

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125387Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA/BLA#: BLA 125-387 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DTOP PDUFA Goal Date: 8/20/11 Stamp Date: 2/18/2011

Proprietary Name: Eylea

Established/Generic Name: aflibercept injection

Dosage Form: intravitreal injection

Applicant/Sponsor: Regeneron

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 of wet ^{(b) (4)} AMD

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.

Age related macular degeneration does not exist in children.

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).

f 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) 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).

Additional 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

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

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"/>

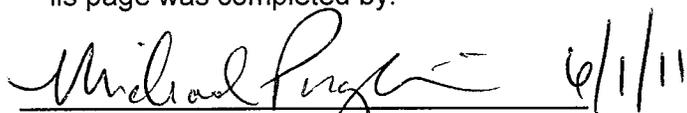
Are the indicated age ranges (above) based on weight (kg)? No; Yes.

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:



 Regulatory Project Manager

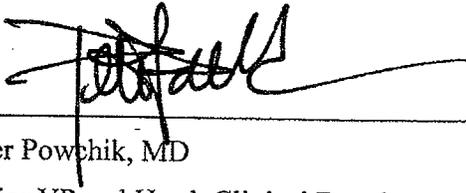
(Revised: 6/2008)

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

3. DEBARMENT CERTIFICATION

Regeneron Pharmaceuticals, Inc 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.

Seth Yoser was selected as an investigator for the VGFT-OD-0605 study. He screened 1 patient on January 22, 2008 but no patient from his site was randomized and included in the study. No patients were treated by Seth Yoser for the VGFT-OD-0605 study. His site was terminated and closed by Regeneron Pharmaceuticals on date June 20, 2008. He was debarred by FDA effective date May 20, 2010 with Federal register date August 18, 2010.



Peter Powchik, MD
Senior VP and Head, Clinical Development

2011.01.19

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # BLA # 125387	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Eylea Established/Proper Name: aflibercept Dosage Form: intravitreal injection		Applicant: Regeneron Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Michael Puglis		Division: DTOP
<p>NDA: 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>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: 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>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft 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 18, 2011</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
❖ 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 _____		<input type="checkbox"/> Received

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.

Application Characteristics ²	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority</p> <p>Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch</p> <p><input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch</p> <p><input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E</p> <p><input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41)</p> <p><input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H</p> <p><input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide</p> <p><input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan</p> <p><input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU</p> <p><input type="checkbox"/> REMS not required</p> <p>Comments:</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)	<input checked="" type="checkbox"/> Yes, dates 10/24/11
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• 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 type="checkbox"/> Other

² 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 BLA: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? 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. 	<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? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<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? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<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? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<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)? (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.) 	<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). (If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)). 	<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>
<p>CONTENTS OF ACTION PACKAGE</p>	
<p>❖ Copy of this Action Package Checklist³</p>	<p>Included</p>
<p>Officer/Employee List</p>	
<p>❖ 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>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Action Letters</p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) AP- 11/18/11</p>
<p>Labeling</p>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<p>Included - dated 11/17/11</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>Included</p>
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.

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 type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" 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. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	Included - dated 11/17/11
❖ 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>) 	Acceptable -5/25/11 5/25/11, 11/4/11
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 8/5/11 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 10/13/11 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews 8/22/11
Administrative / Regulatory Documents	
Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	3/18/11
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input checked="" type="checkbox"/> Not a (b)(2)
❖ 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
❖ Pediatrics (<i>approvals only</i>)	
<ul style="list-style-type: none"> • Date reviewed by PeRC <u>6/1/11</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ 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
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Internal memoranda, telecons, etc.	Included
Minutes of Meetings	
<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 9/8/10, 9/27/10
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	6/1/09 Tox Guidance, 9/15/09 CMC Guidance
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	6/17/11
<ul style="list-style-type: none"> 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	Included
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/18/11
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/18/11
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/12/11, 11/18/11
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 8 Templates Included
Clinical Information⁵	
Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	see CDTL review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	3/23/11, 7/29/11, 11/18/11
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input 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>)	in 7/29/11 clinical review (page 6)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ 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 Included

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology <input checked="" type="checkbox"/> None	
Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11/18/11
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
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/6/11
❖ 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 type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 3/23/11, 6/30/11
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
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/22/11, 11/15/11
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 4/14/11, 7/22/11, 11/15/11
❖ Microbiology Reviews	<input type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
<input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	3/21/11, 7/29/11, 8/4/11, 10/17/11
❖ 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</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
<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</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites^b</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</i>) (<i>original and supplemental BLAs</i>)	Date completed: 11/14/11 <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)

^b 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.

Puglisi, Michael

From: Ramanadham, Mahesh
Sent: Monday, November 14, 2011 3:15 PM
To: Puglisi, Michael; Suvarna, Kalavati; Thomas, Colleen; Hughes, Patricia; Kennett, Sarah; Fuchs, Chana
Cc: Albrecht, Renata; Boyd, William M; Chambers, Wiley A; Milstein, Judit
Subject: RE: TB EER for BLA 125387

Attachments: TB-EER BLA 125387-000 update (4) (3).doc

Please find the final TB-EER attached, there are no pending or ongoing compliance actions that prevent approval of this supplement.



