8.3 Nursing Mothers

It is not known whether ZALTRAP is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ZALTRAP, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.8 Females and Males of Reproductive Potential

Male and female reproductive function and fertility may be compromised during treatment with ZALTRAP, as suggested by findings in monkeys [see *Nonclinical Toxicology (13.1)*]. These animal findings were reversible within 18 weeks after cessation of treatment. Females and males of reproductive potential should use highly effective contraception during and up to a minimum of 3 months after the last dose of treatment.

17 PATIENT COUNSELING INFORMATION

Advise patients:

Of the potential risks to the fetus or neonate of using ZALTRAP during pregnancy or nursing and of the need to use highly effective contraception in both males and females during and for at least 3 months following last dose of ZALTRAP therapy. Advise the patient to immediately contact the healthcare provider if they or their partner becomes pregnant during treatment with ZALTRAP.

Appendix A- Sponsor's Proposed Zaltrap Labeling

2 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

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/s/

TAMMIE B BRENT HOWARD
07/06/2012

MELISSA S TASSINARI
07/09/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: July 5, 2012

TO: Melanie Pierce, Regulatory Project Manager
Sandra Casak, Medical Officer
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice K. Pohlman, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125418
APPLICANT: Sanofi-Aventis U.S., LLC
DRUG: Aflibercept (Zaltrap™)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION(S): In combination with irinotecan-fluoropyrimidine-based chemotherapy for the treatment of patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen.

CONSULTATION REQUEST DATE: February 17, 2012
INSPECTION SUMMARY GOAL DATE: July 7, 2012
DIVISION ACTION GOAL DATE: August 4, 2012
PDUFA DATE: August 4, 2012

I. BACKGROUND:

Sanofi-Aventis U.S. LLC, seeks approval to market aflibercept, in combination with irinotecan-fluoropyrimidine-based chemotherapy, for the treatment of patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen.

Aflibercept is a novel antiangiogenic agent. Malignant tumors are dependent on angiogenesis to maintain a source of nutrition and oxygen to support their growth and metastasis. Aflibercept is a recombinantly-produced fusion protein consisting of human Vascular Endothelial Growth Factor (VEGF) receptor extracellular domains fused to the Fc portion of human IgG1 (Immunoglobulin G1). Aflibercept binds to all isoforms of VEGF-A, VEGF-B, and to placental growth factor (PlGF). It interferes with the biological actions of VEGF by complexing VEGF in the blood stream and extravascular space and preventing it from interacting with its receptors on endothelial cells.

The application is supported primarily by data from a pivotal study, EFC10262, entitled, A Multinational, Randomized, Double-blind Study, Comparing the Efficacy of Aflibercept Once Every 2 Weeks versus Placebo in Patients with Metastatic Colorectal Cancer Treated with Irinotecan / 5-FU Combination (FOLFIRI) after Failure of an oxaliplatin based regimen. The study was conducted under BB-IND 9948.

Study EFC10262 evaluated the safety and efficacy (overall survival) of aflibercept treatment in patients with MCRC previously treated with an oxaliplatin based regimen. Planned enrollment for Study EFC10262 was 1200 men and women, at least 18 years of age. There were 1226 subjects randomized and 1216 subjects were treated. A total of 176 clinical centers in 28 countries (including the U.S.) enrolled subjects.

Three clinical sites, chosen on the basis of site-specific efficacy data, financial conflicts of interest, and patient number enrolled at each site, were inspected for this BLA. Because this is an NME, the sponsor was also inspected.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#1: Site #203001 Lakomy, Radek, MD Masarykuv Onkologicky Ustav Zlutý Kopec 7 Brno 65653 CZECH REPUBLIC	Protocol: EFC10262 Site#: 203001 Number of Subjects: 40	May 7-11, 2012	Pending Interim classification: NAI
CI#2: Site #203004 Prausova, Jana, MD FN Motol V Uvalu 84 Praha 5 15006 CZECH REPUBLIC	Protocol: EFC10262 Site#: 203004 Number of Subjects: 29	April 30-May 4, 2012	Pending Interim classification: NAI
CI#3: Site #643003 Moiseyenko, Vladimir, MD NN Petrov Research Institute Of Oncology 68 Leningradskaya Street, Pesochny Saint-Petersburg 197758 RUSSIAN FEDERATION	Protocol: EFC10262 Site#: 643003 Number of Subjects: 22	May 14-18, 2012	Pending Interim classification: NAI
Sponsor: Sanofi-Aventis, U.S. 55 Corporate Drive Bridgewater, NJ 08807	Protocol: EFC10262 Site#/Subjects Records Reviewed: 203001 203004 643003 036007	April 24-May 17, 2012	Pending Interim classification: VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **CI#1:** – Lakomy, Radek, MD
(Site # 203001)
Masarykuv Onkologicky Ustav
Zluty Kopec 7
Brno 65653
CZECH REPUBLIC

a. What was inspected: The site screened 46 subjects, and 40 subjects were enrolled. Twenty eight subjects died. The study records of 7 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, adverse events, treatment regimens and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring and safety reports.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data for the subjects enrolled at this site were verified. There was no evidence of under-reporting of AEs. No Form FDA 483 was issued. There were a few minor protocol deviations noted by the FDA field investigator with respect to reporting concomitant medications. These observations, summarized below, should not importantly impact data reliability at this site.

- Subject 1: At Cycle 2, Zofran, Dexamed, and Atropin were not reported. At Cycle 7, Zolpidem was not reported.
- Subject 9: At Cycle 8, Hypogen was not reported.
- Subject 20: At Cycle 4, Torecan was not reported.

c. Assessment of data integrity: Notwithstanding the observations noted above, the data for Dr. Lakomy's site, associated with Study EFC10262 submitted to the Agency in support of BLA 125418, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. **CI#2:** – Prausova, Jana, MD
(Site #203004)
FN Motol
V Uvalu 84
Praha 5 15006
CZECH REPUBLIC

- a. What was inspected:** The site screened 29 subjects, and all 29 subjects were enrolled. Seventeen subjects died. The study records of study subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, and limited test article accountability.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data for the subjects enrolled at this site were verified. All concomitant medications were accurately reported. There were three instances where AEs were not reported to the sponsor; loss of appetite, fatigue and aphthous stomatitis. These unreported AEs occurred in three separate subjects. These observations should not importantly impact data reliability at this site. No Form FDA 483 was issued.
- c. Assessment of data integrity:** Notwithstanding the observations noted above, the data for Dr. Prausova's site, associated with Study EFC10262 submitted to the Agency in support of BLA 125418, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3. **CI#3:** – Moiseyenko, Vladimir, MD
(Site #643003)
NN Petrov Research Institute Of Oncology
68 Leningradskaya Street,
Pesochny
Saint-Petersburg 197758
RUSSIAN FEDERATION

- a. What was inspected:** The site screened 24 subjects, and 22 subjects were enrolled. Eighteen subjects died. The study records of 11 study subjects were audited in accordance with the clinical investigator compliance program, CP

7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring and safety reports.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data for the subjects enrolled at this site were verified. There was no evidence of under-reporting of AEs, with one exception. Specifically, Subject 1 experienced nausea at Cycle 7; this event was not documented in the eCRF. No Form FDA 483 was issued.
- c. Assessment of data integrity:** Notwithstanding the observations noted above, the data for Dr. Moiseyenko's site, associated with Study EFC10262 submitted to the Agency in support of BLA 125418, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

4. Sponsor: Sanofi-Aventis, U.S., LLC
55 Corporate Drive
Bridgewater, NJ 08807

- a. What was inspected:** The sponsor was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection covered adherence to Protocol, and review of the firm's SOPs, monitoring reports, actions related to monitoring deficiencies, Ethics Committee/IRB approvals, completed Form FDA 1572s, communications with the sites, drug accountability and review of data management from the clinical study sites to the submission of the BLA to the Agency. The FDA field investigator specifically audited subject records from 4 clinical study sites; Site 203001 (Dr. Lakomy), Site 203004 (Dr. Prausova), Site 643003 (Dr. Moiseyenko), and Site 036007 (Dr. Van Hazel), against the data listings submitted to BLA 125418.
- b. General observations/commentary:** Records and procedures were clear, and generally well organized. There was nothing to indicate under-reporting of AEs/SAEs. The primary efficacy endpoint data were verified for the four audited sites. Overall site monitoring appeared adequate. Monitoring reports indicated that efforts were made by the sponsor/CRO to ensure site compliance with the protocol. The Sponsor appeared to maintain adequate oversight of the study. The FDA field investigator issued a Form FDA 483 citing inspectional

observations. Noteworthy observations are provided below.

1. Failure to ensure the study is conducted in accordance with the investigational plan. Specifically, with respect to Site 036007 where a total of 23 subjects were randomized,

a. Six subjects were included in the study despite meeting one of the following exclusion criteria.

- Participation in another clinical trial and any concurrent treatment with any investigational drug within 30 days prior to randomization.
- Inadequate bone marrow function.

b. Two subjects did not have a baseline (AST) level assessment to rule out inadequate liver function.

c. Twelve subjects did not receive the correct chemotherapy dosages.

d. Four subjects did not receive the scheduled treatment cycles as required in the protocol.

OSI Reviewer Notes: According to the FDA field investigator the Sponsor identified Site 036007 (Dr. Van Hazel, Australia) to be non-compliant due to repeated attempts by the Sponsor to secure compliance. Initially, only seven subjects were planned to be enrolled at the site. However, the site's enrollment was increased to 24 subjects as approved by the Sponsor despite the persistent non-compliance. By the data cut off date in February 2011, 23 subjects were randomized and received treatments and 20 out of the 23 subjects had completed their treatments.

According to the sponsor records, issues/deviations occurring at the site included the following: instances of failure to perform protocol required tests/procedures; including subjects into the trial despite meeting the exclusion criteria; inconsistencies in calculating the dosages of chemotherapy drugs; allowing sub-investigators to perform protocol related procedures even though they were not listed on the form "Delegation of Duties" and the 1572s prior to trial participation; and failure to maintain adequate training records. However, the firm management did not consider these issues to affect patient safety and data integrity; therefore, the firm did not terminate the site's trial participation. The sponsor notified the FDA on March 15, 2011 of findings from an audit of the site conducted in November 2010.

The OSI reviewer, Lauren Iacono-Connors, communicated these inspectional findings to the DOP2 Clinical Reviewer, Sandra Casak, on June 4, 2012. It was learned that the review division had conducted a sensitivity analysis for this site's impact on overall study outcome prior to even consulting OSI for clinical site inspections as they were already aware of the GCP non-compliance reported by the sponsor. It was agreed that the site's impact on overall study outcome was insignificant based on their analysis. The compliance observations from this one site do not importantly impact study outcome and do not appear to be a systemic site performance issue for the overall

study.

- c. Assessment of data integrity:** The data generated at this site, as it pertains to Study EFC10262 were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The findings are that the data from this Sponsor submitted to the agency in support of BLA 125418 appear reliable.

Note: Observations noted for this site are based on preliminary communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Lakomy, Dr. Prausova, and Dr. Moiseyenko, and the study sponsor, Sanofi-Aventis, the study [EFC10262] data collected appear reliable based on available information.

The preliminary classifications for the three clinical investigator sites are No Action Indicated (NAI). The study sponsor was issued a Form FDA 483 citing inspectional observations and preliminary classification; this inspection is Voluntary Action Indicated (VAI).

The inspection of the sponsor, Sanofi-Aventis, found that there was a site for which there were known GCP compliance issues, and that they failed to adequately bring the site into compliance despite their efforts. According to the FDA field investigator, the Sponsor identified Site 036007 (Dr. Van Hazel, Australia) to be non-compliant due to repeated attempts by the Sponsor to secure compliance. Initially, only seven subjects were planned to be enrolled at the site. However, the site's enrollment was increased to 24 subjects as approved by the Sponsor despite the persistent non-compliance. By the data cut off date in February 2011, 23 subjects were randomized and received treatments and 20 out of the 23 subjects had completed their treatments. A limited review of the impact of these inspectional observations and further discussions with the review division Medical Officer, Sandra Casak, lead to the conclusion that these observations would not impact overall data reliability or study endpoints. The observation appears to be unique to this site and not a systemic study execution failure by the sponsor.

Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. The overall data for study EFC10262 in support of this application may be considered reliable based on available information.

