

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125418Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125418 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Oncology Products 2 PDUFA Goal Date: August 4, 2012 Stamp Date: _____

Proprietary Name: Zaltrap

Established/Generic Name: aflibercept

Dosage Form: Injection for intravenous infusion;4 mg/kg

Applicant/Sponsor: sanofi-aventis

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

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

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

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pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)
- Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

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drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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
03/28/2012

DEBARMENT CERTIFICATION

Sanofi-aventis 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.

A handwritten signature in black ink, appearing to read "Richard P. Gural", written over a horizontal line.

Richard Gural Ph.D.

Head, Global Regulatory Affairs

sanofi-aventis US Inc.

On behalf of sanofi-aventis US LLC

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 125418/0	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: ziv-aflibercept Established/Proper Name: Zaltrap Dosage Form: Injection		Applicant: sanofi-aventis, U.S., LLC Agent for Applicant (if applicable):
RPM: Melanie Pierce		Division: Division of Oncology Products 2
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>August 3, 2012</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input checked="" type="checkbox"/> Yes, dates 7.12.12; 7.25.12; 8.01.12
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other Burst

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) August 3, 2012
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	July 20, 2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	February 2, 2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. • Original applicant-proposed labeling • Example of class labeling, if applicable 	<p>February 2, 2012- PPI is at the end of the PI</p>
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) • Most-recent draft labeling 	<p>Original , February , 2012; Most recent: July 27, 2012</p>
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	<p>February 16, 2012 June 18, 2012 February 14, 2012</p>
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 5/18/12 <input checked="" type="checkbox"/> DMEPA 6/18/12 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 7.20.12 <input checked="" type="checkbox"/> ODPD (DDMAC) 7.11.12 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews Maternal Health 07.09.12; OBP 7..27.12; 6/27/12
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<p>4.12.12-filing review 3.28.12-filing minutes</p> <input type="checkbox"/> Not a (b)(2) <input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included
Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>6.6.12-minutes received 6/25/12 Original page uploaded 3.28.12.</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before</i>) 	<p>6/6/12</p> <input checked="" type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<i>finalized)</i>	
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>) ❖ Communications are ordered by the date the communication was uploaded in DARRTS; original dates of the meeting/tcon or internal minutes are reflected in the parenthesis 	<p>8.02.12-labeling 8.02.12; Tcon minutes (originally held 7.27.12) 8.01.12-labeling (originally sent 7.31.12 7.31.12 Labeling (originally sent 7.30.12) 7.31.12 email-(originally sent 7.25.12) 7.30.12-exclusivity letter 7.27.12 7.23.12-tcon (originally held 7.17.12 7.23.12-labeling; (originally sent 7.17.12) 7.17.12-letter 7.13.12-IR carton container 7.13.12-post-midcycle minutes-(originally held 5.15.12) 7.12.12-tcon (held 7.05.12) 7.12.12 tcon originally (held 6.29.12) 7.10.12-tcon (originally held 7.02.12) 07.06.12-PMC Comments 07.06.12-labeling comments-(originally sent 07.03.12) 06.26.12-IR Memo 06.18.12-IR Memo 06.11.12-IR Memo- 06.11.12-IR Memo 06.11.12; IR-Memo (sent - 06.05.12) 06.01.12-IR Memo 05.21.12-IR Memo 05.16.12-AI Ltr 04.27.12-IR Memo 04.27.12-IR Memo 04.03.12-FL Ltr 3.26.12-IR memo 2.21.12IR Ltr 2.17.12-ack ltr 2.17.12-IR memo</p>
<ul style="list-style-type: none"> ❖ Internal memoranda, telecons, etc. ❖ Communications are ordered by the date the communication was uploaded in DARRTS; original dates of the meeting/tcon or internal minutes are reflected in the parenthesis 	<p>7.25.12 Wrap-up minutes originally held 7.12.12 7.23.12-team meeting #3 minutes (originally held 6.13.12) 7.12.12 labeling meeting (held on 5.30.12)</p>

	7.11.12 Labeling-meeting (held on 6.29.12) 7.11.12 Labeling meeting (held on 6.19.12) 7.11.12 Labeling meeting (held on 6.13.12) 7.11.12 Labeling meeting (held on 6.07.12) 7.10.12 Team meeting minutes (held on 4.27.12) 6.15.12Midcycle minutes; meeting (held on 5.09.12) 4.03.12 Planning minutes (held 2.28.12)
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 7.07.11
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 07.13.07
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8.02.12
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7.26.12
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7.13.12
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 8
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	Concurrence in clinical review-see CDTL review
• Clinical review(s) (<i>indicate date for each review</i>)	07.05.12; 03.30.12-filing rev.
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Pg 41 of the clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None 7.27.12; 7.17.12-Biological Product Working Naming Group
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable

⁶ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 07.05.12
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None concurrence in stat review 7.10.12
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None concurrence in stat. review 7.05.12
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 07.10.12;03.28.12-filing rev.
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None concurrence in pharm/tox review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 07.09.12; 03.30.12-filing rev
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None 7.31.12
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 07.10.12
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 0705.12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None concurrence in Quality review; 07.06.12
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None concurrence in Quality review; 07.06.12
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 07.06.12; 03.29.12-filing rev.
❖ Microbiology Reviews		<input type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		8.03.12-DS 07.03.12; 07.03.12 DP waiver memorandum; DS waiver memorandum 5.10.12; 03.28.12-filing review
<input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		page 7 of the Quality review
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: 05.16.12; 05.16.12; 07.03.12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

MELANIE B PIERCE
08/03/2012



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

Memorandum

Date: August 2, 2012
From: Melanie Pierce, DBOP/OODP/CDER
Subject: Labeling Memo: Zaltrap (ziv-aflibercept): BL STN 125418/0

FDA's proposed revisions to the package insert, sent to sanofi-aventis, U.S., LLC, on August 2, 2012.

Revisions to the package insert include changes made on August 2, 2012 to the following sections:

Full Prescribing Information:

- Revise font size of the main headers.
- Change spacing between main headers for consistency throughout label.

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/s/

MELANIE B PIERCE
08/03/2012



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

Memorandum

Date: August 1, 2012
From: Melanie Pierce, DBOP/OODP/CDER
Subject: Labeling Memo: Zaltrap (ziv-aflibercept): BL STN 125418/0

FDA's proposed revisions to the package insert, sent to sanofi-aventis, U.S., LLC, on August 1, 2012.

Revisions to the package insert include changes made on August 1, 2012 to the following sections:

- Highlights:
 - Add date for initial U.S. Approval:
 - Add Revised date:
- Boxed Warning
- Section 5.7: WARNINGS AND PRECAUTIONS: Proteinuria
- All sections: Inconsistent fonts throughout the label.

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/s/

MELANIE B PIERCE
08/01/2012



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

Memorandum

Date: July 31, 2012
From: Melanie Pierce, DBOP/OODP/CDER
Subject: Labeling Memo: Zaltrap (ziv-aflibercept): BL STN 125418/0

FDA's proposed revisions to the package insert, sent to sanofi-aventis, U.S., LLC, on July 31, 2012.

Revisions to the package insert include changes made on July 31, 2012 to the following sections:

- Highlights
- Section 2.2: DOSAGE AND ADMINISTRATION: Dose Modification/Treatment Delay Recommendations
- Section 2.4: DOSAGE AND ADMINISTRATION: Administration
- Section 5.7: WARNINGS AND PRECAUTIONS: Proteinuria

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/s/

MELANIE B PIERCE
08/01/2012



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

Memorandum

Date: July 25, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; Advice/Information request-email

The following email was sent to Elma Fernandes, Authorized representative for sanofi-aventis on July 25, 2012:

FDA informed sanofi-aventis that [REDACTED] ^{(b) (4)} data from only 3 batches, [REDACTED] ^{(b) (4)} are needed because only one sampling point will be introduced. As a result, the timeline for submission of the final study report can be revised to occur prior to December 2016.

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/s/

MELANIE B PIERCE
07/31/2012



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

Memorandum

Date: July 30, 2012
From: Melanie Pierce, DBOP/OODP/CDER
Subject: Labeling Memo: Zaltrap (ziv-aflibercept): BL STN 125418/0

FDA's proposed revisions to the package insert, sent to sanofi-aventis, U.S., LLC, on July 30, 2012.

Revisions to the package insert include changes made on July 27, 2012 and July 30, 2012 to the following sections:

- Highlights
- Table of Contents
- Boxed Warnings (Highlights and Full Package Insert)
- Section 1: INDICATIONS AND USAGE
- Section 2.2: DOSAGE AND ADMINISTRATION: Dose Modification/Treatment Delay Recommendations
- Section 2.4: DOSAGE AND ADMINISTRATION: Administration
- Section 5.3: WARNINGS AND PRECAUTIONS: Compromised Wound Healing
- Section 5.7: WARNINGS AND PRECAUTIONS: Proteinuria
- Section 6: ADVERSE REACTIONS
- Section 12.1: CLINICAL PHARMACOLOGY: Mechanism of Action
- Section 14: CLINICAL STUDIES
- Section 17: PATIENT COUNSELING INFORMATION

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/s/

MELANIE B PIERCE
07/31/2012



BL STN: 125418/0

GENERAL ADVICE

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

Dear Dr. Fernandes:

Please refer to your Biologics License Application (BLA) submitted under section 351 of the Public Health Service Act (PHS Act) for ZALTRAP (ziv-aflibercept).

We also refer to your April 24, 2012, submission, containing a request for 12- year exclusivity under PHSA section 351(k)(7).

We have the following comments and requests for additional information:

In order to evaluate whether the proposed product meets the exclusivity criteria described in 351(k)(7) of the BPCI Act, please provide the following information.

1. A list of all related products to “aflibercept” for which you or one of your affiliates, including any licensors, predecessors in interest, successors in interest or related entities, are the current or previous license holder. This list should include, but is not limited to, products that have the same primary therapeutic target(s) (i.e., target ligands [VEGF-A, VEGF-B, PlGF-2, PlGF-1]) and share some, but not necessarily all, of the same principal molecular structural features.[1] If your assessment results in no related products, please provide an adequate justification to support your assertion that the proposed product is unrelated to any product.
2. Description of the structural differences between the proposed product and any related products identified in question 1. For purified therapeutic protein products, this should include, but is not limited to, changes in amino acid sequence, differences due to post-translational events, infidelity of translation or transcription, differences in glycosylation patterns or tertiary structure, and differences in biological activities.[2]
3. Description of the change in safety, purity and/or potency between the proposed product and any related products identified in question 1. This should include, but is not limited

[1] See, for example, 21 CFR 316.3(b)(13).

[2] Biological activities can be an important measure of structural changes.

to, a description of how the changes identified in question 2 relate to changes in safety, purity and/or potency.

Please include any other information and data that would assist the FDA in making an exclusivity determination.

If you have any questions, call Melanie Pierce, Senior Regulatory Health Project Manager, at (301) 796-1273.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
07/30/2012



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

Memorandum

Date: July 17, 2012
From: Melanie Pierce, DBOP/OODP/CDER
Subject: Labeling Memo: Zaltrap (aflibercept): BL STN 125418/0

FDA sent the attached label, containing FDA's proposed changes to the package insert, to sanofi-aventis, U.S., LLC on July 17, 2012.

Changes to the package insert were made during a labeling meeting conducted on July 11, 2012 and during subsequent internal sessions on July 12 and 13, and 16, 2012.