TB-EER BLA
125387-000 update (.doc)

Sincerely,

Mahesh Ramanadham, PharmD/M.B.A.
LT., USPHS
Regulatory Compliance Officer
CDER, Office of Compliance
Office of Manufacturing and Product Quality,
Division of Good Manufacturing Practice Assessment
New Drug Manufacturing Assessment Branch
(301)796-3272

From: Puglisi, Michael
Sent: Monday, November 14, 2011 2:53 PM
To: Ramanadham, Mahesh; Suvarna, Kalavati; Thomas, Colleen; Hughes, Patricia; Kennett, Sarah; Fuchs, Chana
Cc: Albrecht, Renata; Boyd, William M; Chambers, Wiley A; Milstein, Judit
Subject: RE: TB EER for BLA 125387

Hi All,

Back in August, I submitted the TB-EER for Eylea (BLA 125387). The response is below (and attached). Please confirm that this is the extent of the documentation needed for the action package. We're trying to reconcile reviews that refer to a 483 at [REDACTED] (b) (4). We plan to approve this BLA by this Friday's PDUFA goal date (11/18/11).
Thanks.

<< File: TB-EER BLA 125387-000 update (4).doc >>

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

From: Ramanadham, Mahesh
Sent: Friday, August 12, 2011 5:29 PM
Subject: Puglisi, Michael; CDER-TB-EER
RE: TB EER for BLA 125387

Hi Michael

NDMAB has completed its review of the TB-EER submitted for BLA 125387. There are no pending or ongoing compliance actions that prevent approval of this supplement.

<< File: TB-EER BLA 125387-000 update (4).doc >>

Sincerely,

Mahesh Ramanadham, PharmD/M.B.A.
LT., USPHS
Regulatory Compliance Officer
CDER, Office of Compliance
Office of Manufacturing and Product Quality,
Division of Good Manufacturing Practice Assessment
New Drug Manufacturing Assessment Branch
(301)796-3272

From: Puglisi, Michael
Sent: Tuesday, August 02, 2011 9:25 AM
To: CDER-TB-EER
Subject: TB EER for BLA 125387

Hi,

Please see the attached and let me know if you have any questions. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
Phone - 301-796-0791
fax - 301-796-9881

<< File: TB-EER BLA 125387-000 update.doc >>

Please provide an updated evaluation of the following drug substance and drug product manufacturing, testing, and packaging/labeling facilities for BLA 125387 (Regeneron, aflibercept ophthalmic solution). The PDUFA date is 18 August.

Drug Substance manufacturing

(b) (4)

Inspected by CDER-DMPQ from (b) (4) and classified VAI. This was pre-licensing inspection for this BLA that found operations acceptable.

Drug Substance (b) (4) Testing Laboratory

(b) (4)

Inspected by (b) (4) from (b) (4) and classified VAI. This GMP inspection found the CTL profile updated and acceptable.

Drug Substance (b) (4) Testing Laboratory

(b) (4)

Inspected by (b) (4) from (b) (4) and classified VAI. This inspection found the CTL profile updated and acceptable.

(b) (4)



Secondary labeling and packaging facility: vial labeling and packaging, final packaging for (b) (4)

(b) (4)
[Redacted text block]



Inspected by (b) (4) from (b) (4) and classified NAI. This was a GMP inspection of this contract packager of (b) (4). The (b) (4) (b) (4) was updated and considered acceptable.



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Transplant and Ophthalmology
Products

Information Request

DATE: September 9, 2011

To: Regeneron Pharmaceuticals, Inc.	From: Michael Puglisi, Regulatory Project Manager
Attention: Laura Pologe	e-mail: Michael.puglisi@fda.hhs.gov
e-mail:	Phone Number: 301-796-0791
Phone Number:	

Subject:

Total no. of pages including cover: 2

Comments:

Hi Laura,

Attached please find an information request from our Micro reviewer for BLA 125387. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-796-1600. Thank you.

Information Request:

1. Please validate container closure integrity using min/max crimping forces. Alternatively, justify why min/max crimping forces cannot be used for container closure integrity validation.

[Redacted] (b) (4)

3. Regarding media fills:

[Redacted] (b) (4)

- b. For the non-conforming environmental monitoring result (PR148353) please provide a summary of the root cause, corrective and preventive actions, and impact on products.

[Redacted] (b) (4)

6. Please provide descriptions and 510(k) documentation for the empty plastic syringe and the 30 G delivery needle packaged with the [Redacted] (b) (4) vial.

7. For drug product samples on stability, performance of container closure integrity testing in lieu of sterility testing is recommended [Redacted] (b) (4)

[Redacted]



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA 125387/0

EXTENSION USER FEE GOAL DATE

August 17, 2011

Regeneron Pharmaceuticals, Inc.
Attention: Laura Pologe, Ph.D.
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, New York 10591-6707

Dear Dr. Pologe:

Please refer to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for Eylea (afibercept injection).