Note: Observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice K. Pohlman, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

LAUREN C IACONO-CONNORS
07/05/2012

JANICE K POHLMAN
07/05/2012

SUSAN D THOMPSON
07/05/2012

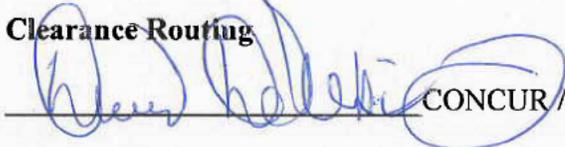
Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum

Date: June 25, 2012
From: Kalavati Suvarna, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB
Sarah Kennett, Ph.D., OPS/OBP/DMA
To: BLA File – STN 125418/0
Subject: Recommendation to waive a pre-license inspection
Sponsor: Sanofi-Aventis, US, LLC
Manufacturing Facility: Sanofi-Aventis Deutschland GmbH, Industriepark Hoechst,
65926 Frankfurt am Main, Germany. FEI: 3003195501
Product: ZALTRAP® (Aflibercept concentrate for solution; VEGF TRAP)
Indication: Treatment of patients with metastatic colorectal cancer previously treated
with an oxaliplatin-containing regimen
Through: Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB

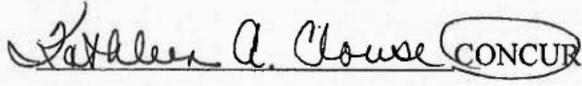
Waiver Recommendation

Based on the most recent inspection of the facility conducted April 23-30, 2012 which is classified NAI, and the fact that Sanofi-Aventis Deutschland GmbH (b)(4) has been approved to manufacture multiple CDER products (b)(4), we recommend that the pre-license inspection of the Sanofi-Aventis drug product manufacturing facility located at Sanofi-Aventis Deutschland GmbH, Industriepark Hoechst, 65926 Frankfurt am Main, Germany. FEI: 3003195501 be waived for STN 125418/0 (submission dated February 2, 2012).

Clearance Routing

 CONCUR / DO NOT CONCUR DATE 6/26/2012

David Doleski
Director, Division of Good Manufacturing Practice Assessment, Office of Compliance,
CDER

 CONCUR / DO NOT CONCUR DATE 06/25/2012

Kathleen A Clouse, Ph.D.
Director, Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS,
CDER

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/s/

KALAVATI C SUVARNA
07/03/2012



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

FINAL LABEL AND LABELING REVIEW

Date: June 26, 2012

Reviewer: Kimberly Rains, Pharm.D.
Office of Biotechnology Products, Immediate Office

Through: Sara Kennett, Ph.D.
Division of Monoclonal Antibodies

Division Deputy Director: Patrick Swann, Ph.D.
Division of Monoclonal Antibodies

Application Number: STN 125418/0

Name of Drug: Zaltrap[®] (aflibercept)

Applicant: Regeneron Pharmaceuticals, Inc.

Material Reviewed: Carton and Container Labels

Submission Dates: February 2, 2012, May 30, 2012, July 23, 2012

EXECUTIVE SUMMARY

The carton and container labels for ZALTRAP[®] (aflibercept) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 5/1/12-8/1/12, USP 35/NF 30. Labeling deficiencies were identified, mitigated and resolved. Please see comments in the conclusions section. The labels are acceptable with the interim proper name, xxx_aflibercept. An amendment will be filed with the agreed upon proper name.

Background

STN 125418/0 for aflibercept is an original Biologic License Application (BLA) in combination with irinotecan-fluoropyrimidine-based chemotherapy indicated for patients with metastatic colorectal cancer (MCRC) previously treated with an oxaliplatin-

containing regimen. The product is supplied as a 100 mg/ 4 mL and a 200 mg/ 8 mL solution in single-use vials.

Labels Reviewed:

ZALTRAP[®] (afibercept) Container Labels
Vial

ZALTRAP[®] (afibercept) Carton Labels
Single Vial Carton and Three Vial carton

Start of Sponsor Material

Vial Labels



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- L. 21 CFR 201.17 Drugs; location of expiration date – The expiration date appears under the lot number on the carton labels. This conforms to the regulation.
- M. 21 CFR 201.25 Bar code label requirements – A bar code appears on all carton labels. This conforms to the regulation.
- N. 21 CFR 201.50 Statement of identity – The proper name (established name), aflibercept is stated on the label with the trade name (proprietary name), ZALTRAP. This conforms to the regulation.
- O. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity is declared as either, “100 mg/4 mL and 200 mg/8 mL” on all carton labels. This conforms to the regulation.
- P. 21 CFR 201.55 Statement of dosage – The label states “**Dosage and Administration:** [REDACTED]” on all carton labels. This conforms to the regulation.
- Q. 21 CFR 201.100 Prescription drugs for human use – The labels display “Rx Only” and other pertinent information. This conforms to the regulation.

Conclusions

The following deficiencies and recommendations were noted in the review of the ZALTRAP[®] container and carton labels.

1. Container
 - a. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60. **Justification provided and acceptable.**
 - b. Each vial size presentation is capable of bearing a full label. Per 610.60, add the manufacturer’s license number. **Change made and acceptable.**
 - c. Please provide a justification for two distinct labels for the 100 mg/4 mL vial strength. **Justification provided and acceptable.**
2. Carton label
 - a. Add the required statement, “No U.S. Standard of Potency” per 21 CFR 610.61. **Change made and acceptable.**
3. Carton and Container
 - a. Revise the proper name, aflibercept to ensure that it is at least ½ the size of the proprietary name and has prominence commensurate with the proprietary name taking into account all pertinent factors including

typography, layout, contrast and other printer features per 21 CFR 201.10(g)(2). **Change made and acceptable.**

- b. Add the dosage form, Injection, immediately following the proper name and remove the statement (b)(4) preceding the route of administration. *See recommended format. **Change made and acceptable.**

*Recommended format

Zaltrap
(afibercept)
Injection

XXX mg/ Y mL
(XX mg/mL)

Accepted format:

Zaltrap
(xxx_afibercept)
Injection for Intravenous Infusion
XXX mg/ Y mL (XX mg/mL)

4. Vial cap (b)(4)
- a. Please provide all proposed printed information on the vial cap (b)(4)
(b)(4) **Information provided and acceptable.**

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/s/

KIMBERLY M RAINS
07/27/2012

SARAH B KENNETT
07/27/2012

PATRICK G SWANN
07/27/2012



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

FINAL LABEL AND LABELING REVIEW

Date: June 26, 2012

Reviewer: Kimberly Rains, Pharm.D.
Office of Biotechnology Products, Immediate Office

Through: Sara Kennett, Ph.D.
Division of Monoclonal Antibodies

Division Deputy Director: Patrick Swann, Ph.D.
Division of Monoclonal Antibodies

Application Number: STN 125418/0

Name of Drug: Zaltrap[®] (aflibercept)

Applicant: Regeneron Pharmaceuticals, Inc.

Material Reviewed: Carton and Container Labels

Submission Dates: February 2, 2012 and May 30, 2012

EXECUTIVE SUMMARY

The carton and container labels for ZALTRAP[®] (aflibercept) were reviewed and found to comply with most of the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 5/1/12-8/1/12, USP 35/NF 30. Labeling deficiencies were identified. Please see comments in the conclusions section.

Background

STN 125418/0 for aflibercept is an original Biologic License Application (BLA) in combination with irinotecan-fluoropyrimidine-based chemotherapy is indicated for patients with metastatic colorectal cancer (MCR) previously treated with an oxaliplatin-containing regimen. The product is supplied as a 100 mg/ 4 mL and a 200 mg/ 8 mL solution in single-use vials.

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/s/

KIMBERLY M RAINS
06/27/2012

SARAH B KENNETT
06/27/2012

PATRICK G SWANN
06/27/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: June 18, 2012

Reviewer: James Schlick, RPh, MBA
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Zaltrap
(Aflibercept)
Injection,
100 mg/4 mL (25 mg/mL), 200 mg/8 mL (25 mg/mL)

Application Type/Number: BLA 125418

Applicant: Sanofi-Aventis

OSE RCM #: 2012-400

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Zaltrap (Aflibercept) Injection (BLA 125418) for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND ON AFLIBERCEPT PRODUCTS

Aflibercept is currently marketed as Eylea (Aflibercept) Injection for the treatment of Neovascular (Wet) Age-Related Macular Degeneration (AMD) and is administered as an intravitreal injection. The product was approved on November 18, 2011. Zaltrap (Aflibercept) is indicated in combination with irinotecan and 5-fluouracil/leucovorin chemotherapy for patients with metastatic colorectal cancer (MCRC) previously treated with an oxaliplatin containing regimen. The following section provides a comparison between the two products.

1.2 PRODUCT INFORMATION FOR EYLEA AND ZALTRAP

The following product information for Zaltrap is provided in the February 2, 2012 proprietary name submission.

	Zaltrap	Eylea
Active Ingredient	Aflibercept	Aflibercept
Indication of Use	Indicated in combination with irinotecan and 5-fluouracil/leucovorin chemotherapy for patients with metastatic colorectal cancer (MCRC) previously treated with an oxaliplatin containing regimen	For treatment of neovascular (wet) age-related macular degeneration (AMD)
Route of Administration	Intravenous infusion only	Intravitreal injection
Dosage Form	Injection	Injection
Strength	25 mg/mL	40 mg/mL
Dose and Frequency	4 mg/kg of body weight administered as an intravenous infusion over 1 hour every two weeks. Can be dose reduced to 2 mg/kg based on toxicity	2 mg (0.05 mL) once per month for the first three months, followed by 2 mg once every two months

	Zaltrap	Eylea
How Supplied	100 mg/4 mL and 200 mg/8 mL single use vial; 100 mg vials come in cartons containing one vial and three vials each. The 200 mg strength is only available in single vial cartons.	Available in a single-use vial containing 0.278 mL Aflibercept and is packaged with one 19-gauge x 1 and ½ inch, 5-micron, filter needle for withdrawal of the vial contents, one 30-gauge x ½ inch injection needle for intravitreal injection, and one 1 mL syringe for administration.
Storage	2°C to 8°C (36°F to 46°F).	2°C to 8°C (36°F to 46°F).
Container and Closure System	Supplied in either 5 mL or 10 mL (b) (4) glass vial, sealed with flanged stopper with flip-off cap (b) (4) containing 100 mg or 200 mg of aflibercept.	Single-use, sterile, 3-mL, glass vial

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Reporting Event System (AERS) database (Appendix A) for Aflibercept medication error reports. We also reviewed the Zaltrap labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched (AERS) using the strategy listed in Table 1.

Table 1: AERS Search Strategy	
Date	Date Range: November 18, 2011 to May 11, 2012 Date Searched: May 11, 2012
Drug Names	Active Ingredient: Aflibercept Trade Name: Eylea Verbatim: Eyl%, Afliber%
MedDRA Search Strategy	Medication Errors (HLGT) Product Quality Issue (HLGT)

The AERS database search identified zero reports.

2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications on May 24, 2012, for additional cases and actions concerning Aflibercept. There were no additional medication error cases reported.

2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted February 2, 2012 (Appendix B)
- Carton Labeling submitted February 2, 2012 (Appendix C)
- Insert Labeling submitted February 2, 2012
- Current Eylea Container Labels submitted November 21, 2011 (Appendix D)
- Current Eylea Carton Labeling submitted November 21, 2011 (Appendix E)

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Following evaluation of the labels and labeling, we predict two types of medication error scenarios due to the similarities in established name and overlapping product characteristics. The first scenario involves wrong product selection between Eylea and Zaltrap. The second scenario involves the off label use of hyperosmolar Zaltrap by compounding pharmacies to compound and distribute doses for macular degeneration to eye clinics.

3.1 WRONG PRODUCT SELECTION

Because both Eylea and Zaltrap contain the same active ingredient, there is risk of selecting the wrong product during order entry or during product selection from the pharmacy shelf. Wrong drug order entry may occur if the person entering an order selects the wrong product from a drop down menu or the wrong product if ordered by established name. Because each product has a different strength, this can lead to wrong dose errors. Additionally, both Eylea and Zaltrap are stored in the refrigerator. This means both products could be stored next to each other increasing the potential for the wrong drug to be selected for dispensing.

Since the Eylea vial size contains 0.278 mL (11 mg), most of which is overfill to compensate for the residual volume that can not be removed by normal syringe manipulation, it will require an inordinate amount of Eylea vials to make the usual Zaltrap dose at 4 mg/kg of body weight. Therefore, it is less likely that Eylea will be used to prepare a Zaltrap dose. However, the other concern is the scenario that involves the product selection of Zaltrap to prepare a dose used for intravitreal injection. This can occur even when a correctly entered order contains the established name aflibercept on the prescription label and not the brand name. There is enough drug in the Zaltrap vial for the 2 mg intravitreal dose, and the volume would be 0.08 mL based on a 25 mg/mL strength. If Zaltrap, which is hyperosmolar undiluted, is used to prepare the Eylea dose,

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

it may cause complications if injected into the eye. Because of this, the FDA informed the manufacturer about this potential error, so they made labeling revisions to help distinguish the products from one another. First, the carton size, shape, and labeling are distinct between the two products. Also, Eylea has the statement ‘For Intravitreal Injection’ prominently displayed and the different settings of use for the two products may help to prevent errors. Lastly, since Eylea is a unit dose product, and Zaltrap requires a diluent, most pharmacies create Eylea ordering screens in a unit dose format that would not contain a field for diluent. Conversely, Zaltrap ordering screens would be created in an intravenous infusion format that would have a diluent field and would require a diluent to be specified. These differences may help prevent errors during the order entry step and product selection, thereby, preventing calculation and preparation errors due to the differing strengths of Eylea and Zaltrap.

3.2 COMPOUNDING

DMEPA also envisions compounding pharmacies using Zaltrap intentionally to produce less expensive batch doses for intravitreal injection. Since Zaltrap is hyperosmolar and the strengths of Eylea and Zaltrap are different, it is important to differentiate the products and provide proper warnings to prevent errors from occurring between the two products.