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



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

Memorandum

Date: July 17, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; Advice/Information request-teleconference

FDA Attendees:

Patricia Keegan
Melanie Pierce

sanofi-aventis, U.S., LLC Attendees

Noemi Guma

Date and time of teleconference: July 17, 2012; 4:20 p.m.

Dr. Patricia Keegan informed Noemi Guma, alternate representative for Elma Fernandes, that the nonproprietary name “aflibercept,” is not acceptable for BLA application 125418/0 because it has the same nonproprietary name as EYLEA (aflibercept), which is currently marketed in the U.S.

FDA concluded that a different nonproprietary name would minimize the possibility of medication errors and reduce confusion among healthcare practitioners who may consider use of the same nonproprietary name to mean the biological products are indistinguishable. As a result, sanofi must modify the nonproprietary name to include a 3-4 character prefix before “aflibercept” separated by an underscore. The name must not be promotional, convey a specific meaning or be similar to a currently marketed product. Sanofi must also exercise due diligence to ensure that there are no other restriction on their use. FDA suggested sanofi follow the model used with the boulinum toxin or asparaginase products as a reference.

FDA requested sanofi rank-order the top three candidates and submit to FDA by close of business, Friday, July 20, 2012.

Sanofi expressed understanding, agreed to submit the requested information by Friday, July 20, 2012.

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/s/

MELANIE B PIERCE
07/23/2012



BLA 125418/0

GENERAL ADVICE

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

Dear Dr. Fernandes:

Please refer to your Biologics License Application (BLA), submitted under section 351 of the Public Health Service Act for ZALTRAP “aflibercept.”

We are in the process of completing our review of your application and have the following comments and requests for additional information:

We have determined that your proposed proper name “aflibercept” is not acceptable for this BLA submitted under section 351(a) of the PHS Act. If your proposed product has the same nonproprietary name as EYLEA (aflibercept), which is currently marketed in the U.S., the following may result:

- Medication errors, including:
 - the patient receiving a product different than what was intended to be prescribed
 - confusion among healthcare practitioners who may consider use of the same nonproprietary name to mean that the biological products are indistinguishable
- Limitations in the ability to conduct appropriate pharmacovigilance

To mitigate our above concerns, we are requiring the use of a prefix before “aflibercept” separated by an underscore, “prefix_aflibercept,” as the proper name of the biological product that is the subject of this BLA. Please propose three prefixes (in order of preference) for your nonproprietary name. In your proposal, the prefixes should:

- be 3 to 4 letter characters in length;
- not be promotional;
- not convey a specific meaning; and
- not look or sound similar to, or be confused with, a currently marketed product.

In addition, we encourage you to conduct due diligence on your proposed prefixes to ensure there are no other restrictions on their use in this context.

If you have any questions, call Melanie Pierce, Senior Regulatory Health Project Manager, at (301) 796-1273.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
07/17/2012



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

Memorandum

Date: July 13, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; Advice/Information Request: Carton/Container Labeling

Please refer to your Biologics License Application (BLA) submitted February 2, 2012 under section 351 of the Public Health Service Act (PHS Act) for Zaltrap (aflibercept).

We are in the process of reviewing your application and have the following comments and requests for additional information regarding your carton and container 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.
 - b. Each vial size presentation is capable of bearing a full label. Per 610.60, add the manufacturer's license number.
 - c. Please provide a justification for two distinct labels for the 100 mg/4 mL vial strength.
2. Carton label:
 - a. Add the required statement, "No U.S. Standard of Potency" per 21 CFR 610.61.
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).
 - 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.

*Recommended format

Zaltrap
(aflibercept)
Injection

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)

Division of Medication Error and Prevention Analysis comments:

Container Labels:

5. Revise the presentation of the proper name, '(xxxxxx) (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).

6. Revise the presentation of the proprietary name from all upper case letters (ZALTRAP), to title case (Zaltrap) to improve readability.

7. Remove the statement (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.

Carton Labeling:

8. See container label comment 6 and revise carton labeling accordingly.

9. Revise the statement '(xxxxxxx) (b) (4) for intravenous infusion' to:
'(xxxxxxx)
Injection'

NOTE: The removal of (b) (4) and placement of the word 'Injection'.

10. 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)

11. 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. (b) (4) to 'For intravenous infusion only. Not to be administered by other routes.'

b. (b) (4) to 'Hyperosmotic, must be diluted.'

For intravenous infusion only. Not to be administered by other routes. Color background

- 12. Revise the statements (b) (4) to 'single-use vial(s). Discard unused portion'.

- 13. Change the warning statement (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.

If you have further questions or need clarifications regarding the DMEPA comments, please contact Sue Kang, project manager, at 301-796-4216. For all other questions, please call me at 301-796-1273.

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MELANIE B PIERCE
07/13/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: July 12, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: Wrap up meeting minutes: Zaltrap: BL STN 125418/0

Original Application: BL STN 125418/0:

Product: Zaltrap
Submission Date: February 2, 2012
Received Date: February 3, 2012
Sponsor: sanofi-aventis, U.S., LLC
Indication: Treatment, in combination with irinotecan-fluoropyrimidine- based chemotherapy, of patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen.

A wrap-up meeting for Zaltrap application 125418/0 was held on July 12, 2012. Attendees included: Patricia Keegan, Steve Lemery, Sandra Casak Hong Zhao, Ruby Leong, Alexander Putman, Jenny Zhange, Sarah Kennett, Kimberly Rains, Kevin Krudys, Carole Broadnax, Sue Kang, James Schlick, Barbara Fuller, Robert Pratt, Khalavati Suvarna, Anthony Murgo, Karen Jones, Cynthia LaCivita and Melanie Pierce

All review disciplines recommended approval for ZALTRAP application 125418/0.

Labeling negotiations are still on-going. A teleconference will be scheduled with sanofi-aventis to discuss excluding the patient package insert from the label.

PMC negotiations are still ongoing between FDA and sanofi-aventis.

FDA intends to issue an advice and information letter regarding the use of "aflibercept" as the proper name.

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/s/

MELANIE B PIERCE
07/25/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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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

(b) (4) **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.

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/s/

MELANIE B PIERCE
07/06/2012



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

Memorandum

Date: July 5, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; Advice/Information request-teleconference

The following was communicated to sanofi-aventis via a teleconference on July 5, 2012.

FDA Attendees:

Chana Fuchs
Sarah Kennett

sanofi-aventis, U.S., LLC Attendees

Elma Fernandes
Shamim Ruff
Noemi Guma

FDA referenced section 3.2.S.4.1 Table 1 - *specifications for drug substance*:

Sanofi uses the terminology (b) (4) for release criteria and "regulatory" for shelf-life. FDA considers all the acceptance criteria as regulatory. FDA requested Sanofi change Table 1 to reflect that both release and shelf-life acceptance criteria are regulatory. Sanofi agreed to drop these descriptors so both would be considered regulatory.

Drug Product annual stability protocol is currently for testing at 0, 12, 24, and 36 months timelines. FDA requested that sanofi add more timepoints in the first year. Sanofi agreed to update the protocol to specify testing at 0, 3, 6, 12, 24, and 36 months.

FDA verified that sanofi will send updates to sections 3.2.S.7.3 and 3.2.P.8.3 as these were not included in the emails from before. Sanofi confirmed that the protocol revisions will be submitted July 6, 2012.

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/s/

MELANIE B PIERCE
07/12/2012



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

Memorandum

Date: July 3, 2012
From: Melanie Pierce, DBOP/OODP/CDER
Subject: Labeling Memo: Zaltrap (aflibercept): BL STN 125418/0

FDA sent the attached label, containing FDA's proposed changes to the package insert, to sanofi-aventis, U.S., LLC on July 3, 2012.

Changes to the package insert were made during labeling meetings conducted on the following days:

- May 24, 2012
- May 30, 2012
- June 7, 2012
- June 13, 2012
- June 19, 2012

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

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MELANIE B PIERCE
07/06/2012



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

Memorandum

Date: July 2, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; Advice/Information request-teleconference

The following email was sent by Sue Kang, Project Manager in the Office of Surveillance and Epidemiology, to Elma Fernandes, Regulatory contact for sanofi-aventis, U.S., LLC, on July 2, 2012.

Ms. Fernandes,

I refer you to the Conditionally Acceptable Letter dated February 16, 2012 for Zaltrap (afibercept) BLA 125418. In this letter, it states that the proposed proprietary name will be re-reviewed 90 days prior to the approval of the BLA. The proprietary name has been re-reviewed and the Division of Medication Error Prevention and Analysis (DMEPA) still finds the name acceptable, as long as your BLA is approved by the goal date.

If you have any further questions regarding your proprietary name submission, please do not hesitate to contact me.

Kind regards

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/s/

MELANIE B PIERCE
07/10/2012



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

Memorandum

Date: June 29, 2012

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: Labeling Memo: Zaltrap (aflibercept): BL STN 125418/0

FDA's proposed revisions as discussed during the June 29, 2012 labeling meeting.

Attendees: Patricia Keegan, Casak, Sandra; Steven Lemery, Hong Zhao, Jun Yang, Ruby Leong, Andrew McDougal, Alexander Putman

Sections covered include:

- Section 8.1: USE in SPECIFIC POPULATIONS: Pregnancy
- Section 8.3 USE in SPECIFIC POPULATIONS: Nursing Mothers
- Section 8.8 USE in SPECIFIC POPULATIONS: Females and Males of Reproductive Potential
- Section 12.1: CLINICAL PHARMACOLOGY: Mechanism of Action
- Section 12.3: CLINICAL PHARMACOLOGY: Pharmacokinetics
- Section 13.1: NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, Impairment of Fertility
- Section 13.2: NONCLINICAL TOXICOLOGY: Animal Toxicology and/or Pharmacology

- [REDACTED] (b) (4)

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/s/

MELANIE B PIERCE
07/11/2012



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

Memorandum

Date: June 29, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; Advice/Information request-teleconference

The following was communicated to sanofi-aventis on June 29, 2012, via a teleconference.

FDA Attendees:

Melanie Pierce
Sarah Kennett
Chana Fuchs

sanofi-aventis, U.S., LLC Attendees

Elma Fernandes
Michael Bloomstein
Danielle Grelet
Shamim Ruff
Dinesh Prandare
Shreeram Agharkar

Specification acceptance criteria:

Drug Product (DP) is the link to the clinical studies, so the DP criteria are key, and stability limits also need to be linked back to what was used in the clinical studies.

It appears that sanofi's process for generating proposed criteria included opposite thinking for those parameters where a criterion for drug substance (DS) was identified, an addition was made for stability of DS, (b) (4) and an addition was made for DP stability.

EYELA data cannot automatically be used for Zaltrap, since they are different with respect to DP, (b) (4)

In addition, in the BLA specifications discussions (with reference to the stability summary), a statistical evaluation is performed according to ICH Q1E; ICH Q1E is a guideline for evaluation of stability for setting shelf life (when the acceptance criterion is known), not for determining stability specifications. (b) (4)

Careful consideration must be given when using linear regression for biotechnology products, because many times it is not appropriate; these products often do not behave in the same manner as small molecules.

Potency Bioassay – (b) (4)

- Assay variability is taken into account by using actual data
- No material was released outside or near this range
- There may be an occasional out of specification (OOS) results. The assay variability

aspect of this can be managed at least in part by OOS procedures and the possibility of retesting, if there was any error or system/assay/sample suitability issues, or repeat testing, where additional numbers of datapoints can overcome some amount of assay variability.

- Note that there should be an assay control in your assay; this is a control that is different from the reference standard and would be qualified as an assay control (basically, it would be a different lot of DS or DP for which you have a good grasp of its response in this assay- and also the binding assay). This control would be run similarly to the samples and would have its own set of suitability requirements. An assay control could help in identifying assays that should be invalid or in OOS investigations.