We received your August 12, 2011, amendment to this application on August 12, 2011, and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to November 18, 2011, to provide time for a full review of the amendment.

We also acknowledge receipt of your August 1, 2011, amendment which ^{(b) (4)}
^{(b) (4)} and your August 10, 2011, amendment ^{(b) (4)}

dosage form under consideration in this application is the 40 mg/mL ^{(b) (4)} vial.

If you have any questions, please contact Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

MEMORANDUM OF TELECONFERENCE

MEETING DATE: August 9, 2011
TIME: 12:30 pm
LOCATION: Teleconference
APPLICATION: BLA 125387
DRUG NAME: Eylea (aflibercept injection)
SPONSOR: Regeneron Pharmaceuticals, Inc.

FDA ATTENDEES:

Renata Albrecht/ Director, Division of Transplant and Ophthalmology Products (DTOP)
William Boyd/ Clinical Team Leader, DTOP
Patrick Swann/ Deputy Director, Division of Monoclonal Antibodies
Michael Puglisi/ Project Manager, DTOP
David Roeder/ Associate Director for Regulatory Affairs, Office of Antimicrobial Products
Judith Milstein/Chief, Project Management Staff, DTOP

EXTERNAL CONSTITUENT ATTENDEES:

Laura Pologe/ Regulatory Affairs
William Roberts/ Regulatory Affairs
Ned Braunstein/ Executive Director, Regulatory Affairs

BACKGROUND:

On August 3, 2011, the Division forwarded to Regeneron a list of issues identified during the review of this BLA, in preparation for a teleconference scheduled for August 4, 2011. During the August 4, 2011, teleconference the Division indicated that the intention of the teleconference was to provide an update on the status of the issues identified and to provide Regeneron an opportunity to ask specific questions about the issues identified by the Product Quality and Microbiology Staff reviewers. As a follow up to that teleconference, Regeneron sent an e-mail on August 8, 2011, with responses to the issues listed in the August 3, 2011 correspondence, which would be the topic for discussion at a teleconference previously scheduled for August 9, 2011.

DISCUSSION POINTS:

Dr. Albrecht stated that the intention of our recent communications was to provide Regeneron an opportunity for clarification of the deficiencies conveyed to them in the August 3, 2011 correspondence and not to resolve those issues before the PDUFA goal date. Dr. Albrecht further stated that it was not feasible to review Regeneron's draft response of August 8, 2011, before the PDUFA goal date.

Mr. Roeder explained the process involved in taking a regulatory action. He stated that according to PDUFA, the Agency can take an Approval action or a Complete Response action on a BLA. He further explained that a Complete Response action means that the Agency has reviewed the application, but not necessarily amendments, and that further information is needed to approve it. A Complete Response letter would provide a list of the information needed to approve the application. He further stated that there would be a 6-month review period upon the receipt of the Sponsor's complete resubmission.

 8/10/11

Michael Puglisi
Regulatory Project Manager

Puglisi, Michael

From: Puglisi, Michael
Sent: Wednesday, August 03, 2011 4:32 PM
To: 'Laura Pologe'
Subject: Comments for BLA 125387

Attachments: BLA Comments (2) (2).doc

Hi Laura,

Please see the attached and let me know if you have any questions. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881



BLA Comments (2)
(2).doc (149 ...)

BLA 125387

Applicant: Regeneron Pharmaceuticals Inc.

Eylea (afibercept injection)

Submission date: February 17, 2011

Receipt date: February 18, 2011

Dear Dr. Pologe,

In preparation for the teleconference scheduled for Thursday, August 4, 2011, we are enclosing the comments from the Product Quality and Microbiology Sterility sections of the afibercept BLA for discussion and clarification.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application.

Product Quality Comments:

Items 1 - 24 were previously conveyed to you in an information request dated June 20, 2011. We acknowledge your amendments to the BLA dated June 29, July 5 and 8, 2011. Please note that we have not reviewed these three amendments at this time.

In addition, we request clarification regarding the items below which are presented in italicized and underlined font.

Finally, we request that items 8a, 11a, 22, 37, and 43, (underlined text) be addressed although they may be addressed in the future, for example, they may become Post Marketing Commitments (PMC).

1. Regarding the cell banks:



2. As currently presented, it is not possible to assess the appropriateness of most of the in process controls (IPCs) identified in section 3.2.S.2.2.

a. Provide data to support the IPCs. For each IPC, historical data for each lot that was used for calculating mean should be presented; the IPC historical range, mean, and standard deviation (SD) should also be included.

b. For those IPC limits set using historical mean ^{(b) (4)} D, provide justification for setting IPC limits based on ^{(b) (4)} SDs.

c. Describe the actions taken for out-of-trend excursions (IPC values that fall outside the internal action limits). Identify any IPC that would not follow the general OOT actions and the action(s) that would be taken. For example, excursions past the limit of in vitro cell age (LIVCA), which is based on LIVCA validation data in the BLA, would require submission of a supplement supporting a new LIVCA prior to product release and should not be administered only through a general established deviation procedure and Regeneron's QA release process.