4 CONCLUSIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information to help mitigate confusion between Eylea and Zaltrap.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this BLA:

- A. General Comment to the Division
 - 1. DMEPA has learned during the course of this review that the established name, aflibercept, could be changed to a different established name based on safety concerns with potential product mix ups. If the established name stays as aflibercept, we request the applicant be asked to notify major pharmacy management systems, [REDACTED] (b) (4) of the new Zaltrap product and to highlight the difference in osmolarity, product preparation, administration, and strength between Eylea and Zaltrap.
- B. Container Labels
 - 1. Revise the presentation of the proper name, ‘(xxxxxx) [REDACTED] (b) (4) for Intravenous Infusion’ to read, ‘(xxxxxx)’ and ensure that it is at least ½ the size of the proprietary name and has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printer features per 21 CFR 201.10(g)(2).
 - 2. Revise the presentation of the proprietary name from all upper case letters (ZALTRAP), to title case (Zaltrap) to improve readability.

3. Remove the statement [REDACTED] (b)(4). In the same space add the statement ‘For intravenous infusion only. Must be diluted. Not to be administered by other routes.’ Place this statement in a box with a border around it. Make the font a different color than black. For example, red lettering with a black line.

C. Carton Labeling

1. See container label comments B.2 and revise carton labeling accordingly.
2. Revise the statement ‘(xxxxxxx) [REDACTED] (b)(4) for intravenous infusion’ to:

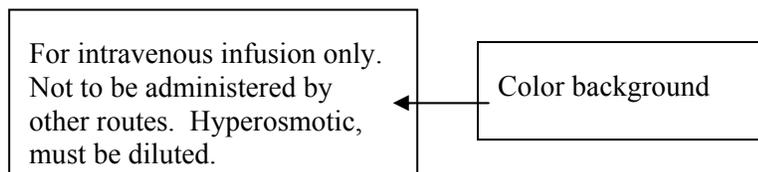
‘(xxxxxxx)
Injection’

NOTE: The removal of ‘[REDACTED] (b)(4) for intravenous infusion’ and placement of the word ‘Injection’.

3. Ensure the concentration per mL statement “25 mg/mL” is just below the total drug content on the three count 100 mg/4 mL carton labeling. For example:

100 mg/4 mL
(25 mg/mL)

4. Revise the following statements as indicated and place the statements in one box with white lettering and a high contrast background. Additionally, the statements should be in the same order as indicated in the example below.
 - a. [REDACTED] (b)(4) to ‘For intravenous infusion only. Not to be administered by other routes.’
 - b. [REDACTED] (b)(4) to ‘Hyperosmotic, must be diluted.’



5. Revise the statements, [REDACTED] (b)(4) to ‘single-use vial(s). Discard unused portion’.
6. Change the warning statement [REDACTED] (b)(4) to read ‘Hyperosmotic, must be further diluted. For intravenous infusion only. Not to be administered by other routes.’ Place this statement in a box with white lettering and a high contrast background.

D. Insert Labeling

1. General Comments
 - a. Revise the presentation of the proper name ‘(xxxxx) [REDACTED] (b)(4) for Intravenous Infusion’ to read, ‘(xxxxxx)’ throughout the product labeling.
2. Highlights of Prescribing Information



If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

APPENDICES

APPENDIX A: DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

APPENDIX B: ZALTRAP CONTAINER LABELS



2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JAMES H SCHLICK
06/18/2012

TODD D BRIDGES
06/18/2012

CAROL A HOLQUIST
06/18/2012

**Interdisciplinary Review Team for QT Studies Consultation:
QT Study Review**

BLA	125418
Brand Name	Zaltrap
Generic Name	Aflibercept
Sponsor	Sanofi – Aventis
Indication	Treatment of metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen
Dosage Form	Intravenous infusion
Drug Class	Fusion protein
Therapeutic Dosing Regimen	4 mg/kg q2w
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	As a single-agent: 5 mg/kg q2w In combination with chemotherapy: 4 mg/kg q2w or 6 mg/kg q3w
Submission Number and Date	SDN 001, 29 Feb 2012
Review Division	DOP2

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No large changes (i.e., >20 ms) in QTc interval were detected following aflibercept 6 mg/kg in cancer patients. 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 at 2 hours post-dose. Because of the lack of demonstrated assay sensitivity, the results should be interpreted as having ruled out an effect of about 20 ms.

In this double-blind, placebo-controlled study, 87 cancer patients were randomized to 6 mg/kg aflibercept or placebo. An overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Aflibercept (FDA Analysis)

Treatment	Time	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Aflibercept 6 mg/kg	Cycle 3, 2h	8.0	(0.3, 15.7)

The dose used in this study was 6 mg/kg administered intravenously every three weeks. The proposed therapeutic dose is 4 mg/kg every two weeks. The 6-mg/kg dose in the QT study resulted in free aflibercept C_{max} values 2-fold those achieved with the 4-mg/kg dose in the registration trial. These exposures cover the current high exposure scenario which is a 30% increase in free aflibercept exposure in patients >100 kg. VEGF-bound

aflibercept reaches steady state by the sixth dose, so the timing of samples in the third cycle may not capture peak effects of VEGF-bound aflibercept at steady-state. Within the range of concentrations observed in the study, no apparent concentration-QT relationship was identified.

2 PROPOSED LABEL

2.1 SPONSOR PROPOSED LABEL

Sponsor did not propose any language related to QT in the package insert.

2.2 PRODUCT INFORMATION

We have the following label recommendations which are suggestions only. We defer the final labeling decisions to the review division.

12.2 ECG Effects

 (b) (4)

However a small increase in the mean QTc interval (i.e., < 10 ms) cannot be excluded because of study design limitations.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Aflibercept is a recombinant fusion protein of human vascular endothelial growth factor (VEGF) receptor extracellular domains and the Fc portion of human immunoglobulin G1 (IgG1). Aflibercept acts as a decoy receptor that binds to VEGF-A with higher affinity than the natural receptors. Aflibercept also binds to VEGF-B and placenta growth factor (PlGF). Aflibercept has demonstrated antitumor and antiangiogenic activity as a single-agent and in combination with various chemotherapies in a variety of tumor models.

3.2 MARKET APPROVAL STATUS

Zaltrap is not approved for marketing in any country

3.3 PRECLINICAL INFORMATION

Reviewer's comments: Sponsor did no report safety pharmacology studies as per ICH S7B guidance.

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4.

A summary of studies in the integrated safety database is provided in Table 2.

In all studies ECGs were systematically performed at baseline and during study treatment only when clinically indicated. Therefore, there was no analysis of this parameter across clinical studies.

Table 2: Summary of integrated safety database

	Pivotal phase 3 study	Single-agent Phase 1 and Phase 2 studies	Phase 1 Combination with chemotherapy		Phase 3 studies in other indications	
Indication	MCRC	Solid tumors Ovary-NSCLC	Solid tumors		NSCLC	MPC
Study #	EFC10262	TED6115/6116	TCD6117	FOLFOX	EFC10261	EFC10547
Associated chemotherapy (if applicable)	FOLFIRI	ARD6122	TCD6118	Ir/LV5FU2	SUPPORTIVE for safety	SUPPORTIVE for safety
		ARD6123	TCD6121	Gemcitabine		
		ARD6772	TCD6121	Gemcitabine/erlotinib	Docetaxel 75 mg/m ²	Gemcitabine
		EFC6125	TCD6119	TCF		
		TCD6120	Docetaxel 75 mg/m ²			
		TCD6120	Docetaxel/cisplatin			
		TCD6120	Docetaxel 100 mg/m ²			
TCD6120	Pemetrexed					
Aflibercept schedule & dose	4 mg/kg q2w	0.3 to 7.0 mg/kg q2w	2.0 to 6.0 mg/kg q2w 2.0 to 9.0 mg/kg q3w		6.0 mg/kg q3w	4.0 mg/kg q2w
Number of treated patients	1216 (611 aflibercept)	Pooled data: 404 (overall) including 258 at 4 mg/kg	336		905 (452 aflibercept)	541 (270 aflibercept)
Total number of patients exposed to aflibercept			2073			

NSCLC: non small-cell lung cancer; MCRC: Metastatic colorectal cancer ; MPC: metastatic pancreatic cancer; FOLFOX: oxaliplatin/5FU/leucovorin; FOLFIRI: irinotecan / 5-FU combination; TCF: docetaxel/cisplatin/5FU; q2w: every 2-week regimen; q3w: every 3-week regimen

Source: eCTD 2.7.4, Table 3.

Reviewer’s comments: During study treatment ECG were collected when clinically indicated and were not included in the safety analysis. The incidence of adverse events of concern as per ICH E14 guidance such as ventricular arrhythmias or ventricular tachycardia reported in the aflibercept arm was not significantly different from that reported in the placebo group.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of aflibercept’s clinical pharmacology.

4 SPONSOR’S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 9948. The sponsor submitted the study report TES10897 for Zaltrap, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

“A randomized, double-blind, placebo-controlled study comparing aflibercept versus placebo on the QTc interval in cancer patients treated with docetaxel”.

4.2.2 Protocol Number

TES10897 (QUTIE)

4.2.3 Study Dates

8 April 2009 – 8 November 2010

4.2.4 Objectives

The primary objective is “...to assess the effect on QTcF interval (QTc Fridericia) of aflibercept versus placebo, in cancer patients.” The secondary objectives are

- “to assess the effects of aflibercept versus placebo on heart rate (HR), QT, QTcB (Bazett’s correction), and QTcN (population specific correction formula) intervals
- “to assess the overall clinical safety of the two treatment arms
- “to assess the pharmacokinetic (PK) profile of aflibercept (administered every 3 weeks) at Cycle 1 and Cycle 3”

Source: Sponsor’s report, page 3

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, double-blinded, 2-treatment-arm, parallel design with 15 cycles.

4.2.5.2 Controls

The Sponsor used negative (placebo + docetaxel) control. No positive control was utilized in this study.

4.2.5.3 Blinding

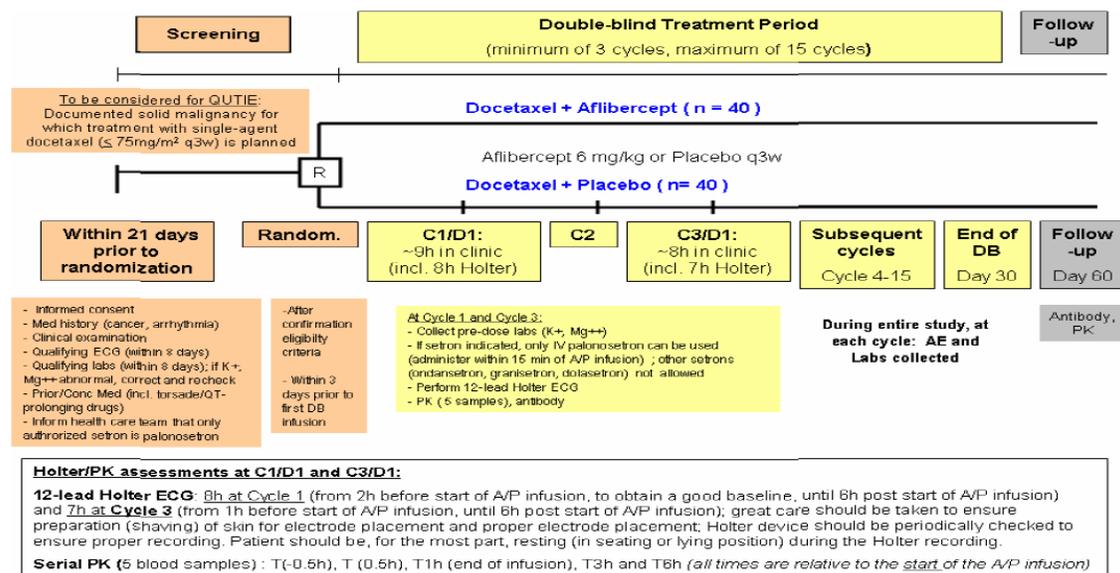
All treatment arms were double blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

“Eligible patients were centrally randomized (utilizing permuted block randomization schedule) via an interactive voice response system (IVRS) in a 1:1 ratio to one of the 2 treatment groups (aflibercept or placebo) on top of docetaxel, and treated double-blind for at least 3 cycles. Randomization was stratified by planned use or not of palonosetron during the first 3 cycles.”

Figure 1: Sponsor's Treatment Arms



Source: Sponsor's report, pages 28 and 30 (Figure 1).

4.2.6.2 Sponsor's Justification for Doses

“Since aflibercept is to be tested at potentially therapeutic doses in cancer patients, the selected aflibercept dosing regimen to be investigated in QUTIE was the dose investigated in the ongoing efficacy randomized, double-blind, placebo-controlled studies (ie, 6.0 mg/kg q3w). With this 6 mg/kg regimen, peak free aflibercept was expected to be higher than at 4 mg/kg, and bound steady-state aflibercept were comparable with 6 mg/kg q3w and 4 mg/kg q2w. Also, at 6 mg/kg q3w, free aflibercept exceeded bound aflibercept concentration at the end of the dosing interval, indicating effective trapping of the circulating VEGF, with the potential therefore to achieve the desired efficacy.”