A PMC will be set to add conductivity testing to the DP release specification. PMCs will be sent to sanofi separately for agreement and to provide dates for submission.

Container Closure Integrity was not on the list we sent, because that list was based on the release specifications table, but we expect CCI to remain on the stability protocols.

There is a typo (originally mine) in the endotoxin acceptance criterion for DP. It should be (b) (4)

For the annual lots that are included in the post approval stability commitment for DP, the vial presentations selected should vary from year to year to ensure a balanced program (e.g., 100 mg vial the first year and a 200 mg vial the following year). This, of course, would be flexible around the presentations are actually manufactured in any given year. If this concept can be written into the post approval stability section, we will not need to include this in a PMC.

(b) (4)



Endotoxin:

The effect that is currently of concern is not the focus of the cited publication, although figures in this publication may show a similar effect. (b) (4)



Sanofi-aventis expressed understanding and proposed to respond by Tuesday, July 2, 2012.

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/s/

MELANIE B PIERCE
07/12/2012



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

Memorandum

Date: June 26, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; Advice/Information request

Please refer to your Biologics License Application (BLA) submitted February 2, 2012 under section 351 of the Public Health Service Act (PHS Act) for Zaltrap (afibercept).

We are in the process of reviewing your application and have the following comments and requests for additional information:

1. Based on the data available so far from your commercial drug product manufacturing, please revise the (b) (4) bioburden limit (b) (4). The (b) (4) protocol should also specify these same limits.
2. In the amendment eCTD sequence 0010 dated April 18, 2012, you state in response to item no 19, that a deviation assessment will be made for failure to meet the bioburden acceptance criterion. Calculations of bioburden (b) (4) should not be used (b) (4). Please note that your (b) (4) protocol should clearly state that (b) (4) will not be permitted when the bioburden acceptance criterion is not met.
3. Please clarify the following with respect to drug product manufacturing:
(b) (4)
4. Please provide (b) (4)
(b) (4) Please provide calculation of safety margin (b) (4)
5. Please clarify the positive control used for testing of container closure integrity during stability (red dye immersion test). It should be noted that different (b) (4) were not evaluated during the validation of the red dye immersion test for container closure integrity. Also product-filled vials were not tested to determine if product has any interference. We recommend that you add a spectrophotometric method for detection of dye in addition to visual inspection.

6. Please note that validation data on minimum and maximum loads using summer and winter profiles for the commercial shipping container were not included. A shipping validation study should be conducted.

Please respond by 6/29/2012.

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

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/s/

MELANIE B PIERCE
06/26/2012

Pierce, Melanie

From: Greeley, George
Sent: Monday, June 25, 2012 11:22 AM
To: Pierce, Melanie
Cc: Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Keegan, Patricia
Subject: BLA 125418 Zaltrap (Amended)

Importance: High

Attachments: 1_Pediatric_Page.pdf

Hi Melanie,

The email serves as confirmation of the review for Zaltrap (Aflibercept) conducted by the PeRC PREA Subcommittee on June 6, 2012.

The Division presented a full waiver in pediatric patients for this product because this disease/condition does not exist in children. Zaltrap was studied for the treatment, in combination with irinotecan-fluoropyrimidine based chemotherapy, of patients with metastatic colorectal cancer previously treated with an oxiliplatin-containing regimen.

The PeRC agreed with the Division to grant a full waiver in pediatric patients because the disease/condition does not exist in children.

The PeRC recommends:

- ***Division should consider whether this product would be appropriate for issuance of a Written Request.***
- ***There are other indications to consider for this product and the Division should contact DTOP when drafting a Written Request.***

The pediatric page is attached for Zaltrap. Please upload the pediatric page into DARRTS at your earliest.



1_Pediatric_Page.pdf (110 KB)

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

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/s/

MELANIE B PIERCE

07/10/2012

pediatric waiver granted, see attached memo.



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

Memorandum

Date: June 19, 2012

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: Labeling Memo: Zaltrap (aflibercept): BL STN 125418/0

FDA's proposed revisions as discussed during the June 19, 2012 labeling meeting.

Attendees: Patricia Keegan, Casak, Sandra; Steven Lemery, Hong Zhao, Jun Yang, Kevin Krudys, Ruby Leong, James Schlick

Sections covered include:

- Section 6.2: ADVERSE REACTION: Immunogenicity
- Section 7: DRUG INTERACTIONS
- Section 12: CLINICAL PHARMACOLOGY: Pharmacokinetics

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/s/

MELANIE B PIERCE
07/11/2012



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

Memorandum

Date: June 18, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; Advice/Information request

Please refer to your Biologics License Application (BLA) submitted February 2, 2012 under section 351 of the Public Health Service Act (PHS Act) for Zaltrap (aflibercept).

We are in the process of reviewing your application and have the following comment and request for additional information:

CHEMISTRY, MANUFACTURING and CONTROLS:

Regarding the (b) (4) submitted in the June 1, 2012 response to information request:

1. Release and characterization evaluations:

(b) (4)

2. Stability evaluations:

(b) (4)

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

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/s/

MELANIE B PIERCE
06/18/2012



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

Memorandum

Date: June 13, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: Team Meeting # 3 Minutes: Zaltrap (afibercept): BL STN 125418/0

Original Application: BL STN 125418/0:

Product: Zaltrap (afibercept)

Submission Date: February 3, 2012

Received Date: February 3, 2012

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

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

Review Team:

Regulatory Project Manager	Melanie Pierce
Clinical Reviewer	Sandra Casak
Pharm/Tox Reviewer	Alexander Putman
Clinical Pharmacology Reviewer	Ruby Leong
Biostatistician	Jenny Zhang
Quality Reviewer	Sarah Kennett
Quality RPM (label review)	Kimberly Rains
Pharmacometrics Reviewer	Kevin Krudys
OSE Project Manager	Sue Kang
OSE (DMEPA)	James Schlick
OSE (DMEPA)	Barbara Fuller
OSE (DPV)	Bob Pratt
Facilities	Patricia Hughes
	Michelle Clark-Stuart
	Khalavati Suvarna
MHT Reviewer	Tammie Brent-Howard

TIMELINES:

- Day 30-Filing/planning meeting
- Day 45-Application Orientation

PRIORITY

February 28, 2012
February 10, 2012

Team Meeting minutes

BL STN: 125418/0

- Filing Meeting scheduled March 28, 2012
- Day 60-Filing Notification April 3, 2012
- Day 74-Deficiencies Identified April 17, 2012
- Mid-Cycle Scheduled May 9, 2012
- Primary Reviews Due July 7, 2012
- Secondary Reviews Due July 11, 2012
- Communication PMRs/PMCs/REMS July 7, 2012
- Communication of labeling July 7, 2012
- Wrap-up meeting Due July 12, 2012
- CDTL Review July 14, 2012
- Division Director sign-off July 25, 2012
- Office Director sign-off August 4, 2012
- Action Due Date August 4, 2012

UPCOMING MEETINGS:

- Filing March 28, 2012
- Mid-Cycle May 9, 2012
- Labeling May 24, 2012
May 30, 2012
June 7, 2012
June 13, 2012
June 19, 2012
July 11, 2012
- Team April 27, 2012
May 23, 2012
June 13, 2012
- Wrap-up July 12, 2012

Attendees: Sandra Casak, Steve. Lemery, Kalavati. Suvarna, Ruby. Leong, Kevin. Krudys, Sarah Kennett, Chana Fuchs, Kimberly Rains, Alexander Putman, Andrew McDougal, James Schlick, Michelle Clark-Stuart

Clinical:

- No updates; reviews are complete. One PMC will be generated

Statistical:

- No updates; review is close to completion

Nonclinical:

- No updates; review is close to completion are needed

Clinical Pharmacology:

- Review is ongoing-No PMCs or PMRs are needed

Quality:

- Numerous information requests will be sent to the Sponsor

Team Meeting minutes

BL STN: 125418/0

Facilities

- Drug substance and drug product inspections are waived
- Clinical inspections in the Czech Republic and Russia are acceptable. Inspection of the New Jersey site encountered problems. FDA asked for additional analyses; sanofi provided the requested information which was determined to be acceptable by FDA.
- One PMC and an additional information request will be sent to the Sponsor

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/s/

MELANIE B PIERCE
07/23/2012



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

Memorandum

Date: June 13, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: Labeling Memo: Zaltrap (aflibercept): BL STN 125418/0

FDA's proposed revisions as discussed during the June 13, 2012 labeling meeting.

Attendees: Patricia Keegan, Casak, Sandra; Steven Lemery, Sarah Kennett, James Schlick, Kimberly Rains

Sections covered include:

- Section 2.3: DOSAGE and ADMINISTRATION: Dose Modification/Treatment delay Recommendation
- Section 6.2: ADVERSE REACTION: Immunogenicity
- Section 11: DESCRIPTION
- Section ^{(b) (4)}: CLINICAL STUDIES (b) (4)
- Section 16.1: HOW SUPPLIED/STORAGE and HANDLING; How Supplied
- Section 17: PATIENT COUNSELING INFORMATION

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/s/

MELANIE B PIERCE
07/11/2012



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

Memorandum

Date: June 11, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; Advice

Dr. Sandra Casak communicated the following email to sanofi-aventis on June 11, 2012.

I have a question regarding the timing of the blood pressure assessments used for Figures 24, 25, 26 & 27 of the final study report of VELOUR, showing the mean blood pressure assessments by cycle. Were these measurements assessed prior to aflibercept/irinotecan dosing, after dosing, at Day 8 of each cycle, or these are averages of different assessments within 1 cycle? My question has to do with the fact that there is an increase in BP between baseline and 1st cycle, indicating that the assessment was performed after dosing, however in the study chart physical examination is scheduled to be performed before each cycle.

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/s/

MELANIE B PIERCE
06/11/2012



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

Memorandum

Date: June 11, 2012

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: BLA 125418/0; Advice/Information request

Please refer to your Biologics License Application (BLA) submitted February 2, 2012 under section 351 of the Public Health Service Act (PHS Act) for Zaltrap (aflibercept).

We are in the process of reviewing your application and have the following comment and request for additional information:

CHEMISTRY, MANUFACTURING and CONTROLS:

(b) (4)

in the June 1 response). This information has not been found in most of the method SOPs that have been provided to the BLA.

7. BLA section 3.2.S.3.2.1.2.1.5 (p. 17) states that Sanofi commits to providing results of (b)(4) evaluations by May 2012. Submit the results and assay validation to the BLA.

If you have any questions, please do not hesitate to call me at 301-796-1273.

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/s/

MELANIE B PIERCE
06/11/2012



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

Memorandum

Date: June 7, 2012

From: Melanie Pierce, DOP2/OHOP/CDER

Subject: Labeling Memo: Zaltrap (aflibercept): BL STN 125418/0

FDA's proposed labeling revisions as discussed during the June 7, 2012 labeling meeting:

Attendees: Casak, Sandra; Lemery, Steven; Zhang, Jenny (Jing); Brent Howard, Tammie; Schlick, James

Sections covered include:

- 2.2: DOSAGE and ADMINISTRATION: Dose Modification/ Treatment Delay Recommendations
- 5.6: WARNINGS and PRECAUTIONS: Proteinuria
- 5.10 WARNINGS and PRECAUTIONS: Compromised Wound Healing
- 14 : CLINICAL STUDIES
- 17: PATIENT COUNSELING INFORMATION

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MELANIE B PIERCE
07/11/2012



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

Memorandum

Date: June 5, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; Advice

FDA communicated the following email to sanofi-aventis on June 5, 2012:

You committed, in the original submission, to submitting results of a validated [REDACTED] (b) (4) [REDACTED] assay to the BLA "by May 2012." We have not seen this come in yet (and there is no indication that the section [REDACTED] (b) (4) [REDACTED] has been updated). Can you provide an update?