d. Section 3.2.S.2.4.1 (p. 11) states that "IPCs with limited predictive power will be removed from consideration." The IPCs identified in section 3.2.S.2.2 should not be removed without the proper submissions to the BLA.

v. As Regeneron has only small scale model studies for resin lifetime of protein A, cation, anion and HIC resins, concurrent validation studies have been implemented for the full scale process. Provide the comprehensive protocols for concurrent validation of resin lifetime and validation of TFF membrane lifetime.

vi. Provide all available data from any concurrent validation of resin lifetime studies at full scale.

d. Regarding hold time:

i. Provide data supporting the hold time validation acceptance criteria.

ii. Submit results (raw data) from IEF testing for the samples that did not meet acceptance criteria for hold time validation.

(b) (4)

v. Table 13 in section 2.3.S.2 lists the completion status of processing hold times as “concurrent validation.” Please clarify your intentions. Until validation of hold times is complete and data are submitted to the BLA, the hold times may not be considered part of the approved BLA process.

vi. For (b) (4) hold times, it is stated that microbial results met their acceptance criteria “demonstrating that the evaluated hold times are acceptable for this process” (section 3.2.S.2.5.7 p. 108). However, product quality assessment was included in the study design and testing is “currently in progress.” Therefore, the hold time validations are not complete, and the hold times will not be acceptable as part of the approved BLA process.

vii. Regarding media hold times (Table 78, section 3.2.S.2.5.7, p. 109), bioburden acceptance criteria are presented; however, footnote “a” states that “a bioburden specification is not applicable.” The media and media solution hold studies are performed to ensure that the hold times and conditions are appropriate with respect to the quality of the solutions for use in manufacture; bioburden is a critical parameter for media and solutions, and therefore should be included in these hold studies. Hold times should be based on materials prepared and stored as they would be for use in manufacturing. Therefore, the media and solutions should be filtered and stored under conditions comparable to those used during the manufacturing process, and appropriate bioburden criteria should be set and met. Provide appropriate media and solutions hold times and validation data to justify these times.

(b) (4)

f. The section on Leachates from Contact Surfaces (3.2.S.2.5.9) does not provide any information on the assessments made for the components used and gives the impression that this assessment has not yet been done for the current process. Identify whether assessment of leachates for contact surfaces has been finalized and include the evaluation results for those products/steps requiring further evaluation based on your decision process.

g. Regarding the production-scale conformance batches:

i. Provide the validation protocols, including acceptance criteria.

ii. Provide the genealogy for all batches from C07003 through C07006. (b) (4)

iii. Provide data justifying the use of (b) (4) SD outside of the historical average for those situations where (b) (4) SD was used.

iv. Provide all the validation data, including all operating parameters, performance values, and quality assessments. Include a column containing the historical ranges for each.

v. The action limits for operation and performance values were not discussed; identify any results that were outside the action limits that were identified in section 3.2.S.2.4.

vi. Regeneron's conclusion of the performance results for DS intermediate (section 3.2.S.2.5.11.1, p. 125) is that "in total, the outlying performance results comprised less than (b) (4) of the total results evaluated. These data suggests that the performance of the aflibercept manufacturing process is highly consistent." This statement is not supported by the information provided as this is not the total of the outlying performance results but is the performance results with particular results excluded. Two paragraphs earlier, it is stated that "in total, 123 of 2472 performance results (72 of 616 performance parameters) fell outside the (b) (4) standard deviation historical limits." Therefore, the actual outlying performance results comprised (b) (4) of the total results evaluated. No data were provided to allow an assessment of the results that were excluded by Regeneron. In your response to item g(iii), identify those datapoints that were excluded. For each of these datapoints, provide a justification for the validity of its exclusion.

vii. Clarify why there is a minimum load requirement for the (b) (4)

(section 3.2.S.2.5.10.2, p. 133).

viii. Provide good quality reproductions of the IEF gels and individual band quantitation data for the conformance lots and any additional lots from which data will be used for setting specification acceptance criteria.

4. Regarding DS characterization:

a. Provide data for characterization of higher order (secondary/tertiary) structure in addition to the disulfide bonding assessment obtained using peptide mapping.

b. Regarding MALLS analyses:

iii. Provide information regarding the locations of the truncations for species that initiate at the N-terminus.

iv. Provide to section 3.2.S.3.2.3.2 Table 14 the results for % aggregate for all lots, as these data should be available, and update the aggregation range to include the additional data.

(b) (4)

There appear to be HMW bands in the reduced SDS-PAGE gel shown in Figure 7 (section 3.2.S.3.2.3.1.2). However, in section 3.2.S.3.2.3.2 (p. 34), it is stated that “the lack of high molecular weight species in SDS-PAGE analysis suggests that aflibercept aggregates formed under stress conditions are reversible in SDS-PAGE and non-covalent in nature.” It appears that there are discrepancies in the identification of the nature of the aflibercept aggregates; in addition, SDS-PAGE analyses of material stored under stress conditions are not described in this section. Clarify the apparent discrepancies and include data supporting the statements and conclusions made.

k. ISOQUANT analysis was used for the characterization of deamidation. Given that deamidation of asparagine can result in non-isomerized aspartate, and, therefore, that this assay would not monitor all potential deamidation reactions, provide information on non-isomerized forms of deamidated species that may be present.