Source: Clinical Study Report, Page 38.

Reviewer's Comment: The 6-mg/kg dose is acceptable. It is the highest therapeutic dose level studied in patients. The proposed therapeutic dose is 4 mg/kg every two weeks. The 6-mg/kg dose in the QT study resulted in free aflibercept C_{max} values 2-fold those achieved with the 4-mg/kg dose in the registration trial. Bound aflibercept C_{max} in the QT study was similar to trough concentrations observed in Phase 2 studies. These exposures cover the current high exposure scenario which is a 30% increase in free aflibercept exposure in patients >100 kg. There is no relevant effect of renal or hepatic impairment or drug-drug interactions.

4.2.6.3 Instructions with Regard to Meals

No information given.

Reviewer's Comment: Aflibercept is administered intravenously, so no interaction with meals is expected.

4.2.6.4 ECG and PK Assessments

ECGs were extracted from the 12-lead ECG Holter on Cycle 1 at 1.5, 1 and 0.5 h pre-dose and 0.5, 1, 2, 3, 4 and 6 h post-dose and Cycle 3 at 0.5 h pre-dose and 0.5, 1, 2, 3, 4 and 6 h post-dose. Blood samples for measurement of free and VEGF-bound aflibercept were collected on Cycles 1 and 3 at 0.5 h pre-dose and 0.5, 1, 3 and 6 h post-dose. Note that the 1 h post-dose sample corresponds to the end of the infusion. An additional PK sample was collected at the final Day 60 follow-up visit.

Reviewer's Comments: The proposed ECG and PK sampling times are appropriate to capture peak free aflibercept ($T_{max} = 1$ h). Steady-state for free aflibercept is reached at the 5th cycle, but accumulation is minimal (accumulation ratio ~1.1). VEGF-bound aflibercept reaches steady state by the 6th dose, so the timing of samples in the third cycle may not capture peak effects of VEGF-bound aflibercept at steady-state. The sponsor does not provide the accumulation ratio for VEGF-bound aflibercept.

4.2.6.5 Baseline

The sponsor used a within day baseline.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. The ECG signal was recorded on the compact flash memory cards (flash cards) provided to the Sites. Cardiac Safety Specialists reviewed all ECGs for correct lead and beat selection and adjudicate calipers, which have been pre-placed using the algorithm. Finally each ECG was submitted to a Cardiologist for clinical evaluation and verification of the caliper placement.

Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Eighty-seven patients with metastatic colorectal cancer were enrolled in the study. 14 patients completed the entire study. Patients primarily did not complete the study due to disease progression and adverse events. There was no difference in patient withdrawal between the treatment and placebo arm.

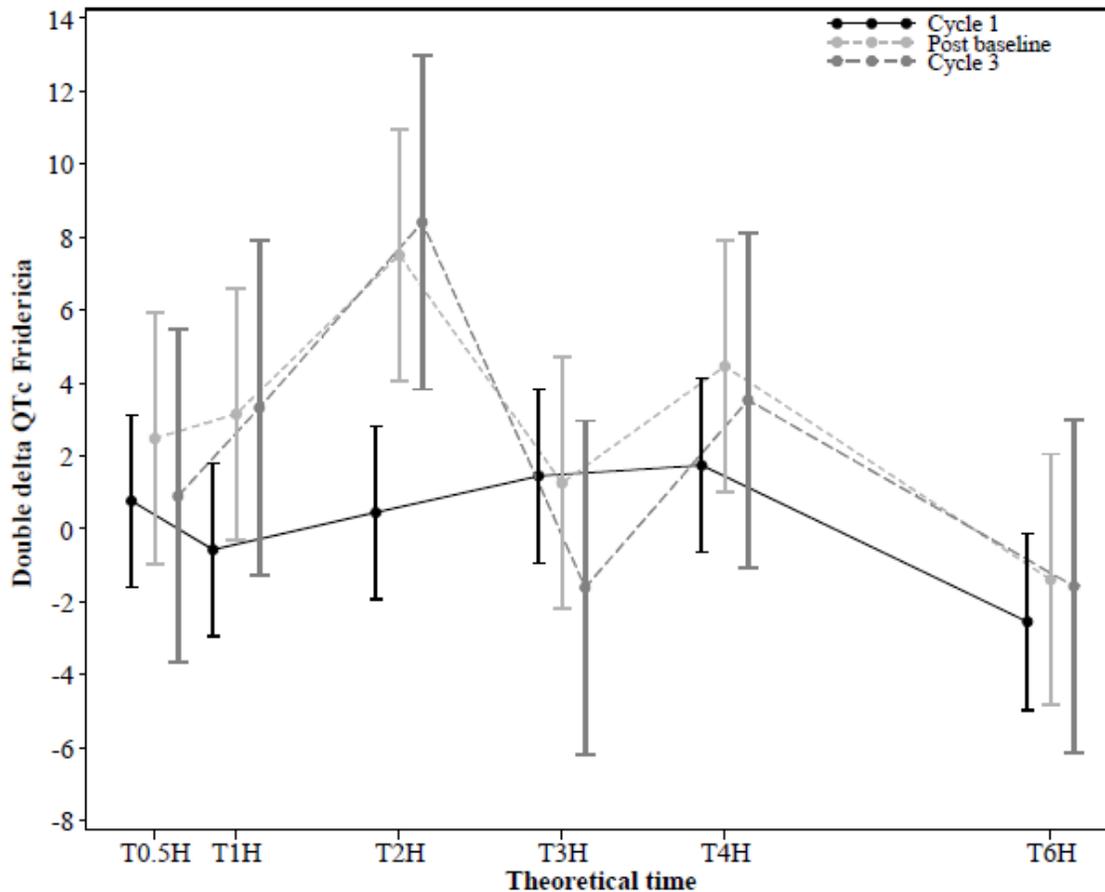
4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The sponsors analyzed QTcF across all time points using patients with at least one baseline and post-baseline evaluation (43 placebo patients, 41 treatment patients). The sponsor estimated the LS mean using an ANCOVA model with treatment, gender, and palonoson use as fixed terms, baseline measurement as a covariate, and subject nested within treatment-by-gender as a random term. Results were calculated for Cycle 1 data, Cycle 3 data, and both cycle data combined.

The sponsor found that the largest upper CI bound was below 10 ms for Cycle 1, and above 10 ms for Cycle 3 and post-baseline data (see Figure 2).

Figure 2: Sponsor's Mean and 90% CI $\Delta\Delta$ QTcF for Zaltrap



Source: Sponsor's study, Figure 4, page 74.

4.2.8.2.2 Assay Sensitivity

Due to the serious nature of the disease under treatment, the sponsor did not include positive control to demonstrate assay sensitivity.

4.2.8.2.3 Categorical Analysis

The sponsor found that there were no patients with QTcF > 500 ms or QTcF change from baseline > 60 ms.

4.2.8.3 Safety Analysis

In the aflibercept treatment group, the following all grades events were more commonly observed compared with placebo: with a difference of more than 10%: gastrointestinal events (nausea, stomatitis, constipation, GI and abdominal pains), decrease appetite, dysphonia, dyspnea, cough, hypertension, hemorrhage (including mainly epistaxis and bleeding from GI origin), and infections and neutropenic complications.

In the placebo arm, all grades dysgeusia (5 patients) and myalgia (6 patients) were more frequent than in the aflibercept arm (3 patients each respectively).

Fewer patients in the placebo group experienced at least 1 Grade 3/4 TEAEs, regardless of the relationship to the study treatment compared to the aflibercept group (56.8% compared to 81.4%).

The increased incidence of Grade 3/4 TEAEs in the aflibercept group versus the placebo group was due to the higher percentages of Grade 3 or 4 neutropenia/febrile neutropenia (32.6% vs 18.2%), fatigue/asthenia (27.9% vs 6.8%) and hypertension (11.6% vs 0%).

There were 27 deaths (12 placebo, 15 Aflibercept) reported. Twenty three deaths were due to disease progression, 2 were due to related AEs (septic shock under placebo and pneumonia under aflibercept) and 2 were due to “other reasons”: sudden death (placebo Patient) and symptomatic deterioration due to head and neck cancer (aflibercept Patient) not considered by the investigator to represent disease progression.

Reviewer’s comments: One patient in the aflibercept group experienced Grade 3 or 4 ejection fraction decreased versus none in the placebo group. No ventricular arrhythmias or clinically relevant ECGs changes were reported.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 3 (free aflibercept) and Table 4 (bound aflibercept). C_{max} values for free aflibercept in the QT study were 2-fold the values observed in the pivotal clinical trial ($C_{max} = 66 \mu\text{g/mL}$) at 4 mg/kg every two weeks, the intended clinical dose.

Table 3: Mean \pm SD (%CV) [Geometric Mean] of Free Aflibercept Pharmacokinetic Parameters

Free aflibercept	N	C_{max} ($\mu\text{g/mL}$)
Cycle 1	43	132 \pm 39 (29) [127]
Cycle 3	29	125 \pm 45 (36) [112]

Source: Clinical Study Report, Table 49, Page 131.

Table 4: Mean ± SD (%CV) [Geometric Mean] of Bound Afibercept Pharmacokinetic Parameters

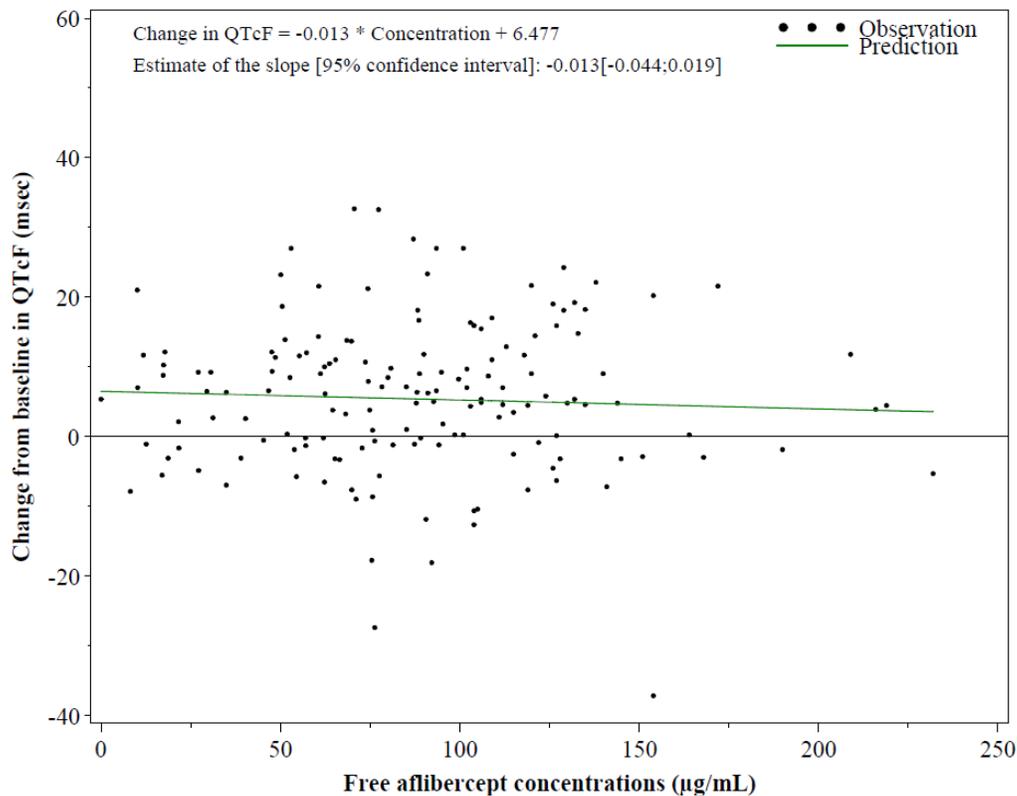
Bound afibercept	N	C _{max} (µg/mL)
Cycle 1	43	0.0580 ± 0.0381 (66) [0.0493]
Cycle 3	29	3.42 ± 0.91 (27) [3.29]

Source: Clinical Study Report, Table 50, Page 132.