In addition, we are in the process of reviewing the label and determined that the PPI portion of the label is not necessary at this time. Please let me know if you have any concerns.

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/s/

MELANIE B PIERCE
06/11/2012



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

Memorandum

Date: June 1, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; CMC Information request

Please refer to your Biologics License Application (BLA) submitted February 2, 2012 under section 351 of the Public Health Service Act (PHS Act) for Zaltrap (afibercept).

We are in the process of reviewing your application and have the following comments and requests for additional information:

CHEMISTRY, MANUFACTURING AND CONTROLS:

(b) (4)



If you have any questions, please do not hesitate to call me at 301-796-1273.

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/s/

MELANIE B PIERCE
06/01/2012



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

Memorandum

Date: May 30, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: Labeling Memo: Zaltrap (aflibercept): BL STN 125418/0

FDA's proposed labeling revisions as discussed during the May 30, 2012 labeling meeting:

Attendees: Patricia Keegan, Steven Lemery, Sandra Casak, Kun He, Jenny Zhang, Sarah Kennett, Hong Zhao, Ruby Leong, Kimberly Rains, James Schlick, Kalavati Suvarna.

Sections covered include:

Black Box Warning, Indications and Usage: Dosage and Administration (2.1, 2.2, 2.3), Warning and Precautions sections of the package insert (5.1, 5.2, 5.4, and 5.11).

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/s/

MELANIE B PIERCE
07/12/2012



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

Memorandum

Date: May 21, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; CMC Information request

Please refer to your Biologics License Application (BLA) submitted February 2, 2012 under section 351 of the Public Health Service Act (PHS Act) for Zaltrap (aflibercept).

We are in the process of reviewing your application and have the following comments and requests for additional information:

CHEMISTRY, MANUFACTURING AND CONTROLS:

1. It appears that there are multiple clinical studies (TED6113, TES10897, EFC6125, ARD6122, ARD6772, and ARD6123) for which no drug product (DP) lot information was provided in the quality sections. For at least some of these studies, lot numbers listed in the clinical study reports do not correspond to lot numbers listed in the batch analysis section. It is not clear whether these clinical studies were not listed under DP lots that are included in the current batch analysis section or the DP lots used for these studies were not included in the current batch analysis section. Identify the DP lots used for these studies. Update the batch analysis section as appropriate.

(b) (4)

Please respond by June 4, 2012.

If you have any questions, please do not hesitate to call me at 301-796-1273.

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/s/

MELANIE B PIERCE
05/21/2012



BLA 125418/0

INFORMATION REQUEST

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

Dear Dr. Fernandes:

Please refer to your biologics license application (BLA) submitted February 2, 2012, received February 3, 2012, under section 351 of the Public Health Service Act for Zaltrap (aflibercept).

We reviewed the prescribing information submitted in your application and request you make the following changes:

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 or XX/XXXX.

TABLE OF CONTENTS:

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.

FULL PACKAGE INSERT:

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)

We request a prompt written response to the items enumerated above in order to continue our evaluation of your BLA.

Submit revised content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at: <http://www.fda.gov/oc/datacouncil/spl.html>.

If you have any questions, please contact Melanie Pierce, Senior Regulatory Health Project Manager, at (301) 796-1273.

Sincerely,

{See appended electronic signature page}

Karen D. Jones
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KAREN D JONES
05/16/2012



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

Memorandum

Date: May 15, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: Post-Midcycle Meeting Minutes: Zaltrap (aflibercept): BL STN 125418/0

Original Application: BL STN 125418/0:

Product: Zaltrap (aflibercept)

Submission Date: February 3, 2012

Received Date: February 3, 2012

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

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

FDA MEETING ATTENDEES

Patricia Keegan
Steven Lemery
Sandra Casak
Hong Zhao
Ruby Leong
Kevin Krudys
Sarah Kennett
Chana. Fuchs

SPONSOR ATTENDEES

Elma Fernandes
Noemi Guma
Mike Bloomstein
Danielle Grelet
Pankaj Bhargava
Mike Kopreski
Dinesh Purandare
Bill Roberts
Laura Simpson
Israel Lowy
Steve Fisk
Kris Ghosh
Bill Trompeter
Amy Walsh

Post- Midcycle Meeting minutes
BL STN: 125418/0

A teleconference was held with sanofi-aventis on May 15, 2012 to provide an update on the review of the Zaltrap (aflibercept) application.

FDA began the meeting by stating that all review disciplines will identify any major concerns that would preclude approval.

Chemistry, Manufacturing and Controls will send additional information requests will be sent regarding the validation of polysorbate.

Pharmacology/Toxicology has no issues to communicate at this time.

Clinical Pharmacology did not have any approval issues but expressed concern with sanofi's dosing strategy (body weight dose vs. flat dose) as larger weight patients may be at a higher risk for increased aflibercept exposure. FDA suggested sanofi investigate alternate dosing strategies for future studies.

Clinical and Statistics did not have any updates to convey. No additional requests for additional information were expected at this point in the review.

FDA stated that the 12- year patent exclusivity request under PHSA section 351(k)(7), submitted April 24, 2012 for Zaltrap, is currently under review. A decision will be made but not necessarily at the time of the application action date.

Sanofi-aventis agreed to submit the 120 day safety update report on or before May 28, 2012.

The call ended.

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/s/

MELANIE B PIERCE
07/13/2012



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

Memorandum

Date: May 9, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: Mid-cycle Meeting Minutes: Zaltrap (aflibercept): BL STN 125418/0

Original Application: BL STN 125418/0:

Product: Zaltrap (aflibercept)

Submission Date: February 3, 2012

Received Date: February 3, 2012

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

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

TIMELINES:

- Day 30-Filing/planning meeting February 28, 2012
- Day 45-Application Orientation February 10, 2012
- Filing Meeting scheduled March 28, 2012
- Day 60-Filing Notification April 3, 2012
- Day 74-Deficiencies Identified April 17, 2012
- Mid-Cycle Scheduled May 9, 2012
- Post Mid-cycle Meeting May 15, 2012
- Primary Reviews Due July 6, 2012
- Secondary Reviews Due July 11, 2012
- Communication PMRs/PMCs/REMS July 6, 2012
- Communication of labeling July 6, 2012
- Wrap-up meeting Due July 12, 2012
- CDTL Review July 13, 2012
- Division Director sign-off July 25, 2012
- Office Director sign-off August 3, 2012
- Action Due Date August 3, 2012

UPCOMING MEETINGS:

- Mid-Cycle May 9, 2012
- Labeling May 24, 2012
May 30, 2012
June 7, 2012
June 13, 2012
June 19, 2012
July 11, 2012
- Team April 27, 2012
May 23, 2012
June 13, 2012
- Wrap-up July 12, 2012

PRESENTATION SCHEDULE:

Clinical/Statistical:	50 Minutes
Quality:	10-15 minutes
Clinical Pharmacology:	10-20 minutes
Facilities:	5 minutes

MEETING ATTENDEES:

Richard Pazdur, Anthony Murgo, Patricia Keegan, Steven Lemery, Sandra Casak, Hong Zhao, Ruby Leong, Michael Krudys, Christine Garnett, Michele Clark-Stuart, Kalavati Suvarna, Patricia Hughes, Andrew McDougal, Alexander Putman, Jenny Zhang, Kun He, Tammie Brent Howard Sue Kang, Sarah Kennett, Chana. Fuchs, Robert Pratt, James Schlick, and Barbara Fuller.

SUMMARY OF FINDINGS:

- Clinical/Statistical:
 - VELOUR: median OS prolonged 1.4 months in pts with mCRC who had prior treatment with oxaliplatin (30% incl. bevacizumab). HR 0.81 (0.71;0.93), p=0.0032.
 - Subgroup and secondary endpoint analyses are consistent with these findings.
 - Aflibercept increased the toxicity of the FOLFIRI regimen.
 - VEGF/R inhibition-related toxicities are within the range of bevacizumab experience. Hypertension and proteinuria appear to be more frequent, but that maybe a function of monitoring.
 - Strong RPLS signal was observed in NCI trials when aflibercept combined with cisplatin/pemetrexed in NSCLC.
- Clinical Pharmacology:
 - There are no meaningful drug interactions.
 - Weight based dosing is not optimal for this drug product.

Mid-cycle Meeting minutes
BL STN: 125418/0

- There are no anticipated PMRs or PMCs for this application at this point in the review.

- Chemistry, Manufacturing and Controls:
 - Postmarketing items identified: Re-evaluation of release and shelf-life specifications for DS and DP (after xx commercial manufacturing runs for which all tests are performed).
 - Additional information requests will be communicated to the Sponsor.

- Facilities:
 - Deficiency for shipping validation for drug substance [REDACTED] (b) (4) were identified and resolved.
 - There are no approvability issues at this point in the review.

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/s/

MELANIE B PIERCE
06/15/2012



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

Memorandum

Date: April 27, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; Information request

Please refer to your Biologics License Application (BLA) submitted February 2, 2012 under section 351 of the Public Health Service Act (PHS Act) for Zaltrap (aflibercept).

We are in the process of reviewing your application and have the following comments and requests for additional information:

1. For the [REDACTED] ^{(b) (4)} testing method, please provide the following information:
 - a. The critical test parameters and protocol used for integrity testing of the 5 mL and 10 mL vials.
 - b. Description/Design of the test chamber
 - c. Does the system use a [REDACTED] ^{(b) (4)} reference?
 - d. How are the positive controls for the test method prepared?
 - e. The protocol used to determine system suitability and results from the system suitability test.
 - f. How often is the system suitability test performed?
 - g. How is the reject criteria set?
 - h. What is the sensitivity of the method compared to dye challenge and microbial ingress test methods. Please provide full protocol details of the cross-qualification studies for each vial type (5 mL and 10 mL). The dye used in these studies should be specified. The details of the microbial ingress test should also be provided.
2. Please provide data [REDACTED] ^{(b) (4)}
3. Please explain how [REDACTED] ^{(b) (4)} samples are collected. What is the sample volume that is tested?
4. Please provide data to support the statement [REDACTED] ^{(b) (4)}
[REDACTED] or adjust the [REDACTED] ^{(b) (4)} bioburden limits based on commercial manufacturing data. We recommend adding a bioburden sampling point [REDACTED] ^{(b) (4)}

5. For the shipping studies (Report QUA-PA-2011-16148), please indicate how many vials were tested for container closure integrity.
6. For the endotoxin test, please provide the following information:
 - (a) Detailed protocol and results used to assess suitability
 - (b) State the dilution used for routine release testing
 - (c) Please readjust the endotoxin release specification to include a two-fold safety margin.

7. Please provide the endotoxin specifications for incoming flanged caps (b) (4)

8. For the drug product manufacturing steps, please provide the temperature and duration for each operational step.

9. (b) (4)

10. (b) (4)

11. Please provide validation protocol and summary data (b) (4)

12. Please provide the routine parameters used (b) (4)

13. Please clarify (b) (4)

14. Please provide the (b) (4) protocol that was used (b) (4)

15. For the facility please provide the following information:

(b) (4)

APPEARS THIS WAY ON ORIGINAL



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/s/

MELANIE B PIERCE
04/27/2012



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

Memorandum

Date: April 27, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; Information request-Clinical Pharmacology

Please refer to your Biologics License Application (BLA) submitted February 2, 2012 under section 351 of the Public Health Service Act (PHS Act) for Zaltrap (aflibercept).