5. Regarding specifications:

a. Provide justification for a proposed bioassay acceptance criterion of (b) (4) for DS intermediate, when the proposed acceptance criterion for DS is (b) (4)

b. Provide justification for a proposed charge heterogeneity acceptance criterion of 70% for DS intermediate, when the proposed acceptance criterion for DS is (b) (4)

c. Provide justification for the proposed DS protein concentration acceptance criterion (b) (4)

(b) (4)

d. Describe and justify the use of stability data for setting proposed acceptance criteria for release (section 3.2.S.4.5.1). Include an assessment of how release at extremes that are supported by stability data would not allow for failure of aflibercept by the expiration timeline.

6. Regarding analytical procedures:

a. Clarify the statement that appearance and color and pH methods are “based on” USP and Ph. Eur. If different from the compendial method, provide information on the changes from compendia and the validation data where appropriate.

b. Provide data supporting the use of material diluted to 1 mg/ml for the SEC assay that is intended to monitor levels of aggregate.

(b) (4)

8. Regarding reference standard (RS):

a. In section 3.2.S.5.1.2 Regeneron states that Qualification of future lots of reference standard will be performed using the commercial specifications. Please be aware that qualification of a RS based on the lot release acceptance criteria is not necessarily acceptable. Criteria must be in place to prevent drift in product quality. For example, assays that use RS as a comparator, such as the potency assay, would require a new RS to be very similar to the existing reference standard, and those requirements should be reflected in the protocol for qualification of a new RS. Please note that release of new RS would require submission of the protocol and data to the BLA for approval prior to use.

b. Characterization results for the current RS lot (b) (4) at qualification and data from earlier RS lots at the 24 month stability time point (section 3.2.S.5.1.3, Table 3) show that the molecular weights for HMW species and main species determined by SEC-MALLS were significantly lower for the 24 month stability samples than for the fresh qualification sample, indicating that there could have been an (b) (4) change in each monomer during storage. Address the apparent instability of the RS under its storage condition of -80°C.

9. Regarding DS container closure:

a. Regarding the microbial aerosol challenge (section 3.2.S.6.1.7.3), identify the manufacturing steps involving (b) (4) and justify the use of (b) (4) during container closure integrity testing. Clarify if step 18.3.2 of batch record document number MR1054, describing (b) (4), is the same as the (b) (4)

b. Justify the use of the (b) (4) leachable/extractable testing (section 3.2.S.6.1.4, Table 2).

c. Clarify the calculation of (b) (4) (3.2.S.6.1.4.2, p. 7), as the FTIR results listed in Table 4 are significantly higher than (b) (4)

d. Justify the methods used for concentration of samples from extractables testing, given that the concentration methods could lead to loss of some types of extractables.

10. Regarding DS stability:

a. For SDS-PAGE and IEF testing, provide good quality reproductions of the gels containing the first and last available timepoints for all lots on stability.

b. Provide freeze-thaw stability data for DS intermediate and DS. Alternatively, provide the controls that are in place to prevent thawed DS intermediate or DS from being refrozen and thawed again for use in future manufacturing.

11. Regarding post-approval stability protocol and stability commitment:

a. Regeneron states in both section 3.2.S.7.2 and in the overall quality summary that one lot of drug substance will be placed on stability annually and that any failures will be reported.

b. We note that drug substance stability allows a (b) (4) Identify the causes for this change in protein concentration. We also note that color and appearance are not tested to the same criteria at stability as at release. Please justify these differences.

12. Provide stability data for all formulated bulk lots tested. Include data for all timepoints available and provide good quality reproductions of SDS-PAGE and IEF gels for the first and last available timepoints for each of the lots.
13. Regeneron's formulation development studies to support upper and lower ranges and effect on product quality is ongoing. Very limited data were submitted to the BLA in section 3.2.P.2.1.4. Conclusions made based on these limited data need further justification:
- Provide updated stability data and justification of conclusions made based on only 2 months of real time data. The submitted 1st and 2nd month timepoints for the "proven acceptable range" studies have no potency assessments for any of the completed portions of the study or for any available time point for the real time or accelerated portions of the study, no SDS-PAGE or IEF assessments for the real time or accelerated portions of the study, and no instron, imaged microscopy, FTIR assessments. Provide updated data to this section.
 - The studies for assessment of effects of (b) (4) on product quality are not complete. Provide updated data to this section. In addition, provide justification for the filtering of data to exclude (b) (4)
 - Update the data from the studies assessing effects of (b) (4) on product quality.
 - Update the data from the studies assessing the effects of manufacturing steps on product quality.
 - Regarding the assessment of effects of exposure to (b) (4) on stability, section 3.2.P.2.1.7.3 states that the control was DP that was "not exposed to (b) (4). Clarify this statement; i.e. was DP manufactured without the use of (b) (4) or was there no additional exposure to (b) (4)
14. Regarding manufacturing process development:
- On the subject of comparability:
 - The comparative stability study was not complete at the time of BLA submission. Update the stability data for the comparisons of the JHP- and Vetter-filled DP and Hollister-Stier-filled DP and for the sterilized and unsterilized prefilled syringes. (b) (4)
 - Regarding the decay profiles, as no primary data were provided, the degradation profile of individual aspects (e.g. the identity of HMW variants, LMW variants, charge variants that are generated) cannot be assessed; provide appropriate data to the BLA for review.
 - Provide assessments of rates of degradation for the stressed (45°C) stability comparability studies based on statistical analyses.
 - Provide data with respect to charge variants supporting the comparability of stability of DP in vials (b) (4)