4.2.8.4.2 Exposure-Response Analysis

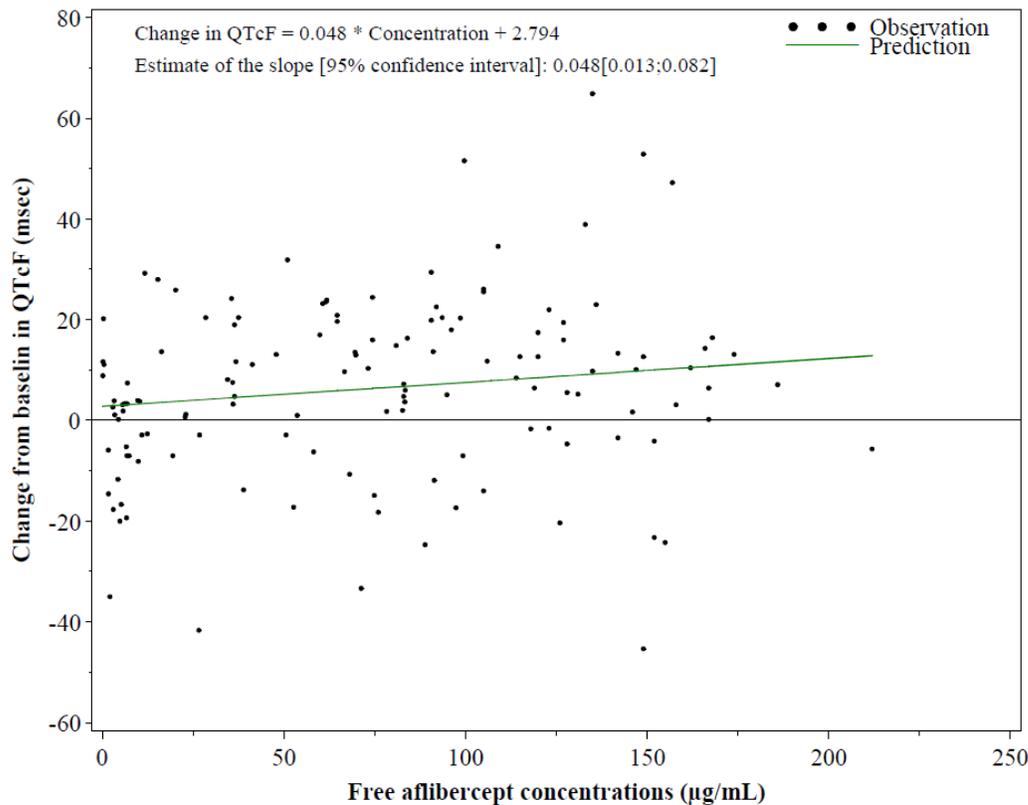
The sponsor examined the relationship between baseline adjusted QTcF changes and log free afibercept concentrations using a linear mixed model. Mean and upper one-sided 95% confidence bounds were estimated at relevant concentrations for this model. The results for Cycle 1 and Cycle 3 are presented in Figure 3 and Figure 4, respectively.

Figure 3: Change from Baseline QTcF vs. Free Afibercept Concentrations (Cycle 1)



Source: Clinical Study Report, Figure 15, Page 133.

Figure 4: Change from Baseline QTcF vs. Free Aflibercept Concentrations (Cycle 3)



Source: Clinical Study Report, Figure 16, Page 134.

Reviewer's Comments: The reviewer performed an independent concentration-QTcF analysis pooling concentrations across both cycles. Plots of $\Delta\Delta$ QTcF vs. free and bound aflibercept concentrations are presented in Figure 9 and Figure 10, respectively.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcN). QTcN is a QT correction method that is population-based ($QTcN = QT/RR^{-0.3835}$). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcF and QTcN distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcN), and the interaction term of RR and correction type. The slopes of QTcF and QTcN versus RR are compared in magnitude as well as statistical significance in difference. As shown in the following table, it appears that QTcN had smaller absolute slopes than QTcF. To be consistent with the sponsor's primary objective, QTcF was used in the FDA analysis.

Table 5: Comparison of QTcF and QTcI Using the Mixed Model

Treatment Groups	Slope of QTcF	Slope of QTcN	P value
Zaltrap	0.0207	-0.0018	0.0000
Placebo	0.0354	0.0039	0.0000
All	0.0282	0.0020	0.0000

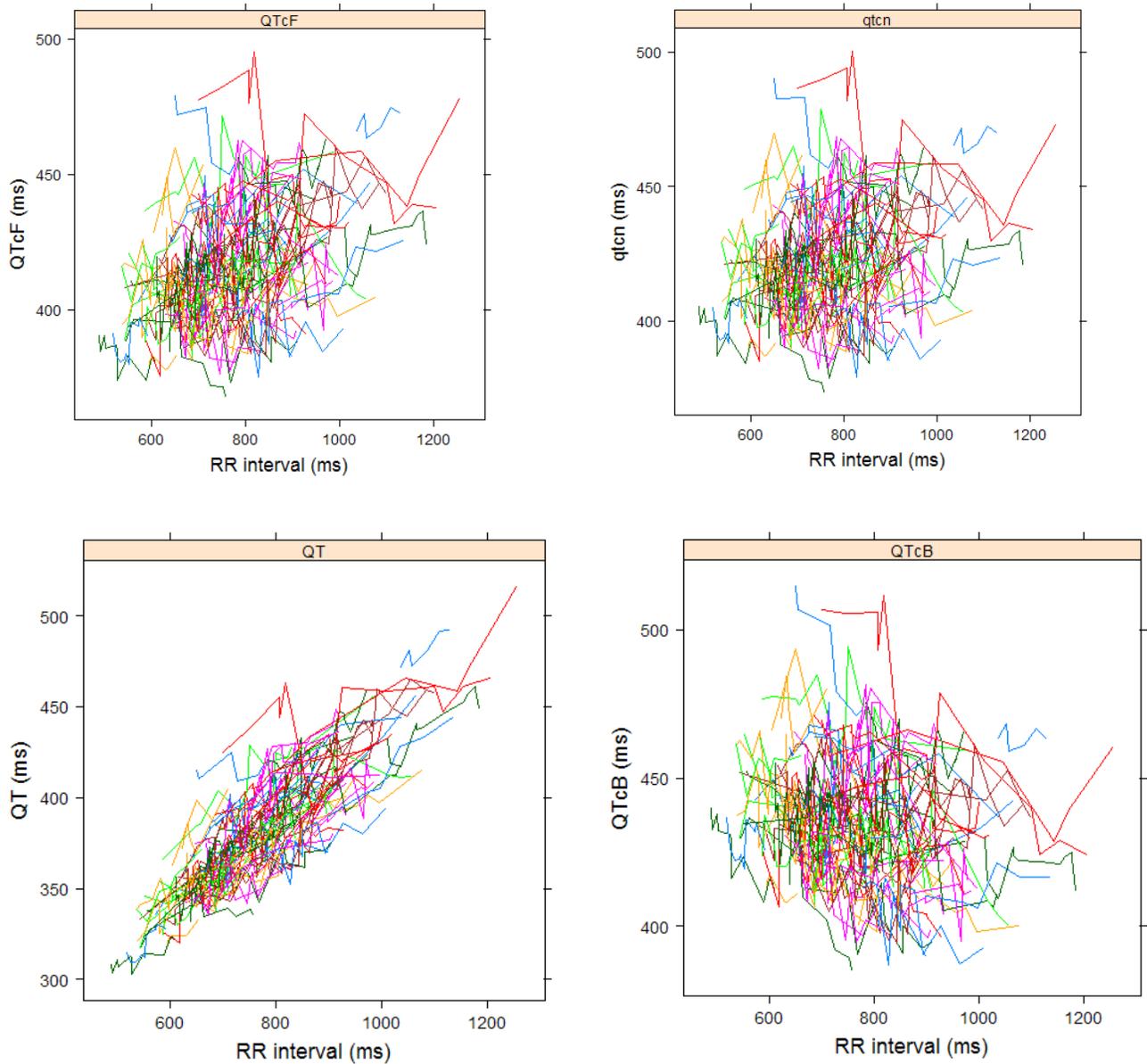
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in the following table, it appears that QTcF and QTcN have similar slopes. Therefore, this statistical reviewer used QTcF for the primary statistical analysis to be consistent with the sponsor's choice of QTcF for their primary analysis.

Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	QTcF		QTcN	
	N	MSSS	N	MSSS
Zaltrap	41	0.0190	41	0.0202
Placebo	43	0.0066	43	0.0055
All	84	0.0126	84	0.0127

The relationship between different correction methods and RR is presented in **Figure 5**.

**Figure 5: QT, QTcB, QTcN and QTcF vs. RR
(Each Subject's Data Points are Connected with a Line)**



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Zaltrap

The statistical reviewer used a mixed model to analyze the Δ QTcF effect. The model includes treatment and sex as fixed effects and subject as a random effect. Baseline

values are also included in the model as a covariate. The analysis results are listed in Table 7, Table 8, and Table 9.

Table 7: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Zaltrap (Both Cycles)

Time	Δ QTcF: Zaltrap			Δ QTcF: Placebo			$\Delta\Delta$ QTcF		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	43	3.2	1.2	41	4.7	1.3	84	1.5	(-1.5, 4.4)
1	43	4.1	1.5	40	5.4	1.5	83	1.3	(-2.2, 4.8)
2	42	-3.1	1.4	41	1.1	1.4	83	4.2	(0.8, 7.5)
3	43	6.4	1.6	40	8.3	1.7	83	1.9	(-1.9, 5.8)
4	43	5.5	1.6	40	8.9	1.7	83	3.4	(-0.5, 7.2)
6	43	9.6	1.5	40	8.0	1.5	83	-1.6	(-5.1, 1.9)

Table 8: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Zaltrap (Cycle 1)

Time	Δ QTcF: Zaltrap			Δ QTcF: Placebo			$\Delta\Delta$ QTcF		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	43	3.3	1.2	41	4.0	1.2	84	0.7	(-2.2, 3.6)
1	43	4.3	1.6	40	3.9	1.7	83	-0.4	(-4.3, 3.4)
2	42	-2.0	1.4	40	-1.1	1.4	82	0.9	(-2.4, 4.3)
3	43	5.4	1.8	39	7.7	1.9	82	2.2	(-2.2, 6.7)
4	43	7.2	2.0	39	9.5	2.1	82	2.2	(-2.7, 7.1)
6	41	9.6	1.7	37	7.7	1.7	78	-1.9	(-5.9, 2.1)

Table 9: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Zaltrap (Cycle 3)

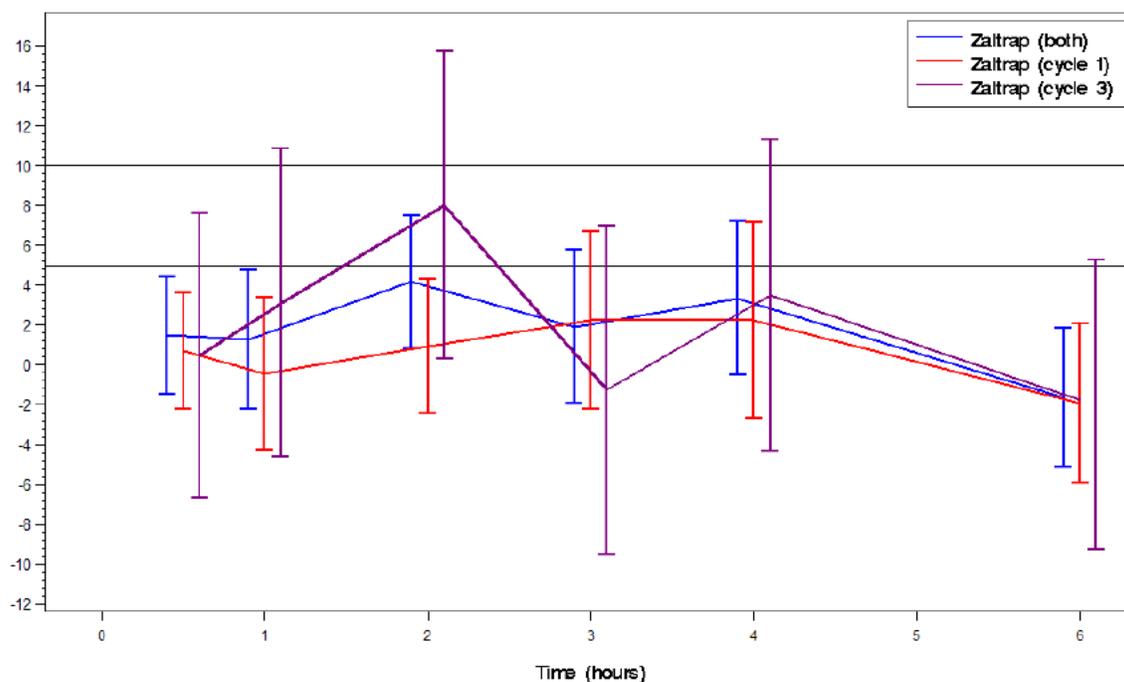
Time	Δ QTcF: Zaltrap			Δ QTcF: Placebo			$\Delta\Delta$ QTcF		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	30	4.6	2.9	28	5.1	3.0	58	0.5	(-6.6, 7.6)
1	30	4.5	3.1	27	7.6	3.3	57	3.1	(-4.6, 10.8)
2	31	-4.0	3.1	27	4.0	3.3	58	8.0	(0.3, 15.7)
3	31	8.7	3.4	28	7.4	3.5	59	-1.3	(-9.5, 7.0)
4	30	3.8	3.2	28	7.3	3.3	58	3.5	(-4.3, 11.3)
6	30	9.9	3.0	28	7.9	3.1	58	-2.0	(-9.3, 5.3)

The largest upper bounds of the 2-sided 90% CI for the mean difference between Zaltrap (both cycles) and placebo, Zaltrap (cycle 1) and placebo, and Zaltrap (cycle 3) and placebo were 7.2 ms, 7.1 ms, and 15.7 ms, respectively.

5.2.1.2 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcF for different treatment groups.

Figure 6: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse



All CIs are unadjusted.

5.2.1.3 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, and greater than 480 ms. There was 1 (2.4%) subject who experienced QTcF between 480 ms and 500 ms in Zaltrap.