We are in the process of reviewing your application and have the following comments and requests for additional information:

CLINICAL PHARMACOLOGY:

Please provide the following data to facilitate evaluation of the effect of aflibercept on other drugs:

1. Oxaliplatin PK data from the internal clinical study report BDY-INT3010-EN-E01 referenced on page 57 of the Summary of Clinical Pharmacology Studies.
2. Cisplatin PK data from the internal clinical study report XRP6976E-1001 referenced on page 57 of the Summary of Clinical Pharmacology Studies.

If you have any questions, please do not hesitate to call me at 301-796-1273.

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/s/

MELANIE B PIERCE
04/27/2012



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

Memorandum

Date: April 27, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: Team Meeting # 1 Minutes: Zaltrap (afibercept): BL STN 125418/0

Original Application: BL STN 125418/0:

Product: Zaltrap (afibercept)

Submission Date: February 3, 2012

Received Date: February 3, 2012

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

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

Review Team:

Regulatory Project Manager	Melanie Pierce
Clinical Reviewer	Sandra Casak
Pharm/Tox Reviewer	Alexander Putman
Clinical Pharmacology Reviewer	Ruby Leong
Biostatistician	Jenny Zhang
Quality Reviewer	Sarah Kennett
Quality RPM (label review)	Kimberly Rains
Pharmacometrics Reviewer	Kevin Krudys
OSE Project Manager	Sue Kang
OSE (DMEPA)	James Schlick
OSE (DMEPA)	Barbara Fuller
OSE (DPV)	Bob Pratt
Facilities	Patricia Hughes
	Michelle Clark-Stuart
	Khalavati Suvarna
MHT Reviewer	Tammie Brent-Howard

TIMELINES:

- Day 30-Filing/planning meeting
- Day 45-Application Orientation

PRIORITY

February 28, 2012
February 10, 2012

Team Meeting minutes
BL STN: 125418/0

- Filing Meeting scheduled March 28, 2012
- Day 60-Filing Notification April 3, 2012
- Day 74-Deficiencies Identified April 17, 2012
- Mid-Cycle Scheduled May 9, 2012
- Primary Reviews Due July 7, 2012
- Secondary Reviews Due July 11, 2012
- Communication PMRs/PMCs/REMS July 7, 2012
- Communication of labeling July 7, 2012
- Wrap-up meeting Due July 12, 2012
- CDTL Review July 14, 2012
- Division Director sign-off July 25, 2012
- Office Director sign-off August 4, 2012
- Action Due Date August 4, 2012

UPCOMING MEETINGS:

- Filing March 28, 2012
- Mid-Cycle May 9, 2012
- Labeling May 24, 2012
May 30, 2012
June 7, 2012
June 13, 2012
June 19, 2012
July 11, 2012
- Team April 27, 2012
May 23, 2012
June 13, 2012
- Wrap-up July 12, 2012

Attendees; Sandra Casak, P. Keegan, A. Murgo, S. Lemery, K. Suvarna, R. Leong, K. Krudys, P. Hughes, T. Howard, K. Krudys, J. Zhang, Chana Fuchs, K. Rains, S. Kennett

Clinical:

- Provided updates regarding the midcycle and presentation.
- Intends to have a discussion with OMP-Barbara Fuller, at the midcycle to determine if the PPI is necessary for the Zaltrap label.
- Will follow-up with Tradename issues with ORP maybe OCC.
- Will follow-up with ORP regarding the utility of the exclusivity request for Zaltrap. Presently, the company must ask at the time of submission for exclusivity for a biologic. Problems are:
 - Exclusivity has not been granted for a biologic.
 - No procedure presently in place for exclusivity requests.
 - Will need additional information from the company prior to review of the request (to go out in an AI letter).

Statistical:

- No updates

Team Meeting minutes

BL STN: 125418/0

Nonclinical:

- No updates will follow up with the Nonclinical reviewer

Clinical Pharmacology:

- No updates

Quality:

- Will have another information request to send out next week.

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/s/

MELANIE B PIERCE
07/10/2012



BLA 125418/0

FILING COMMUNICATION

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

Dear Dr. Fernandes:

Please refer to your Biologics License Application (BLA) dated February 3, 2012, submitted under section 351 of the Public Health Service Act for Zaltrap, (afibercept).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is August 4, 2012.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by July 7, 2012.

During our filing review of your application, we identified the following potential review issues:

CHEMISTRY, MANUFACTURING and CONTROLS:

[Redacted content]

(b) (4)

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

FACILITIES:

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

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Melanie Pierce, Regulatory Project Manager, at (301) 796-1273.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
04/03/2012



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

Memorandum

Date: March 28, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: Filing Meeting Minutes: Zaltrap (aflibercept): BL STN 125418/0

Original Application: BL STN 125418/0:

Product: Zaltrap (aflibercept)

Submission Date: February 3, 2012

Received Date: February 3, 2012

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

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

Review Team:

Regulatory Project Manager	Melanie Pierce
Clinical Reviewer	Sandra Casak
Pharm/Tox Reviewer	Alexander Putman
Clinical Pharmacology Reviewer	Ruby Leong
Biostatistician	Jenny Zhang
Quality Reviewer	Sarah Kennett
Quality RPM (label review)	Kimberly Rains
Pharmacometrics Reviewer	Kevin Krudys
OSE Project Manager	Sue Kang
OSE (DMEPA)	James Schlick
OSE (DPV)	Bob Pratt
Facilities	Patricia Hughes
	Michelle Clark-Stuart
	Khalavati Suvarna
MHT Reviewer	Tammie Brent-Howard

TIMELINES:

- Day 30-Filing/planning meeting
- Day 45-Application Orientation
- Filing Meeting scheduled

PRIORITY

February 28, 2012
February 10, 2012
March 28, 2012

Filing Meeting minutes
BL STN: 125418/0

- Day 60-Filing Notification April 3, 2012
- Day 74-Deficiencies Identified April 17, 2012
- Mid-Cycle Scheduled May 9, 2012
- Primary Reviews Due July 7, 2012
- Secondary Reviews Due July 11, 2012
- Communication PMRs/PMCs/REMS July 7, 2012
- Communication of labeling July 7, 2012
- Wrap-up meeting Due July 12, 2012
- CDTL Review July 14, 2012
- Division Director sign-off July 25, 2012
- Office Director sign-off August 4, 2012
- Action Due Date August 4, 2012

Meeting attendees: Patricia Keegan, Steven Lemery, Sandra Casak, Hong Zhao, Ruby Leong Michele Clark-Stuart, Kalavati Suvarna, Patricia Hughes, Andrew McDougal, Alexander Putman, Jenny Zhang, Kun He, Kimberly Rains, Sue Kang, Sarah Kennett, Kevin Krudys, Anthony Murgo, Chana. Fuchs and Sarah Kennett

This application will be a priority review.

FDA is still waiting for feedback regarding validation of assays at sanofi-have to respond by COB March 28, 2012. Will try to follow-up for SGEs in lieu of ODAC for Zaltrap

OSI inspections scheduled;-2 in Czechoslovakia another, possibly Russia or Australia.

Potential Filing issues:

- Clinical-no filing issues
- Statistical-no filing issues
- Nonclinical-no filing issues
- Clinical pharmacology-no filing issues
- CMC-potential filing issues to be conveyed in the filing letter
- Facilities-no filing issues-information request to be sent regarding the June 15-18 DP facilities inspections.

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/s/

MELANIE B PIERCE
04/03/2012



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

Memorandum

Date: March 26, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; Information request

Please refer to your Biologics License Application (BLA) submitted February 2, 2012 under section 351 of the Public Health Service Act (PHS Act) for Zaltrap (aflibercept).

We are in the process of reviewing your application and have the following comments and requests for additional information:

CHEMISTRY, MANUFACTURING and CONTROLS:

1. Regarding assay validation of drug product (DP), provide the following to support lot release and stability testing activities at sanofi-aventis. If these are not available for the sanofi-aventis facility, confirm that DP lot release and stability testing is going to be performed ^{(b) (4)} with appropriately validated or qualified assays:

(b) (4)

2. Regarding assay validation of drug substance (DS), provide assay qualification or validation of the compendial methods used for testing aflibercept DS appearance, color, and pH.

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

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/s/

MELANIE B PIERCE
03/26/2012



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

Memorandum

Date: February 28, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: Planning Meeting Minutes: Zaltrap (aflibercept): BL STN 125418/0

Original Application: BL STN 125418/0:

Product: Zaltrap (aflibercept)

Submission Date: February 3, 2012

Received Date: February 3, 2012

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

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

Review Team:

Regulatory Project Manager	Melanie Pierce
Clinical Reviewer	Sandra Casak
Pharm/Tox Reviewer	Alexander Putman
Clinical Pharmacology Reviewer	Ruby Leong
Biostatistician	Jenny Zhang
Quality Reviewer	Sarah Kennett
Quality RPM (label review)	Kimberly Rains
OSE Project Manager	Sue Kang
OSE (DMEPA)	James Schlick
Facilities	Patricia Hughes
	Michelle Clark-Stuart
	Khalavati Suvarna

TIMELINES:

• Day 30-Filing/planning meeting	February 28, 2012
• Day 45-Application Orientation	February 10, 2012
• Filing Meeting scheduled	March 28, 2012
• Day 60-Filing Notification	April 3, 2012
• Day 74-Deficiencies Identified	April 17, 2012
• Mid-Cycle Scheduled	May 9, 2012

PRIORITY

- Primary Reviews Due July 7, 2012
- Secondary Reviews Due July 11, 2012
- Communication PMRs/PMCs/REMS July 7, 2012
- Communication of labeling July 7, 2012
- Wrap-up meeting Due July 12, 2012
- CDTL Review July 14, 2012
- Division Director sign-off July 25, 2012
- Office Director sign-off August 4, 2012
- Action Due Date August 4, 2012

Meeting attendees: Patricia Keegan, Steven Lemery, Sandra Casak, Hong Zhao, A. Putman, M. Clark-Stuart, K. Suvarna, P. Hughes, A. McDougal, Jenny Zhang, K. Rains, S. Kang, J. Schlick, S. Kennett, K. Jones, K. Krudys.

DISCUSSION TOPICS:

- The team decided that Zaltrap will not be presented at ODAC. As an alternative, the team will consult Special Government Employees (SGEs).
- The drug substance facility is scheduled to be inspected [REDACTED] ^{(b)(4)}. Priority status may be contingent on the ability to conduct facilities inspections and CMC issues.
- The CMC team determined that the application should be adequate for filing from a CMC perspective but deficiencies will need to be addressed in future communications.
- OSI expects to inspect at least three manufacturing sites including sanofi-aventis.
- A label review will need to be completed by the RPM, OBI and Clinical reviewer.
- The Facilities group will convey a comment regarding the storage of diluted drug product in the filing letter.
- The team recommended not having the patient information sheet as part of the labeling. Will follow up with the patient label group to determine if the patient information section is necessary.

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/s/

MELANIE B PIERCE
04/03/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

BLA 125418/0

Sanofi-aventis, US, LLC
Attention: Elma Fernandes, Ph.D.
Regulatory Development, Oncology
200 Crossings Boulevard
Box 4-209B
Bridgewater, NJ 08807

Dear Dr. Fernandes:

Please refer to your your Biologics License Application (BLA) submitted February 3, 2012, under section 351 of the Public Health Service Act (PHS Act) for “Zaltrap (aflibercept)”

We also refer to your February 3, 2012, correspondence requesting an application navigation meeting for Zaltrap (aflibercept). Based on the statement of purpose, objectives, and proposed agenda, we will consider this an informal Type C meeting. Meeting minutes will not be issued.