15. There are inconsistencies among the quality overall summary (2.3.I) Table 1, the manufacturer information in sections 2.3.P and 3.2.P, and the attachment to FDA Form 356h regarding manufacturers and the activities occurring at each manufacturing site. Update all of the sections to reflect the correct manufacturing and testing activities occurring at each site for each of the drug product presentations.

(b) (4)

17. Regarding controls of critical steps and intermediates:

a. Submit formulated bulk stability data for all lots placed on stability. Include all time points available.

b. In sections 3.2.P.3.4, it is not clear what type(s) of limit are associated with the given parameters and criteria. The limits are listed as action limits in section 3.2.P.3.3. Clarify and discuss the action taken. (b) (4)

18. Regarding process validation

a. Formulated bulk – (b) (4)

(b) (4)

(b) (4)

v. While section 3.2.P.3.5.1.1 (p.3) states that a validation study designed to establish process hold times is currently in progress, section 3.2.P.3.5.1.3 indicates that this validation is complete. Clarify this discrepancy and submit the full validation results to the BLA. Although some results are listed in section 3.2.P.3.5.1.3 table 5, it is not clear whether this is the final completed validation data or some interim data while validation is in progress.

vi. Evaluate the hold time for effects on product quality and submit the data to the BLA. We note that there was some assessment of a hold in

(b) (4)

(b) (4)

(b) (4)



20. According to the container closure section for (b) (4) vials (3.2.P.7 p.5), the secondary packaging contains one vial, one filtration needle, and one package insert; there is no mention of a syringe or delivery needle. Clarify the contents of the final packaging.

(b) (4)



(b) (4)



(b) (4)



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Micro/Sterility Comments:

1. The shipping validation information indicates that due to the damage observed after (b) (4), the blister pack design will be modified and the shipping validation studies will be (b) (4).
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
2. Define the following process parameters for (b) (4).
 - a. The acceptable range for humidity.
 - b. The minimum aeration time.
 - c. The acceptance criterion for weight of (b) (4) into the chamber in terms of product load.
3. Regarding the cycle development and process validation studies for (b) (4).
 - a. Provide the following information for the biological indicators (BIs): organism, type (spore strip, etc.), manufacturer's D-value, population, and confirmation of

(b) (4)



4. Define the acceptable ranges for temperature, humidity, and chamber pressure for the  (b) (4)



5. Regarding the cycle development and process validation studies for  (b) (4)



(b) (4)



6. Provide the sensitivity of the bubble leak test for package integrity in terms of the breach size detectable.

(b) (4)



8. Regarding container closure integrity testing of drug product in vials:

(b) (4)

- b. Indicate whether container closure integrity has been validated for the (b) (4) (b) (4) vials using worst-case filling speed and crimping forces.
- c. Provide the bacterial concentration at the end of the microbial ingress tests performed for the (b) (4) vials.

(b) (4)

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b4 (CCI/TS) immediately following
this page

(b) (4)

16. Insufficient information is provided for the sterility test method

(b) (4)

In addition, we request clarification on the following:

(b) (4)

In addition, we request the following items be addressed although they may be addressed in the future, for example, Post Marketing Commitments (PMC).

19. Performance of the container closure integrity test in lieu of the sterility test for drug product stability samples at expiry is recommended.

(b) (4)

21. Regarding hold time validation studies performed at (b) (4) hold time studies for microbial control at scale is facility-specific and should be performed for each facility even if the processes are the same and identical equipment is used. Provide at scale end of hold bioburden and endotoxin data from three lots of drug product manufactured at the (b) (4)

Puglisi, Michael

From: Puglisi, Michael
Sent: Tuesday, July 05, 2011 10:34 AM
To: 'Laura Pologe'
Subject: Clinical Information Request for BLA 125387

Hi Laura,

Below please find an information request from our clinical reviewer concerning BLA 125387. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comment:

For VIEW #1, please analyze the primary endpoint of subjects with maintained vision at week 52 for the FAS population with LOCF and PP population with observed cases removing the 13 patients from site #114 retina care specialists (Dr. Mark Michels).

MEMORANDUM OF TELECONFERENCE

MEETING DATE: June 24, 2011
TIME: 4:00 pm
LOCATION: WO22-6336
APPLICATION: BLA 125387
DRUG NAME: Eylea (afibercept injection)
SPONSOR: Regeneron Pharmaceuticals, Inc.