Table 10: Categorical Analysis for QTcF

Treatment Group	N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms	Value > 480 ms
Zaltrap	41	35 (85.4%)	5 (12.2%)	1 (2.4%)
Placebo	43	32 (74.4%)	11 (25.6%)	0 (0.0%)

Table 11 lists the categorical analysis results for Δ QTcF. There is 1 (2.4%) subject who experienced Δ QTcF greater than 60 ms in Zaltrap.

Table 11: Categorical Analysis of Δ QTcF

Treatment Group	N	Value ≤ 30 ms	30 ms < Value ≤ 60 ms	Value > 60 ms
Zaltrap	41	35 (85.4%)	5 (12.2%)	1 (2.4%)
Placebo	43	36 (83.7%)	7 (16.3%)	0 (0.0%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 12, Table 13, and Table 14. The largest upper bounds of the 2-sided 90% CI for the mean difference between Zaltrap (both cycles) and placebo, Zaltrap (cycle 1) and placebo, and Zaltrap (cycle 3) and placebo are -1.0 bpm, 0.7 bpm, and 7.1 bpm, respectively.

Table 12: Analysis Results of Δ HR and $\Delta\Delta$ HR for Zaltrap (Both Cycles)

Time	Δ HR: Zaltrap			Δ HR: Placebo			$\Delta\Delta$ HR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	43	-1.9	1.1	41	-5.7	1.1	84	-3.9	(-6.4, -1.3)
1	43	-2.3	1.1	40	-6.0	1.1	83	-3.7	(-6.3, -1.0)
2	42	0.6	1.1	41	-4.2	1.2	83	-4.8	(-7.5, -2.1)
3	43	-0.4	1.2	40	-5.0	1.3	83	-4.6	(-7.5, -1.7)
4	43	1.4	1.2	40	-3.8	1.2	83	-5.2	(-8.1, -2.3)
6	43	1.5	1.2	40	-2.9	1.2	83	-4.4	(-7.2, -1.5)

Table 13: Analysis Results of Δ HR and $\Delta\Delta$ HR for Zaltrap (Cycle 1)

Time	Δ HR: Zaltrap			Δ HR: Placebo			$\Delta\Delta$ HR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	43	-2.9	1.1	41	-5.5	1.2	84	-2.7	(-5.4, 0.1)
1	43	-3.8	1.2	40	-6.1	1.3	83	-2.4	(-5.4, 0.7)
2	42	1.2	1.3	40	-4.4	1.4	82	-5.6	(-8.9, -2.4)
3	43	-0.4	1.3	39	-7.0	1.4	82	-6.6	(-9.8, -3.3)
4	43	1.1	1.6	39	-5.2	1.7	82	-6.3	(-10.1, -2.4)
6	41	0.5	1.5	37	-4.5	1.6	78	-5.0	(-8.7, -1.3)

Table 14: Analysis Results of Δ HR and $\Delta\Delta$ HR for Zaltrap (Cycle 3)

Time	Δ HR: Zaltrap			Δ HR: Placebo			$\Delta\Delta$ HR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	30	-0.4	2.3	28	-5.5	2.4	58	-5.0	(-10.8, 0.7)
1	30	-0.2	2.3	27	-5.3	2.4	57	-5.1	(-10.8, 0.6)
2	31	-0.6	2.2	27	-3.3	2.4	58	-2.7	(-8.4, 3.0)
3	31	-1.7	2.4	27	-0.8	2.6	58	0.9	(-5.2, 7.1)
4	30	-0.1	2.2	28	-0.8	2.2	58	-0.7	(-6.0, 4.7)
6	30	2.1	2.2	28	-1.0	2.3	58	-3.2	(-8.8, 2.4)

5.2.3 PR Analysis

The same statistical analysis was performed based on the PR interval. The point estimates and the 90% confidence intervals are presented in Table 15, Table 16, and Table 17. The largest upper limits of 90% CI for the PR mean differences between Zaltrap (both cycles) and placebo, Zaltrap (cycle 1) and placebo, and Zaltrap (cycle 3) and placebo are 13.8 ms, 15.7 ms, and 12.6 ms, respectively.

The outlier analysis results for PR are presented in Table 18. There are 7 (17.1%) and 5 (11.6%) subjects who experienced PR greater than 200 ms in Zaltrap and placebo, respectively.

Table 15: Analysis Results of Δ PR and $\Delta\Delta$ PR for Zaltrap (Both Cycles)

Time	Δ PR: Zaltrap			Δ PR: Placebo			$\Delta\Delta$ PR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	43	1.4	1.4	41	4.5	1.4	84	3.1	(-0.1, 6.3)
1	43	3.3	1.3	40	4.9	1.4	83	1.6	(-1.5, 4.8)
2	42	3.3	1.4	41	7.1	1.4	83	3.9	(0.6, 7.1)
3	43	0.3	1.3	40	5.4	1.4	83	5.1	(2.0, 8.2)
4	43	-2.6	1.7	40	7.2	1.8	83	9.8	(5.7, 13.8)
6	43	-0.9	1.3	40	3.0	1.3	83	3.9	(0.9, 6.8)

Table 16: Analysis Results of Δ PR and $\Delta\Delta$ PR for Zaltrap (Cycle 1)

Time	Δ PR: Zaltrap			Δ PR: Placebo			$\Delta\Delta$ PR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	43	1.1	1.9	41	5.3	1.9	84	4.2	(-0.2, 8.7)
1	43	3.8	1.8	40	5.4	1.9	83	1.6	(-2.7, 6.0)
2	42	3.0	1.6	40	7.2	1.6	82	4.2	(0.5, 7.9)
3	43	1.4	2.0	39	5.7	2.1	82	4.3	(-0.4, 9.0)
4	43	-2.3	2.4	39	7.7	2.5	82	10.0	(4.2, 15.7)
6	41	-1.2	1.6	37	4.3	1.7	78	5.5	(1.6, 9.4)

Table 17: Analysis Results of Δ PR and $\Delta\Delta$ PR for Zaltrap (Cycle 3)

Time	Δ PR: Zaltrap			Δ PR: Placebo			$\Delta\Delta$ PR		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	30	1.6	2.7	28	2.9	2.8	58	1.3	(-5.2, 7.8)
1	30	1.9	2.6	27	3.8	2.7	57	2.0	(-4.3, 8.3)
2	31	3.1	3.1	27	8.0	3.3	58	5.0	(-2.7, 12.6)
3	31	-1.0	2.2	27	4.4	2.4	58	5.4	(-0.0, 10.8)
4	30	-3.5	2.3	28	2.8	2.3	58	6.2	(0.8, 11.6)
6	30	-0.5	2.4	28	0.6	2.5	58	1.0	(-4.7, 6.7)

Table 18: Categorical Analysis for PR

Treatment Group	N	PR < 200 ms	PR >=200 ms
Zaltrap	41	34 (82.9%)	7 (17.1%)
Placebo	43	38 (88.4%)	5 (11.6%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 19, Table 20, and Table 21. The largest upper limits of 90% CI for the QRS mean differences between Zaltrap (both cycles) and placebo, Zaltrap (cycle 1) and placebo, and Zaltrap (cycle 3) and placebo are 1.4 ms, 1.3 ms, and 2.5 ms, respectively.

The outlier analysis results for QRS are presented in Table 22. There are 2 (4.9%) subjects with QRS greater than 110 ms in Zaltrap.

Table 19: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Zaltrap (Both Cycles)

Time	Δ QRS: Zaltrap			Δ QRS: Placebo			$\Delta\Delta$ QRS		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	43	0.2	0.4	41	-0.6	0.4	84	-0.8	(-1.7, 0.2)
1	43	0.2	0.4	40	-0.7	0.4	83	-0.9	(-1.9, -0.0)
2	42	1.4	0.4	41	1.3	0.4	83	-0.1	(-1.1, 0.9)
3	43	1.0	0.4	40	0.4	0.4	83	-0.6	(-1.6, 0.3)
4	43	0.3	0.4	40	0.7	0.4	83	0.4	(-0.5, 1.4)
6	43	-0.1	0.5	40	-0.2	0.5	83	-0.2	(-1.3, 1.0)

Table 20: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Zaltrap (Cycle 1)

Time	Δ QRS: Zaltrap			Δ QRS: Placebo			$\Delta\Delta$ QRS		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	43	0.8	0.5	41	0.2	0.6	84	-0.6	(-1.9, 0.6)
1	43	0.6	0.4	40	-0.4	0.4	83	-1.0	(-2.0, 0.0)
2	42	1.8	0.5	40	1.5	0.5	82	-0.3	(-1.5, 0.8)
3	43	1.4	0.5	39	0.5	0.5	82	-0.9	(-2.2, 0.3)
4	43	1.0	0.5	39	1.1	0.5	82	0.1	(-1.2, 1.3)
6	41	0.9	0.6	37	0.3	0.6	78	-0.6	(-2.0, 0.8)

Table 21: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Zaltrap (Cycle 3)

Time	Δ QRS: Zaltrap			Δ QRS: Placebo			$\Delta\Delta$ QRS		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
0.5	30	-0.9	0.7	28	-2.4	0.7	58	-1.5	(-3.2, 0.2)
1	30	-0.5	0.8	27	-1.4	0.8	57	-0.9	(-2.9, 1.0)
2	31	0.7	0.8	27	1.0	0.8	57	0.3	(-1.6, 2.2)
3	31	0.1	0.8	28	-0.1	0.8	59	-0.3	(-2.1, 1.6)
4	30	-0.7	0.7	28	-0.0	0.8	58	0.7	(-1.1, 2.5)
6	30	-1.6	0.9	28	-1.3	0.9	58	0.4	(-1.8, 2.5)

Table 22: Categorical Analysis for QRS

Treatment Group	N	QRS < 110 ms	QRS \geq 110 ms
Zaltrap	41	39 (95.1%)	2 (4.9%)
Placebo	43	43 (100%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean free and bound aflibercept concentration-time profiles from Cycle 3 are illustrated in Figure 7 and Figure 8, respectively.

Figure 7: Mean Free Aflibercept Concentration-Time Profile for 6 mg/kg During Day 1 of Cycle 3

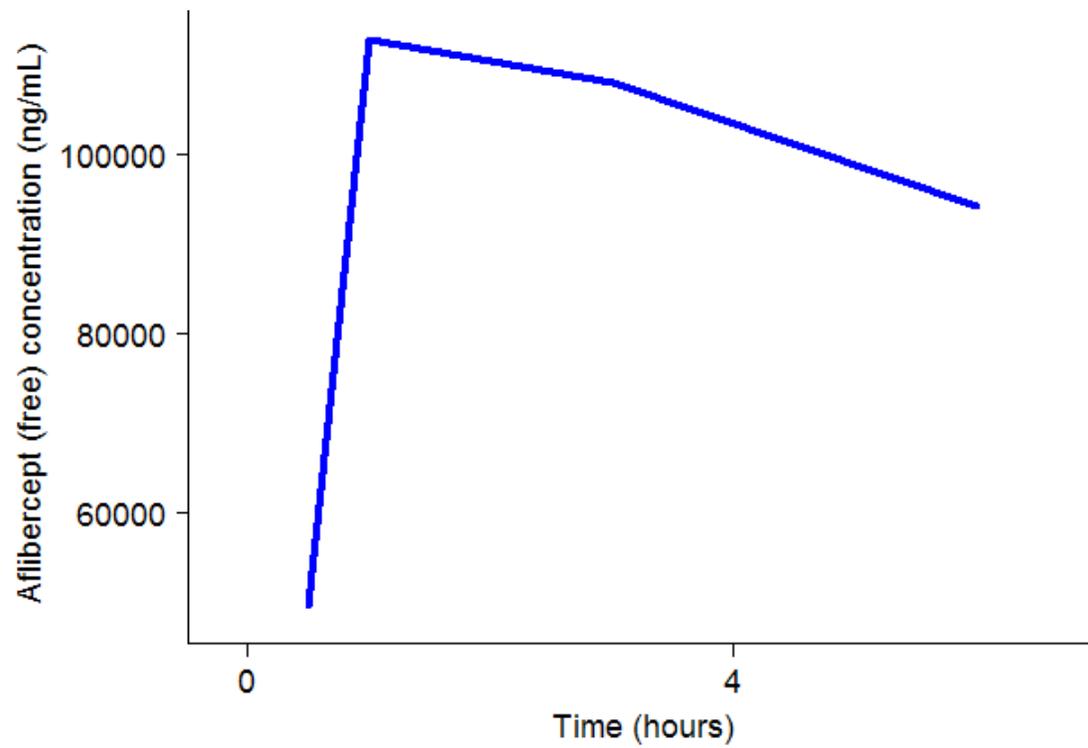
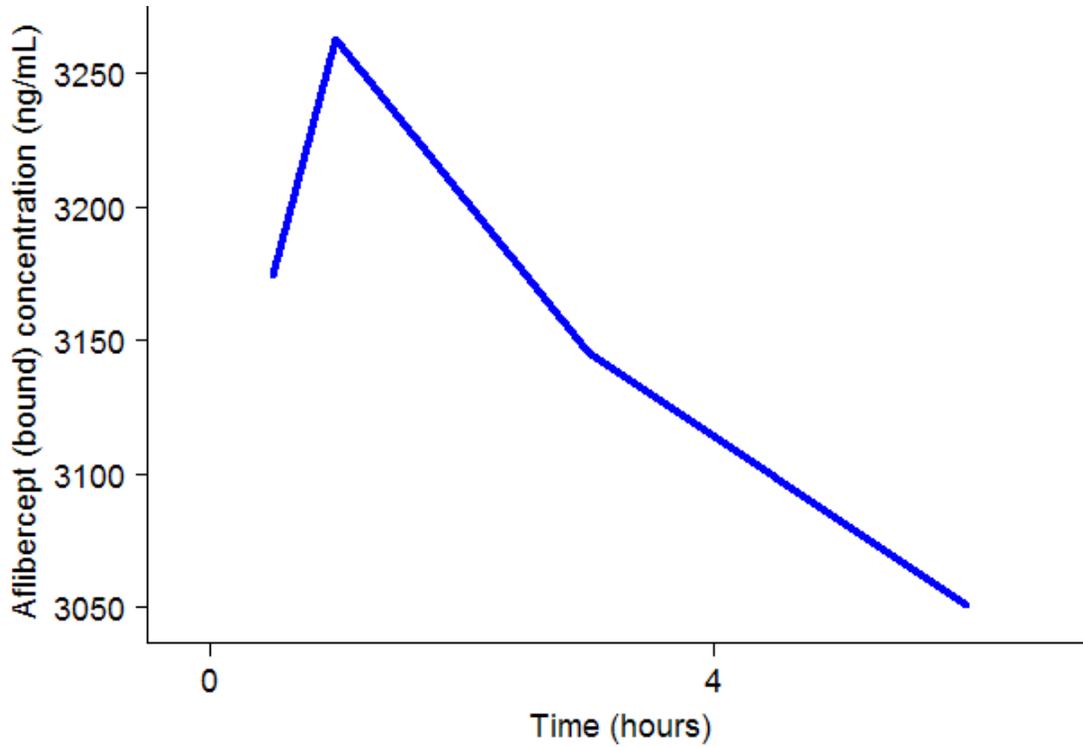