Meeting details are as follows:

Date: Thursday, March 1, 2012

Time: 11:00 a.m to 12:30 p.m., EST

Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20993

FDA Participants are as follows:

Patricia Keegan Karen Jones
Steve Lemery
Sandra Casak
Hong Zhao
Ruby Leong
Kun He
Jenny Zhang
Andrew McDougal
Chana Fuchs
Sarah Kennett

Please submit desk copies and/or slides to me at the following address:

Melanie Pierce
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2363
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

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

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MELANIE B PIERCE
02/21/2012



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

Memorandum

Date: February 17, 2012
From: Melanie Pierce, DOP2/OHOP/CDER
Subject: BLA 125418/0; Information request

Please refer to your Biologics License Application (BLA) submitted February 2, 2012 under section 351 of the Public Health Service Act (PHS Act) for Zaltrap (aflibercept).

We are in the process of reviewing your application and have the following comments and requests for additional information:

1. Please confirm addresses and phone numbers for all clinical sites with greater than 15 patients. Please also include electronic mail addresses for each Clinical Investigator.
2. Please provide a drug product manufacturing schedule. The manufacturing site is ready for inspection but a schedule was not included. Please also clarify if you will be manufacturing the product during the review cycle.

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

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/s/

MELANIE B PIERCE
02/17/2012



BL STN: 125418/0

BLA ACKNOWLEDGEMENT

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

Dear Dr. Fernandes:

We have received your Biologics License Application (BLA) submitted under section 351 of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Zaltrap[®] (aflibercept)

Date of Application: February 2, 2012

Date of Receipt: February 3, 2012

Our Submission Tracking Number (STN): BL 125418/0

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

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

If you have any questions, call Melanie Pierce, Senior Regulatory Health Project Manager at (301) 796-1273.

Sincerely,

{See appended electronic signature page}

Karen D. Jones
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KAREN D JONES
02/17/2012



BLA 125418

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

sanofi-aventis U.S. Inc.
55 Corporate Drive
Mail Stop: 55D-225A
Bridgewater, New Jersey 08807

ATTENTION: Elma Fernandes, PhD
Director, Global Regulatory Affairs

Dear Dr. Fernandes:

Please refer to your Biologics License Application (BLA) dated February 2, 2012, received February 3, 2012, submitted under section 351 of the Public Health Service Act for Aflibercept Injection, 100 mg/4 mL and 200 mg/8 mL.

We also refer to your February 2, 2012, correspondence, received February 3, 2012, requesting review of your proposed proprietary name, Zaltrap. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Zaltrap will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your February 2, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Melanie Pierce at (301) 796-1273.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
02/16/2012



IND 9948

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Elma Fernandes, PhD
Director, Regulatory Affairs
sanofi-aventis
200 Crossing Blvd PO Box 6890
Mail Code: BX2-712B
Bridgewater, NJ 08807-0890

Dear Dr Fernandes:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Vascular Endothelial Growth Factor Fc Fusion Protein (human, recombinant, CHO cells, Regeneron)."

We also refer to the meeting between representatives of your firm and the FDA on July 7, 2011. The purpose of the meeting was to review the final results of the pivotal Phase 3 study VELOUR in second-line metastatic colorectal cancer and discuss the format of a proposed biologics license application.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Melanie Pierce, Senior Regulatory Health Project Manager at (301) 796-1273.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES ATTACHED

MEMORANDUM OF MEETING MINUTES

SPONSOR Regeneron Pharmaceuticals
MEETING DATE: July 7, 2011
TIME: 1:00 p.m.-2:00.p.m.
LOCATION: White Oak Bldg 22, conference room 1315
APPLICATION: IND 9948
DRUG NAME: Vascular Endothelial Growth Factor Fc Fusion Protein
(human, recombinant, CHO cells, Regeneron)
TYPE OF MEETING: Type B/pre-sBLA
MEETING FORMAT Face-to-Face
MEETING CHAIR: Steven Lemery
MEETING RECORDER: Melanie Pierce

LIST OF FDA ATTENDEES:

Office of Oncology Drug Products

Division of Biologic Oncology Products

Patricia Keegan Division Director
Steve Lemery Clinical Team Leader
Sandra Casak Clinical Reviewer
M. Stacey Ricci Pharmacology/Toxicology Reviewer
Melanie Pierce Regulatory Project Manager

Office of Pharmaceutical Sciences

Office of Biotechnology Products

Division of Monoclonal Antibodies

Sarah Kennett Quality Reviewer

Office of Clinical Pharmacology

Division of Clinical Pharmacology V

Hong Zhao, Clinical Pharmacology Team Leader
Jun Yang Clinical Pharmacology Reviewer

Office of Biostatistics

Division of Biometrics 5

Kun He Biostatistics Team Leader
Jenny Zhang Biostatistics Reviewer

LIST OF SPONSOR ATTENDEES:

sanofi-aventis:

Sylvie Assadourian, M.D., Clinical Research Director
Emmanuelle Boelle, Ph.D., Lead Project Biostatistician

Remi Castan M.D.,
Elma Fernandes, Ph.D.,
Christopher Kripas, M.D.,
Nathalie LeBail, M.D.,
Shamim Ruff, M.Sc.,
Zhenming Shun, Ph.D.,
Tal Zaks, MD,
Pankaj Bhargava, MD,

Clinical Study Director
Director, Global Regulatory Affairs
Senior Director, Global Safety Officer
Project Leader
Vice-President, Global Regulatory Affairs
Senior Director, US Head of Biostatistics for Oncology
Head, Development, Global Oncology Division
Associate VP, Development

Regeneron:

Laura Simpson, Ph.D., RAC,
Alain Thibault, M.D.,

Associate Director, Regulatory Affairs
Vice President, Clinical Sciences, Oncology

BACKGROUND:

On April 28, 2011, Regeneron submitted a type B pre-sBLA meeting request to discuss the format of the proposed BLA application and review the results of the pivotal VELOUR study in patients with second-line metastatic colorectal cancer.

Aflibercept (AVE0005), Vascular Endothelial Growth Factor (VEGF) Trap, is a recombinant fusion protein, consisting of the extracellular domains of human VEGF receptors 1 and 2 (VEGFR-1 and VEGFR-2) fused to the Fc portion of a human IgG1.

Meeting history:

- On July 16, 2007, a meeting between Regeneron Pharmaceuticals, Inc. and FDA was scheduled to discuss the proposed trial EFC10262: a multinational, randomized, placebo-controlled study investigating the effects of FOLFIRI (plus placebo) versus FOLFIRI in combination with aflibercept on overall survival (OS) in patients with metastatic colorectal cancer after failure of an oxaliplatin-containing regimen. After receiving FDA's draft responses to Regeneron's questions on July 13, 2007, Regeneron elected to cancel the meeting.
- On October 11, 2007, Regeneron requested a Type C-CMC meeting to discuss their response to CMC issues raised during a May 16, 2006, CMC meeting. Regeneron also requested feedback from FDA on other development activities such as (b) (4) validation plans, potency, immunogenicity assay development/validation, and immunogenicity sampling plans.
- A statistical analysis plan (SAP) was submitted for the VELOUR study on January 13, 2010. FDA issued a letter dated July 30, 2010 with comments related to the SAP (b) (4)
- On August 25, 2010, Regeneron submitted an amended SAP based on FDA comments from the July 30, 2010 letter. FDA responded with additional comments in a letter issued on September 20, 2010.
- On May 12, 2011, a meeting between Regeneron Pharmaceuticals, Inc. and FDA was held to summarize product development since the type C pre-Phase II meeting held on October 11, 2007, inform FDA how the outstanding CMC issues from the type C pre-Phase 3 meeting will be addressed in the BLA, and obtain feedback on the proposed table of contents of the module 3 quality section.

Clinical Development Plan:

Study EFC10262 (VELOUR) is a prospective, multinational, randomized (1:1), double-blind, parallel arm study comparing aflibercept 4 mg/kg to placebo, in combination with FOLFIRI (irinotecan/5-fluorouracil bolus/infusional/leucovorin) administered intravenously every 2 weeks as second-line treatment for patients with mCRC after failure of an oxaliplatin-based regimen. Patients must have progressed during or following the last dose of the oxaliplatin-based

chemotherapy. Approximately 1,200 patients (i.e., 600 patients per treatment group) were planned to be randomized. Treatment assignment was stratified according to prior therapy with bevacizumab (yes or no), and ECOG performance status (0 versus 1 versus 2). Each patient was to be treated until disease progression, unacceptable toxicity, or withdrawal of consent. Patients with severe renal/liver impairment were excluded from the study.

The primary objective was to demonstrate improvement in OS by comparison to placebo. A total of 863 deaths were required to detect a 20% improvement in OS (hazard rate) with 90% power using the 2-sided log rank test at an overall 0.0499 alpha level. The median survival time was expected to be 11 months in the control group. The study initially included 1 formal interim analysis, for the purpose of efficacy, when 561 death events (65% information fraction) had occurred. The final analysis for progression-free survival (PFS), a secondary efficacy endpoint, based on an independent blinded review of imaging, was to be performed at the time of the interim OS analysis. To maintain the overall alpha level at 5% for PFS and OS, the PFS was tested using a 0.0001 significance level.

Upon request of the DMC, an additional earlier interim analysis of OS was planned to be performed to provide an early evaluation of the benefit-risk ratio, when 315 death events (36.5% information fraction) had occurred. Therefore, the predefined statistical significance level for the final OS analysis was 0.0466 after adjusting the type I error spent for 2 interim analyses using the O'Brien-Fleming spending function.

Efficacy:

The efficacy analyses were based on all randomized patients (Intent-to-Treat [ITT] population: 612 patients in the aflibercept arm and 614 patients in the placebo arm).

Regeneron stated that the study met its primary endpoint demonstrating a statistically significant difference in OS in favor of aflibercept over placebo: stratified HR: 0.817, 95.34% (CI): 0.713 to 0.937; $p = 0.0032$. The median OS was 13.50 months versus 12.06 months in the aflibercept and placebo arms, respectively. Median follow up was 22 months. As planned, at the time of data cut-off for the final OS analysis, there were a total of 863 deaths (70.4% of 1,226 patients enrolled).

Regeneron stated that improvement in PFS [independent review committee (IRC) reviewed] was demonstrated in the aflibercept treatment arm when compared to the placebo arm (stratified HR: 0.758, 99.99% CI: 0.578 to 0.995; $p = 0.00007$). Median PFS was 6.90 months in the aflibercept arm and 4.67 months in the placebo arm. The final analysis of PFS was performed as planned at the time of the second interim analysis at 65% of events for OS (cutoff: 06 May 2010).

Safety:

The most frequently reported adverse events of aflibercept in combination with FOLFIRI ($\geq 20\%$ by preferred term or high-level term, all Grades) were (ranked by decreasing frequency in the aflibercept arm) diarrhea, asthenia/fatigue, stomatitis and ulceration, nausea, infection, hypertension, gastrointestinal and abdominal pains, vomiting, decreased appetite, decreased

weight, epistaxis, alopecia, dysphonia, musculoskeletal and connective tissue pain and discomfort, constipation, and headache.