FDA ATTENDEES:

Michael Puglisi/ Project Manager
Wiley Chambers/ Deputy Division Director

EXTERNAL CONSTITUENT ATTENDEES:

William Roberts/ Regulatory Affairs

DISCUSSION POINTS:

The Sponsor requested a telecon to discuss the established name for the product, (b) (4)

The Sponsor proposed that the established name be (b) (4)

The Agency informed the Sponsor that in this case, the USP has determined the established name and we can not change that. (b) (4)

MPuglisi 6/28/11

Michael Puglisi
Regulatory Project Manager

Puglisi, Michael

From: Puglisi, Michael
Sent: Monday, June 20, 2011 8:43 AM
To: 'Laura Pologe'
Subject: CMC Information Request for BLA 125387

Attachments: Regeneron IR DMA CMC.doc

Hi Laura,

Attached is a CMC information request for BLA 125387. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881



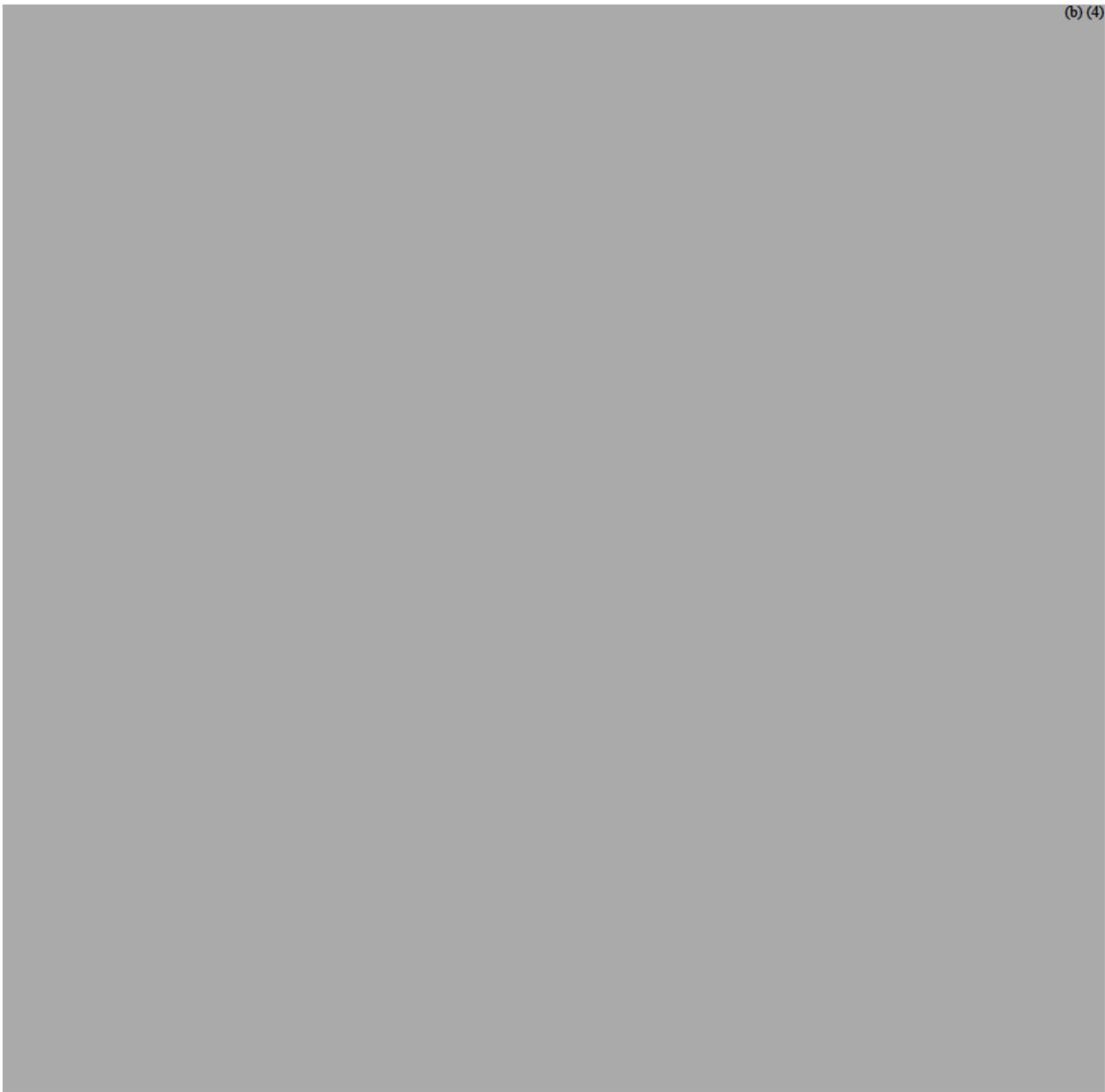
Regeneron IR DMA
CMC.doc (122 ...)