Figure 8: Mean Bound Aflibercept Concentration-Time Profile for 6 mg/kg During Day 1 of Cycle 3



The relationship between $\Delta\Delta\text{QTcF}$ and free aflibercept and bound aflibercept concentrations is visualized in Figure 9 and Figure 10, respectively with no evident exposure-response relationship.

Figure 9: $\Delta\Delta$ QTcF vs. Free Aflibercept Concentration

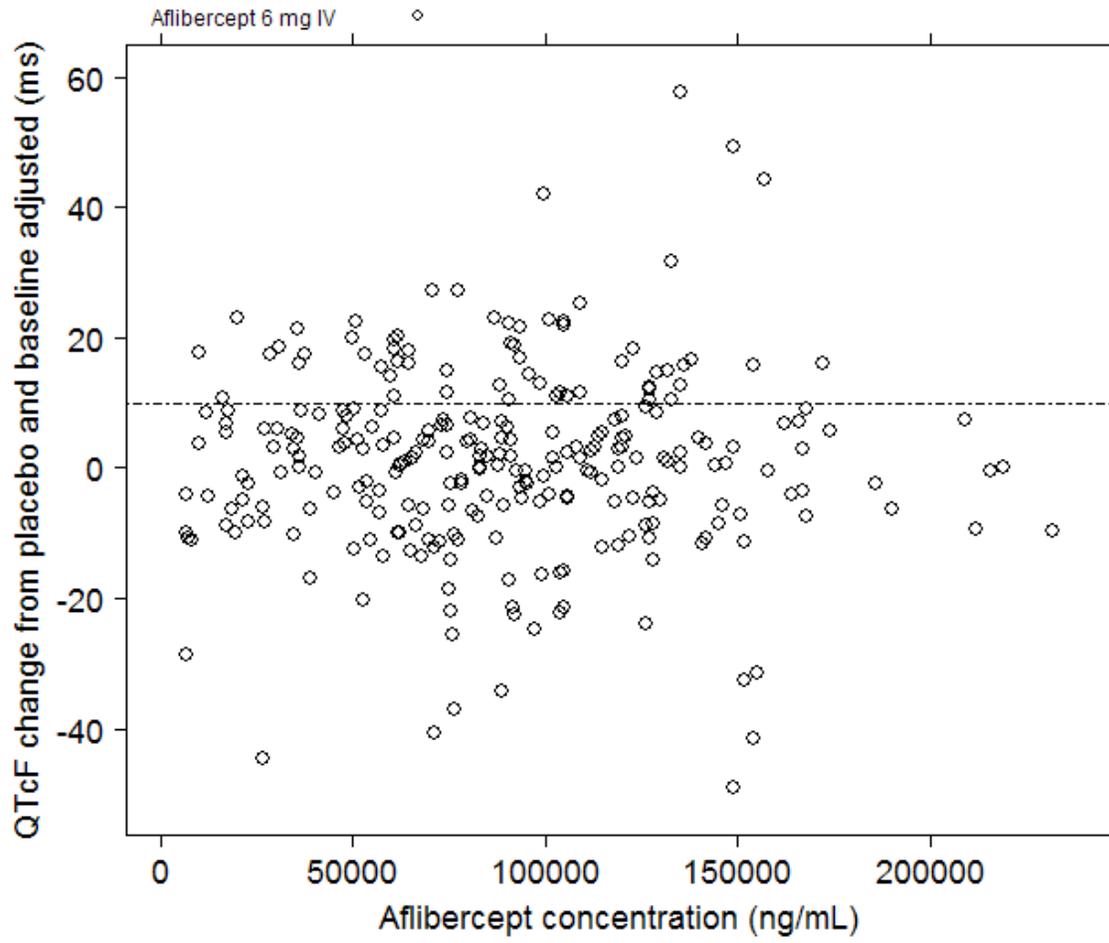
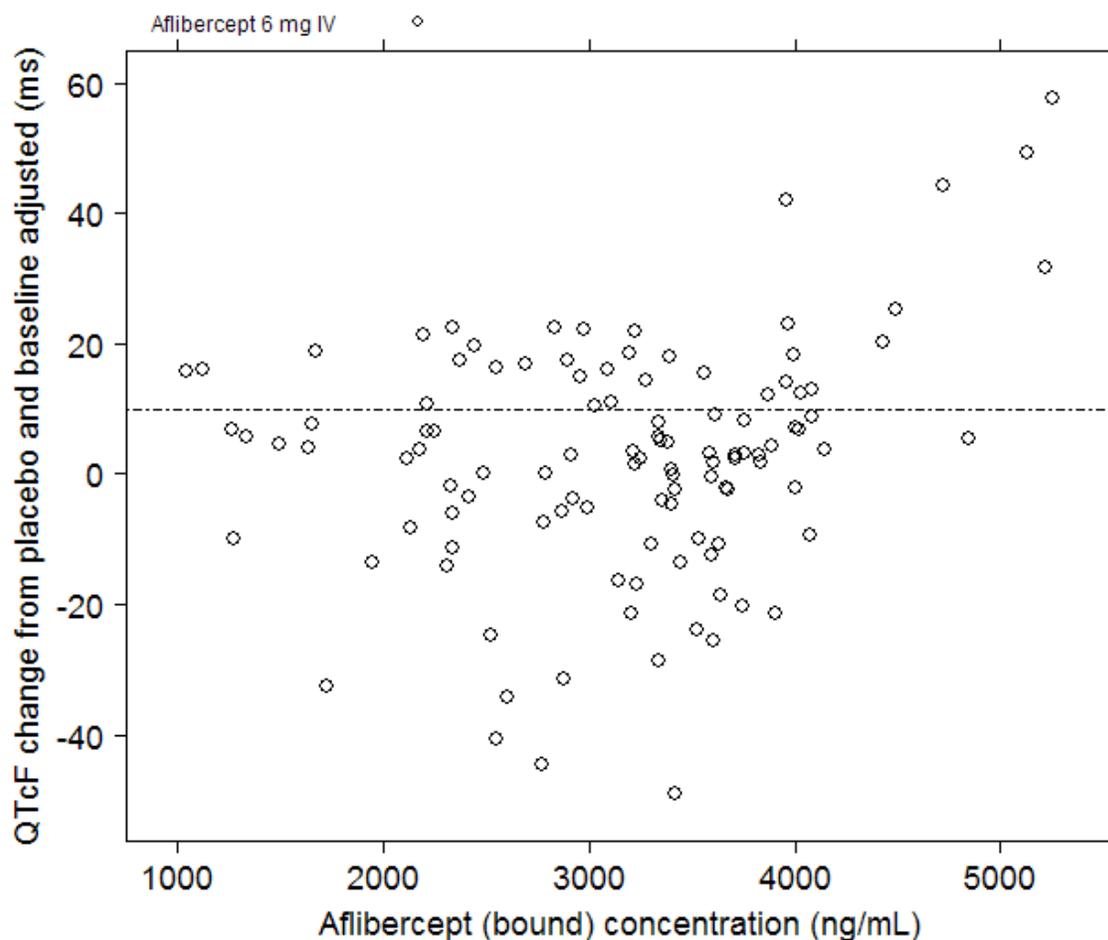


Figure 10: $\Delta\Delta$ QTcF vs. Bound Afibercept Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 82% of the ECGs were annotated in the primary lead II, with less than 0.6% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Seven subjects had a PR > 200 ms. One of them had a postbaseline increase of 111 ms (62% over baseline) which is considered clinically meaningful. Two subjects had a QRS > 110 ms at baseline.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	The recommended dose of aflibercept, administered as an intravenous infusion over 1 hour, is 4 mg/kg of body weight, which is followed by the combination of irinotecan and infusional 5-fluorouracil/leucovorin (FOLFIRI). The treatment cycles were repeated every 2 weeks.	
Maximum tolerated dose	The aflibercept maximum administered dose in monotherapy was 7 mg/kg given as 1 hour IV infusion every 2 weeks. When administered in combination, the maximum administered doses of aflibercept were 9 mg/kg given as 1 hour IV infusion every 3 weeks and 7 mg/kg given as 1 hour IV infusion every 2 weeks, in combination with various chemotherapies.	
Principal adverse events	Following the administration of aflibercept (4 mg/kg) followed by the combination of irinotecan and infusional 5-fluorouracil/leucovorin the most frequent TEAEs (≥20%, all grades, regardless of relationship to the study treatment) By decreasing order of frequency, were reported in the aflibercept treatment arm : diarrhea, asthenic conditions (HLT), stomatitis & ulceration (HLT), nausea, infections and infestations (SOC), hypertension (grouping or HLT), GI and abdominal pains (HLT), vomiting, decreased appetite, weight decrease, epistaxis, alopecia, dysphonia, musculoskeletal and connective pain and discomfort (HLT), constipation and headache. TEAE (PT/HLT/SOC or laboratory abnormalities) with an excess in incidence (all grades) in the aflibercept arm of more than 10% over the placebo arm were: hypertension (41.4% vs 10.7%), dysphonia (25.4% vs 3.3%), proteinuria (62.2% vs 40.7%), epistaxis (27.7% vs 7.4%), stomatitis and ulceration (54.8 vs 34.9%), weight decrease (31.9% vs 14.4%), thrombocytopenia (47.4% vs 33.8%), headache (22.3% vs 8.8%), infections and infestations (46.2% vs 32.7%), diarrhea (69.2% vs 56.5%), neutropenia (67.8% vs 56.3%), asthenic conditions (60.4% vs 50.2%), ALT increase (47.3% vs 37.1%). TEAE with an excess in incidence in the aflibercept arm between 5 and 10% over the placebo arm were: decrease appetite, palmar plantar erythrodysesthesia, dehydration, leucopenia and skin hyperpigmentation.	
Maximum dose tested	Single Dose	Not applicable
	Multiple Dose	Monotherapy: 7 mg/kg given as 1 hour IV infusion every 2 weeks. Combination: aflibercept at 9 mg/kg given as 1 hour IV infusion every 3 weeks and 7 mg/kg given as 1 hour IV infusion every 2 weeks in combination with various chemotherapy.

Exposures Achieved at Maximum Tested Dose	Single Dose	Not applicable
	Multiple Dose	<ul style="list-style-type: none"> Following 1 hour IV infusion at 7 mg/kg (n=12, TED6115), the mean C_{max} of free aflibercept is 159 µg/mL (21%) and mean AUC of free aflibercept is 605 µg.day/mL (46%). Following 1 hour IV infusion at 9 mg/kg (n=3, TCD6120), the mean C_{max} of free aflibercept is 198 µg/mL (19%) and mean AUC of free aflibercept is 805 µg.day/mL (34%).
Range of linear PK	Free aflibercept exposure increased slightly more than dose-proportionally between 1 and 2 mg/kg, then increased approximately proportionally between 2 and 4 mg/kg. POPPK analysis (POH0253) showed a dose proportional increase of free aflibercept C _{max} and AUC from 2 to 9 mg/kg.	
Accumulation at steady state	Based on population PK analysis, at 4 mg/kg every 2 weeks and 6 mg/kg every 3 weeks, the accumulation ratio for free aflibercept (AUC _{ss} /AUC ₀₋₃₃₆ and AUC _{ss} /AUC ₀₋₅₀₄ , respectively) was 1.2 and 1.1, respectively. After 4 mg/kg every 2 weeks, time to steady state estimated was 70 days (1680 h) which corresponds to the predose of the 6th aflibercept administration with 81% of C _{troughss} reached at the end of the first dose. For the 6 mg/kg q3w regimen, time to steady state was 84 days (2016h) which corresponds to the predose of the 5th aflibercept administration with 92% of C _{troughss} reached at the end of the first dose.	
Metabolites	As aflibercept is a fusion protein, no metabolism study was conducted. The expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino-acids.	
Absorption	Absolute/Relative Bioavailability	Not applicable, the drug is given IV.
	T _{max}	T _{max} of free aflibercept is reached at the end of infusion (1 hour).
Distribution	V _{ss}	Aflibercept exhibited a volume of distribution slightly greater than blood compartment with a patient population estimate of 7.8 L for V _{ss} in patients (POH0265), similar to that observed in healthy subjects.
	% bound	Saturable binding process of aflibercept to endogenous VEGF which translates in (Targeted mediated Drug Disposition).