The events of hypertension (all Grades) were more frequent in the aflibercept treatment arm than in the placebo arm (41.2% versus 10.7%). Hemorrhagic events (any location, all Grades) were twice as frequent in patients treated with aflibercept than in patients who received placebo (37.8% versus 19.0%). The majority of the hemorrhagic events were Grade 1/2 epistaxis. Gastrointestinal events (all Grades) were more frequent in the aflibercept treatment arm than in the placebo arm (93.5% versus 86.1%). General disorder events (including fatigue/asthenia [all Grades]) were more frequent in the aflibercept arm than in the placebo arm (71.5% versus 62.5%). Infections (all Grades) were more frequently reported in patients treated with aflibercept (46.2% versus 32.7%).

Venous thromboembolic events (all Grades) were reported in 9.3% of patients in the aflibercept treatment arm and 7.3% of patients in the placebo arm. Arterial thromboembolic events (all grades) were reported in 2.6% and 1.5% of patients in the aflibercept and placebo arms, respectively.

Within 30 days of last study treatment administration (i.e., during study treatment), 28 of 611 patients (4.6%) in the aflibercept arm and 17 of 605 patients (2.8%) in the placebo arm died. Of these, 13 patients (2.1%) in the aflibercept arm and 11 patients (1.8%) in the placebo arm died as a result of disease progression.

Regeneron claimed the primary endpoint of overall survival was met with a significant improvement in progression-free survival.

Regeneron's responses to FDA's comments were received (via PowerPoint slides) prior to the meeting on July 7, 2011.

PREAMBLE: FDA recognizes that Regeneron submitted a biologics license application for aflibercept under STN 125387. Hence, the present submission should be filed as a supplement to the original BLA. The Agency acknowledges that Regeneron can still propose a new trade name for the drug product intended to be used in the oncology setting under the original BLA.

Discussion during meeting: FDA requested Regeneron submit a proposal and rationale regarding why the product should be considered as a stand-alone BLA. FDA will communicate the decision following internal discussions.

Sponsor Submitted Questions and FDA Response:

CLINICAL/STATISTICS:

1. Does the Agency have any comments on the proposed strategy, analyses, organization, or presentation of results for evaluation of efficacy?

FDA Response: FDA does not agree with the plan to submit a summary of clinical efficacy (SCE) in Module 2 that will also serve as the integrated summary of efficacy (ISE). Please submit a comprehensive ISE in Module 5 of the sBLA that follows the general recommendations set forth in FDA Draft Guidance for Industry: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>. The SCE should provide data summaries of the pivotal trial (mostly text format, but with tables and figures as necessary); however, the ISE should be more extensive than the SCE and include not only text but tables and figures as well as appendices of tables, figures and datasets as necessary.

Discussion during the meeting: Reference slides 4-6: To clarify, Regeneron stated that the length of the ISE will be approximately 100 pages and thus proposed to submit the text portion of the ISE in module 2 and the tables, appendices, and datasets in module 5.3.5.3 (according to FDA guidance). FDA stated that this issue will need to be discussed internally in order to ensure that this approach is acceptable.

2. Does the Agency have any comments on the proposed strategy, analyses (including integration/pooling strategy), organization, or presentation of results for evaluation of safety?

FDA Response: FDA requests that Regeneron confirm that an integrated summary of safety, distinct from the SCS, be provided in Module 5 of the BLA. Please see addendum below regarding analyses that FDA expects in a BLA submission.

FDA agrees with the Regeneron plan to not integrate studies PDY6655, PDY6656, TCD10173, TED6113, and TED6114 into the integrated safety database; however, FDA requests that Regeneron provide these data (safety and demographic) as stand alone datasets and study reports [and include the information from these studies in the SCS/ISE (i.e., in a side-by-side format)]. In the evaluation of events of special interest (see below), FDA requests the submission of the datasets that supported the analyses.

Discussion during the meeting: Reference slides 6-13: Regeneron's proposal as outlined on slides 9 and 10 will be discussed internally as described in question 1. The size of the text portion of the ISS is expected to be approximately 400 pages.

FDA stated that the plan described in slide 12 is acceptable.

3. Does the Agency have any recommendations for additional analyses or data presentations to facilitate the assessment of safety and efficacy?

FDA Response: The dossier should include analyses of events of special interest across all studies, both under Regeneron IND 9948 and NCI IND 100137. In particular, the analysis of RPLS should include the experience of study TCD10767 and all trials under the NCI IND 100137.

Discussion during the meeting: Reference slides 16-17: FDA acknowledged that Regeneron's proposal is acceptable and encouraged Regeneron to obtain and include narrative summaries for special events of interest to the extent that is possible.

4. Does the Agency agree with the proposal for submission of narratives and CRFs?

FDA Response: Yes. In the submission, please include a complete list (with links) of the CRFs and narratives (also linked between them). Additionally, FDA requests the submission of CRFs for all patients across the database who experienced RPLS, perforation, fistula, thrombotic microangiopathy, thrombotic thrombocytopenic purpura or Grade ≥ 4 hemorrhage.

Discussion during the meeting: Regeneron acknowledged FDA's response and had no additional comments.

CLINICAL PHARMACOLOGY:

5. Does the Agency agree with the approach for the following for the BLA:
a. Assessment of population PK,

FDA Response: The proposed population PK analysis plan appears reasonable.

Discussion during the meeting: Regeneron acknowledged FDA's response and had no additional comments.

- b. PK/PD relationship, and

FDA Response: The proposed PK/PD assessment plan appears reasonable.

Discussion during the meeting: Regeneron acknowledged FDA's response and had no additional comments.

- c. Assessment of effect of immunogenicity on PK, safety, and efficacy?

FDA Response: The proposed immunogenicity assessment plan appears reasonable.

Discussion during the meeting: Regeneron acknowledged FDA's response and had no additional comments.

CLINICAL:

6. Does the Agency have any comments on the content, structure, or version of the electronic submission datasets (Study Tabulation Data Models [SDTMs] and the analysis datasets [ADSS]) proposed to be included in the dossier, as described in the Electronic Data Submission Planning Template?

FDA Response: Yes. Please see addendum below (specifically sections pertaining to the submission of data using CDISC standards).

Discussion during the meeting: Regeneron acknowledged FDA's response and had no additional comments.

7. Does the Agency have any comments on the proposed dossier structure and electronic table of contents for the dossier? Does the Agency agree with the approach for Modules 2.7.1 and 2.7.2?

FDA Response: FDA agrees with Regeneron's approach for Modules 2.7.1 and 2.7.2.

Discussion during the meeting: Regeneron acknowledged FDA's response and had no additional comments.

8. Does the Agency agree with the approach for REMS?

FDA Response: No. At this time, consistent with the tolerance of risk in the clinical practice of oncology, FDA does not see the need for a REMS. However, based on the review of the sBLA, FDA will notify Regeneron if the Agency believes that a REMS is necessary to ensure safe use of the drug,

Discussion during the meeting: Regeneron acknowledged FDA's response and had no additional comments.

9. The Sponsor considers [REDACTED] ^{(b) (4)} as the only studies required to meet the 21CFR54 requirements for financial disclosures, following the May 2011 draft guidance "Financial Disclosure by Clinical Investigators, Guidance for Clinical Investigators, Industry, and FDA Staff." Does the Agency agree?

FDA Response: Yes.

Discussion during the meeting: Regeneron acknowledged FDA's response and had no additional comments.

Additional Clinical Pharmacology Comments:

10. The following are the general expectations for submitting pharmacometric data and models:
 - a. All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - b. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
 - c. A model development decision tree and/or table which gives an overview of modeling steps.
 - d. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Discussion during the meeting: Regeneron acknowledged FDA's responses and had no additional comments.

ISSUES REQUIRING FURTHER DISCUSSION:

- See action items below

ACTION ITEMS:

- FDA will follow-up with Regeneron to determine the appropriate locations for the Integrated Summary of Efficacy and Safety.

ATTACHMENTS AND HANDOUTS:

- Regeneron slide deck

POST-MEETING FOLLOW-UP (Questions 1 and 2): Regeneron's plan to split the ISE and ISS between modules 2 and 5, as outlined in slides 6, 9, 10 and 12, is acceptable.

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
07/20/2011

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

Memorandum

Date: July 13, 2007
From: *Melanie Pierce; DBOP/ODDP/CDER*
Subject: Preliminary draft comments to sponsor questions

Meeting Type: Type B
Meeting Category: Pre-Phase 3
Meeting Date and Time: July 16, 2007; 2:00-3:00pm
Meeting Format: Teleconference
IND: 9948
Product: Vascular Endothelial Growth Factor Fc Fusion Protein (human, recombinant, CHO cells, Regeneron)
Meeting Requestor/Sponsor: Regeneron Pharmaceuticals, Inc.

On May 3, 2007, Regeneron Pharmaceuticals, Inc. requested a Pre-Phase 3 meeting to discuss development and registration plans for use of aflibercept (AVE0005, VEGF Trap) in combination with FOLFIRI for the treatment of second-line metastatic colorectal cancer (mCRC). This study is intended as the basis for registration for aflibercept to be used in combination with 5FU-based therapy for second line treatment of patients with mCRC.

The proposed Phase 3 (EFC10262) study is a multinational, randomized, placebo-controlled study investigating the effects of FOLFIRI (plus placebo) versus FOLFIRI in combination with aflibercept on overall survival in patients with metastatic colorectal cancer after failure of an oxaliplatin-containing regimen. Patients will be stratified according to prior therapy with bevacizumab and ECOG PS (0-1 v. 2). Administration is 4 mg/kg of study drug every 2 weeks. The primary endpoint is overall survival (OS) and the secondary endpoint is progression-free survival (PFS) evaluation of safety profiles. There is a planned interim overall survival (OS) analysis when approximately 65% of the OS events have occurred. At this interim, a final PFS analysis will be conducted at the same time. (b) (4)

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Disclaimer: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for July 16, 2007, between Regeneron Pharmaceuticals, Inc. and the Division of Biologic Oncology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments.

If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the Regulatory Project Manager). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, the purpose of the meeting, or questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

Sponsor Submitted Questions and FDA Response:

FDA Preamble:

As a basis for the proposed Phase 3 study, the sponsor cites the following supportive studies:

- TED 6115, a Phase 1 single-agent, dose-escalation study in relapsed or refractory solid tumors in which 7 patients with mCRC were treated with no complete responses (CR) or partial responses (PR) (0% RR).
- TCD6118, a Phase 1 dose-escalation study in advanced solid tumors investigating use of aflibercept with irinotecan/5FU/leucovorin (Saltz regimen) in which 39 patients with mCRC were treated with 3 confirmed PRs (8% RR).
- TCD6120, a Phase 2 dose-escalation study in advanced solid tumors investigating use of aflibercept with docetaxel with or without cisplatin in which 5 mCRC patients were treated with no CRs or PRs (0% RR).
- NCI single-agent, Phase 2 study in refractory mCRC which has enrolled 51 patients with 1 PR (2%). All patients received prior chemotherapy; prior bevacizumab was permitted but not required for study entry.

In summary, 102 patients with mCRC have received aflibercept in these four trials and 4 PRs have been observed. There is a low objective response rate (~4%), suggestive of possible activity, although 3 of the 4 responders also received concurrent chemotherapy. Because of

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these limited data, FDA suggests Regeneron consider a smaller randomized Phase 2b trial of aflibercept and chemotherapy, with an active control arm of chemotherapy alone, to further assess safety and assess the activity of the product prior to initiation of the proposed Phase 3 study.

Clinical:

1. **Does FDA agree with the proposed study design, the patient population and the choice of background chemotherapy for Study EFC10262?**

FDA RESPONSE: Yes, these are acceptable.