Elimination	Route	<ul style="list-style-type: none"> • Catabolism of protein and clearance by its binding to VEGF.
	Terminal t _{1/2}	<ul style="list-style-type: none"> • In cancer patients (TED6115), mean free aflibercept terminal half-life increased from 1.7 day at the dose of 0.3 mg/kg to 3.76 days at the dose of 2 mg/kg and then, remained stable over the 2-9 mg/kg range (5 to 7 days). • In a typical patient at 4 mg/kg, free aflibercept terminal half life was 6 days (POH0265).
	CL	<ul style="list-style-type: none"> • In cancer patients (TED6115), mean free aflibercept clearance decreased from 1.95 L/day at the dose of 0.3 mg/kg to 1.13 L/day at the dose of 2 mg/kg and then, remained stable over the 2-9 mg/kg range (0.9 to 1.3 L/day). • In a typical patient at 4 mg/kg, free aflibercept clearance was 1.0 L/day (POH0265).
Intrinsic Factors	Age	No effect of age was identified (POH0265).
	Weight/Sex	<p>The slight effect of weight on free aflibercept clearance and volume of distribution combined with the weight-based dosing resulted in a slightly higher exposure in patients with higher body weight (AUC was 29% higher in the >100 kg patient category compared to the 50-100 kg category).</p> <p>Gender was the most significant covariate for explaining interindividual variability with a 15.5% higher clearance in males than in females and a 20.6% higher volume of distribution. However, no difference in AUC was noted between male and female probably due to weight-based dosing leading to higher total dose in males than in females. (POH0265).</p>
	Race	No effect of race was identified (POH0265).
	Hepatic & Renal Impairment	<p>Based on PK data from 549 mild, 96 moderate and 5 severe renal impaired patients, dose adjustment is not considered necessary in patients with renal impairment. Limited data are available in hepatic impaired patients (63 mild and 5 moderate).</p> <p>However, based on the available data, dose adjustment is not considered necessary in patients with mild and moderate hepatic impairment (no data in patients with severe hepatic impairment). (POH0265).</p>

Extrinsic Factors	Drug interactions	<ul style="list-style-type: none"> • In combination with various cytotoxic agents (including oxaliplatin, cisplatin, 5-FU, irinotecan, docetaxel, pemetrexed, gemcitabine and erlotinib), free aflibercept clearance was similar or slightly lower than when given as a single agent. The greatest effect was an 11.3% decrease of aflibercept clearance when combined with irinotecan/5-FU/leucovorin (TCD6118) but no effect was observed with FOLFIRI regimen. • No impact of aflibercept was observed on the pharmacokinetics of oxaliplatin, cisplatin, 5-FU, irinotecan, docetaxel, pemetrexed, gemcitabine and erlotinib.
	Food Effects	Not applicable, the drug is given IV.
Expected High Clinical Exposure Scenario	There have been no cases of overdose reported with aflibercept. There is no information on the safety of aflibercept given at doses exceeding 7 mg/kg every 2 weeks or 9 mg/kg every 3 weeks.	

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

/s/

KEVIN M KRUDYS
06/04/2012

NITIN MEHROTRA
06/04/2012

JANICE B BRODSKY
06/05/2012

JOANNE ZHANG
06/05/2012

MONICA L FISZMAN
06/05/2012

NORMAN L STOCKBRIDGE
06/05/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 125418/0

Name of Drug: Zaltap (aflibercept)

Applicant: sanofi-aventis, U.S., LLC

Labeling Reviewed

Submission Date: February 2, 2012

Receipt Date: February 3, 2012

Background and Summary Description

ZALTRAP is an original BLA application that is indicated in combination with irinotecan-fluoropyrimidine-based chemotherapy for patients with metastatic colorectal cancer (MCRC) previously treated with an oxaliplatin-containing regimen.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

Conclusions/Recommendations

HIGHLIGHTS:

1. Change Initial US approval “year” to “20XX”
2. Use command language
3. Avoid using IV as it is commonly mistaken for Roman number IV, use ‘intravenous’ instead
4. REVISED should be in Month/Year format

FULL PACKAGE INSERT

5. The same title for the boxed warning that appears in the Highlights and Full Package Insert must also appear at the beginning of the Table of Contents in upper-case letters and bold type.
6. Use command language
7. Do not use a “slash mark” to separate two doses since it may be mistaken as the number 1. Instead, use “per.”
8. Avoid using IV as it is commonly mistaken for Roman number IV, use ‘intravenous’ instead



All labeling deficiencies identified above will be conveyed to the applicant in an advice letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by May 21, 2012. The resubmitted labeling will be used for further labeling discussions.

Regulatory Project Manager Date

Chief, Project Management Staff Date

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 125418/0

Application Type: New BLA

Name of Drug: Zaltrap (aflibercept)

Applicant: sanofi-aventis, U.S., LLC

Submission Date: February 2, 2012

Receipt Date: February 3, 2012

1.0 Regulatory History and Applicant's Main Proposals

This application provides for a new BLA for Zaltrap (aflibercept) the treatment, in combination with irinotecan-fluoropyrimidine- based chemotherapy, of patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

Comments will be conveyed in an advice and information letter

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. HIGHLIGHTS:
 1. Change Initial US approval "year" to "20XX."
 2. Use command language.
 3. Avoid using IV as it is commonly mistaken for Roman number IV, use 'intravenous' instead.
 4. REVISED should be in Month/Year format.

FULL PACKAGE INSERT

RPM PLR Format Review of the Prescribing Information

5. The same title for the boxed warning that appears in the Highlights and Full Package Insert must also appear at the beginning of the Table of Contents in upper-case letters and bold type.
6. Use command language.
7. Do not use a “slash mark” to separate two doses since it may be mistaken as the number 1. Instead, use “per.”
8. Avoid using IV as it is commonly mistaken for Roman number IV, use ‘intravenous’ instead.

(b) (4)

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by DATE May 21, 2012). The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- Yes** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- Yes** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- Yes** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- Yes** 4. White space must be present before each major heading in HL.

Comment:

- Yes** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

Yes 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

Yes 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

Yes 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

Yes 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

Yes 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

NO 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Asked the Sponsor to Change Initial US approval from "year" to 20XX*

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

Yes 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

Yes 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

Yes 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Yes 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

NA 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment: *New NME*

NA 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

NA 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

NA 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

Yes 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- Yes** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- Yes** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- NA** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment: *Only one contraindication*

Adverse Reactions

- Yes** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- Yes** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Asked Sponsor to change the revision date to Month/Year format*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- Yes** 28. A horizontal line must separate TOC from the FPI.

Comment:

- Yes** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

NO

Selected Requirements of Prescribing Information (SRPI)

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment: *See comment below.*
- NO** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment: *Asked the Sponsor to use the same title for the boxed warning that appears in the Highlights and Full Package Insert must also appear at the beginning of the Table of Contents in upper-case letters and bold type*
- Yes** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- Yes** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- Yes** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- Yes** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- Yes** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- Yes** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- Yes** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers

Selected Requirements of Prescribing Information (SRPI)

8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- Yes** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- Yes** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- NA** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- Yes** 42. All text is **bolded**.

Comment:

- Yes** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- Yes** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Contraindications

NA 45. If no Contraindications are known, this section must state “None”.

Comment: *contains a contraindication*

Adverse Reactions

Yes 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

NA 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: *No Postmarketing Experience subsection*

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: *Asked Sponsor to add the statement for Patient Information labeling*

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

/s/

MELANIE B PIERCE
05/17/2012

KAREN D JONES
05/18/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 125418/0	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Zaltrap Established/Proper Name: aflibercept Dosage Form: Injection for intravenous infusion Strengths: 4 mg/kg		
Applicant: sanofi-aventis, U.S., LLC Agent for Applicant (if applicable): NA		
Date of Application: February 3, 2012 Date of Receipt: February 3, 2012 Date clock started after UN:		
PDUFA Goal Date: August 4, 2012	Action Goal Date (if different):	
Filing Date: April 3, 2012	Date of Filing Meeting: March 28, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) NA		
Proposed indication: Treatment, in combination with irinotecan-fluoropyrimidine- based chemotherapy, of patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input checked="" type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 9948				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>				
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>				
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?				
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not 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.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			Proprietary name granted February 16, 2012
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		Justification for not submitting a REMS was provided
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): October 11, 2007-CMC; June 14, 2007 <i>If yes, distribute minutes before filing meeting</i>	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): July 7, 2011 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 28, 2012

BLA: 125418/0

PROPRIETARY NAME: Zaltrap

ESTABLISHED/PROPER NAME: aflibercept

DOSAGE FORM/STRENGTH: Injection for intravenous infusion

APPLICANT: sanofi-aventis, U.S., LLC

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

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Melanie Pierce	Y
	CPMS/TL:	Karen Jones	N
Cross-Discipline Team Leader (CDTL)	Steven Lemery		Y
Clinical	Reviewer:	Sandra Casak	Y
	TL:	Steven Lemery	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Ruby Leong	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Kun He	Y
	TL:	Jenny Zhang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Alexander Putman	Y
	TL:	Andrew McDougal (acting)	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Sarah Kennett	Y
	TL:	Chana Fuchs	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:	Kimberly Rains	
	TL:		
Facility Review/Inspection	Reviewer:	Michele Clark Stuart/Kalavati Suvarna	Y
	TL:	Patricia Hughes	Y
OSE/DMEPA (proprietary name)	Reviewer:	James Schlick	N
	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

N	Reviewer:	Lauren Iaconno-Connor	N
	TL:	Tejashri Purohit-Sheth	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Kevin Krudys		Y
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments: Will consult SGEs</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: All

<p><i>or efficacy issues</i></p> <ul style="list-style-type: none"> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: Review issues identified in the information request issued on 3.26.12. Resolved on 3.28.12. Additional non-filing comments sent in the filing letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: will be performed by (OMPQ)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Richard Pazdur</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
<p>REGULATORY CONCLUSIONS/DEFICIENCIES</p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
<p>ACTIONS ITEMS</p>	
<p><input checked="" type="checkbox"/></p>	<p>Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).</p>
<p><input type="checkbox"/></p>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).</p>
<p><input type="checkbox"/></p>	<p>If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>

<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

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

/s/

MELANIE B PIERCE
04/12/2012

KAREN D JONES
04/13/2012

Determining when Pre-License/Pre-Approval Inspections are Necessary for Biologic License Applications Submitted to CDER

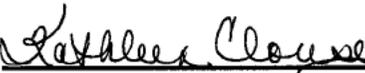
Inspection Waiver Memorandum

Date: 1 April 2012
From: Michelle Y. Clark-Stuart, MGA, Interdisciplinary Scientist, CDER/OC/OMPQ/DGMPA/BMAB
Sarah Kennett, Ph.D., Biologist, OPS/OBP/DMA
To: BLA File – STN #125418/0
Subject: Recommendation to waive a pre-license or pre-approval inspection
Applicant: Sanofi-Aventis US, LLC, U.S. License # 1752
Facility: [REDACTED] (b) (4)
[REDACTED] contract manufacturer
Product: aflibercept, Zaltrap®
Indication: Treatment of patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen
Through: Patricia Hughes, Ph.D., Team Leader, BMAB/DGMPA/OC
Chana Fuchs, Ph.D., Team Leader, DMA/OBP/OPS  4/19/12

Waiver Recommendation

Proposal to waive the pre-license inspection for BLA 125418/0 drug substance manufacturer based on the acceptable compliance status of the contract manufacturer, [REDACTED] (b) (4) [REDACTED] that covered the full Zaltrap® drug substance manufacturing process as described under BLA 125418/0.

Clearance Routing

CONCUR	DO NOT CONCUR	DATE
David Doleski, Acting Director, Division of Good Manufacturing Practice Assessment Office of Compliance, CDER		
<hr/>		
		04/19/2012
CONCUR	DO NOT CONCUR	DATE
Kathleen Clouse, Ph.D., Director, Division of Monoclonal Antibodies, Office of Biotechnology products, Office of Pharmaceutical Science, CDER		

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

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

/s/

MICHELLE Y CLARK STUART
05/10/2012

PATRICIA F HUGHES TROOST
05/10/2012