2. **Does the FDA agree with primary study endpoint of overall survival (OS) and with the secondary endpoints of progression-free survival (PFS), safety and objective response rate for Study EFC10262?**

FDA RESPONSE: Yes, these are acceptable.

3. **Does the FDA agree with the proposed definition of progression which includes both radiological progression and clinical progression (i.e., symptomatic deterioration without tumor progression) assessed by the investigator for the assessment of the PFS endpoint?**

FDA RESPONSE: The use of investigator-assessed symptomatic deterioration in a composite endpoint for determination of clinical progression would be acceptable only if such data were collected and analyzed in accordance with a pre-specified instrument that has been validated to correlate with objective disease progression in this specific disease and treatment setting. The data supporting validation of the instrument's ability to determine tumor progression, including ability to distinguish between deterioration due to tumor progression and deterioration due to anti-cancer therapy toxicity, must be provided in advance of commencing this study.

4. **Does the FDA agree that no third party review of PFS is required considering this is a randomized, controlled, double-blinded study, with a primary endpoint of overall survival, with anticipated enrollment of approximately 1200 patients? The sponsor anticipates that investigator assessment of progression will be adequately robust for the final analysis of PFS and therefore independent review of progression is not planned. Does the Agency agree that this is acceptable for inclusion of PFS in the labeling for the proposed registration objectives discussed in questions 7 and 8?**

FDA RESPONSE: Assuming the blinded nature of the study is strictly maintained, a third party review of radiological source data will not be required. Otherwise, the need for independent review will become a review issue. PFS is not acceptable for regular

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approval; please see responses to questions 7 and 8.

5. Does the FDA agree with the proposed statistical analysis plan?

FDA RESPONSE: No. From Regeneron's criterion for progression-free survival, an aflibercept vs. placebo hazard ratio of (b) (4) or better is needed for statistical significance. A hazard ratio of (b) (4) translates into an (b) (4) improvement in median PFS. It is not reasonably likely that such a finding will predict a statistically significant result in overall survival for the final analysis (which requires an aflibercept vs. placebo hazard ratio of (b) (4) or better for statistical significance, which translates into an improvement in medians of (b) (4) or better).

Please be advised that two Phase 3 studies are generally required for licensure. FDA would accept a single pivotal study to support licensure if results show a highly statistically significant effect on a major clinical benefit endpoint, or an established surrogate for such endpoint that is internally consistent across relevant subgroups. The results of the single pivotal trial must be sufficiently robust and so compelling that it would be unethical to repeat the study. For further information please refer to the FDA document "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" at <http://www.fda.gov/cder/guidance/index.htm>.

See also additional statistical comments 9-13.

6. Does the FDA agree with the planned assessment of pharmacokinetics and immunogenicity?

FDA response: The proposed pharmacokinetic (PK) assessment plan appears to be reasonable. However, the acceptability of PK assessments will be determined after Regeneron submits the BLA and FDA reviews the contents in depth. As recommended in the previous pre-Phase 3 meeting of May 24, 2007 (NSCLC indication), please submit a comprehensive summary of the results of PK assessments in your future pre-BLA meeting package for FDA's preliminary review and comments.

Justification for assessing only a subset of patients for anti-product immune responses will need to be provided. The immunogenicity sampling time points will need to be justified based on the capability of the immunogenicity assay to detect anti-product responses while product is still present, and the *in vivo* half-life of the drug product. Please also note the following:

- a. Please provide a detailed description of the semi-quantitative ELISA and new titre-based assays. This should include information on the assays sensitivity (including the limit of detection and limit of quantitation), reproducibility and linearity. Since the immunogenicity assay has not been reviewed by FDA, it is

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recommended that Regeneron bank all patient samples to ensure their availability for testing by an approved assay.

- b. Regeneron will need to have an assay capable of detecting neutralizing antibodies. Please submit detailed plans and methods in regard to development and validation of an assay capable of detecting neutralizing anti-product antibodies. The impacts of the antibodies on the PK, efficacy, and safety of aflibercept should be assessed, even when the antibodies have no neutralizing ability

7. **Does FDA agree with the proposed potential submission (b) (4) with interim analysis of overall survival for Study EFC10262, and safety, assuming acceptable benefit-risk is demonstrated? The final overall survival analysis will be submitted at a later date as a post-marketing commitment.**

FDA RESPONSE: Regeneron will need to demonstrate that PFS is reasonably likely to predict clinical benefit. In addition, the magnitude of the effect on PFS, and the direction and magnitude of effects on OS at the time of the interim analysis will be subject to review (b) (4)

8. **Does the Agency agree that study EFC10262 to demonstrate superiority in overall survival of aflibercept in combination with FOLFIRI in patients with metastatic colorectal cancer after failure of an oxaliplatin-based regimen is adequately designed to support regular approval for the proposed indication assuming acceptable benefic-risk is demonstrated?**

FDA RESPONSE: FDA agrees that results from EFC10262 may be adequate to support regular approval for second-line therapy in mCRC with the following caveat. In the US, patients typically receive bevacizumab in combination with first-line chemotherapy. In order for results of this trial to be generalized to the US population, a sufficient number of patients in the proposed study should be enrolled who have received prior bevacizumab in combination with chemotherapy. FDA regards subgroup analysis between study arms in patients who have received bevacizumab to be of particular importance.

ADDITIONAL STATISTICAL COMMENTS:

9. Please explain the details on how a biased coin dynamic method will be used to avoid extreme imbalance with an institution.
10. Please submit a copy of the DMC charter.

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11. Please provide the exact timing of the analyses on PFS and overall survival. This submission contains language like "at approximately 556 events." FDA recommends having the analyses of the primary endpoint based on a pre-specified number of events in order to isolate the power and the amount of information in the comparison.
12. FDA recommends that the stratification for ECOG performance status be 0 vs. 1 vs. 2, or 0 vs. 1 or 2. Since the vast majority of patients should have ECOG performance of 0 or 1, stratification by 0-1 vs. 2 does not balance performance status of 0 (or 1) between study arms.
13. In the absence of a statistically significant result for the primary analysis of the primary endpoint, results based on secondary endpoints can not result in (either singly or in combination) an efficacy claim. In the event that there is a statistically significant result for the primary analysis of the primary endpoint, and FDA determines that flaws in the design and/or modifications in the study over time do not confound the reliability and confidence in the results, those secondary endpoints that are significant after proper adjustment for multiplicity may be included in the label. Please include in a future submission, any secondary endpoints for which claims may be included in the labeling and how adjustments will be made for multiplicity to guarantee an overall two-sided 0.05 level for the tests of such secondary endpoints. If only one study is to be used for registration, the overall two-sided level should be smaller (e.g., 0.01).

ADDITIONAL CLINICAL COMMENTS:

14. Prior to registration, Regeneron is required to conduct a study assessing the impact of aflibercept on the QT interval using the principles discussed in the ICH-E14 guidance document (<http://www.fda.gov/cder/guidance/6922fml.htm>). Please submit a proposed QT assessment plan and protocol to FDA for review.
15. Please revise the CRFs to capture the following information:
 - a. A detailed history of prior cardiovascular events, such that a exploratory analyses exploring risk factors for thrombovascular events (TVE), such as correlation with preexisting cardiovascular comorbidities, can be provided in the application; and,
 - b. a targeted assessment of the absence or presence , and if present the location, severity, and time to resolution of, TVEs at each study visit.
16. Trials intended to support drug registration should be designed and conducted such that the appropriate Code of Federal Regulations and all applicable ICH guidelines are followed. In particular, the drug development program and specific study should allow for the following:
 - a. The preparation of a clinical study report following the ICH E3 Structure and

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Content of Clinical Study Reports guidance
(<http://www.ich.org/LOB/media/MEDIA479.pdf>).

- b. The preparation of integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with follow the guidance document Cancer Drug and Biological Products-Clinical Data and Marketing Applications (<http://www.fda.gov/cder/guidance/4332fnl.pdf>).
- c. The assessment of safety as per the Guidance for Industry: Pre-marketing Risk Assessment (<http://www.ich.org/LOB/media/MEDIA479.pdf>).
- d. The preparation of narrative summaries containing the following components:
 - 1) Subject age and gender;
 - 2) Signs and symptoms related to the adverse event being discussed;
 - 3) An assessment of the relationship of exposure duration to the development of the adverse event;
 - 4) Pertinent medical history;
 - 5) Concomitant medications with start dates relative to the adverse event;
 - 6) Pertinent physical exam findings;
 - 7) Pertinent test results (for example: lab data, ECG data, biopsy data);
 - 8) Discussion of the diagnosis as supported by available clinical data;
 - 9) For events without a definitive diagnosis, a list of the differential diagnoses;
 - 10) Treatment provided;
 - 11) Re-challenge results (if performed);
 - 12) Outcomes and follow-up information; and,
 - 13) An informed discussion of the case, allowing a better understanding of what the subject experienced.

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17. When submitting clinical trial data, please be advised that all data should be in CDISC format using the Standard Data Tabulation model 0.
18. Case Report Forms should be designed to collect verbatim terms.

NONCLINICAL COMMENT:

19. As previously communicated in FDA's comments from the May 24, 2007, meeting, FDA requests that Regeneron resubmit all final study reports for all completed nonclinical pharmacology, pharmacokinetic, and toxicology studies previously submitted to this IND. Please also submit any literature publications that Regeneron has either previously referenced or provided in lieu of study reports, for those nonclinical studies that were not conducted in-house. For any ongoing nonclinical studies, please indicate anticipated dates for completion and submission of the completed, final study reports.

ADDITIONAL CMC COMMENT:

20. For CMC related comments please refer to the 'Additional CMC Comments' outlined in the draft comments sent on May 21, 2007, for the May 24, 2007, meeting.

ADDITIONAL CLINICAL PHARMACOLOGY COMMENT:

21. FDA acknowledges that Regeneron is to determine the effect of irinotecan/LV5FU2 on the PK of aflibercept through a cross-study comparison and the effect of aflibercept on the PK of irinotecan (not irinotecan/LV5FU2 combination) through a comparison with published data. As discussed in the previous pre-Phase 3 meeting of May 24, 2007 (NSCLC indication), inter-study comparisons and/or comparisons with published data are not generally acceptable to determine drug-drug interactions (DDI). However, FDA would consider Regeneron's inter-study comparisons and/or comparisons with published data if compelling justifications for not conducting intra-study comparisons are provided. FDA would like to review a comprehensive summary of the drug interaction studies conducted to date and determine, based on the data, whether further drug interaction studies are necessary.

ADDITIONAL GENERAL COMMENTS REGARDING THE DRUG DEVELOPMENT PLAN:

22. Because of the two recent serious adverse event (SAE) reports of sudden death (fatal upper gastrointestinal hemorrhage and fatal hemoptysis, sponsor case numbers 200713497GDDC and 200715942GDDC, respectively), and other serious reported toxicities which may be a result of the pharmacologic class of drugs, please provide the following:

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- a. The standard operating procedures used for dissemination of safety information to investigators participating in clinical studies involving aflibercept.
- b. A detailed description of your plan for assessing cumulative safety information?
- c. The methods used to remind investigators of their responsibilities to inform their local IRBs regarding SAEs and informed consent issues.

Linked Applications

Sponsor Name

Drug Name

IND 9948

REGENERON
PHARMACEUTICALS
INC

Vascular Endothelial Growth Factor Fc
Fusion Protein (human, recombinant, CHO
cells, Regeneron)

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/s/

MELANIE PIERCE
07/13/2007