Drug Substance (DS):



2. The BLA states that if reprocessing should be needed, it would be “evaluated through the proper quality/regulatory systems and would include a scientific evaluation prior to a decision to proceed” (3.2.S.2.2.5, p.40). It is not clear based on this statement that Regeneron is aware that as specific reprocessing steps will not be part of the license, release of reprocessed lots for which the reprocessing activity and associated protocols have not been previously approved by the agency will require FDA approval under supplement. Please acknowledge.

3. Regarding the cell banks:



4. As currently presented, it is not possible to assess the appropriateness of most of the in process controls (IPCs) identified in section 3.2.S.2.2.

a. Provide data to support the IPCs. For each IPC, historical data for each lot that was used for calculating mean should be presented; the IPC historical range, mean, and standard deviation (SD) should also be included.

b. For those IPC limits set using historical mean ^{(b) (4)}SD, provide justification for setting IPC limits based on ^{(b) (4)} SDs.

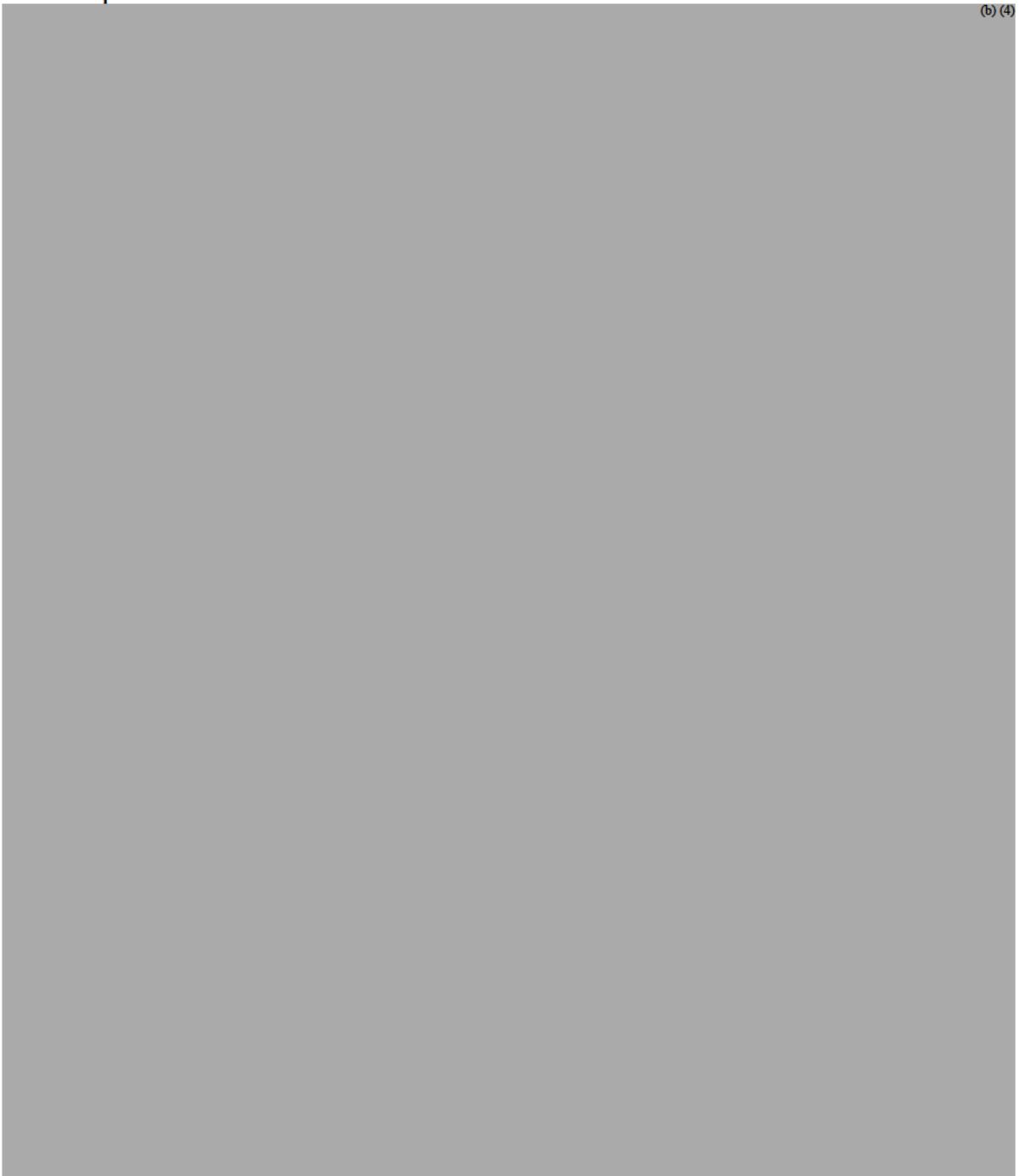
c. Describe the actions taken for out-of-trend excursions (IPC values that fall outside the internal action limits). Identify any IPC that would not follow the general OOT actions and the action(s) that would be taken. For example, excursions past the limit of in vitro cell age (LIVCA), which is based on LIVCA validation data in the BLA,

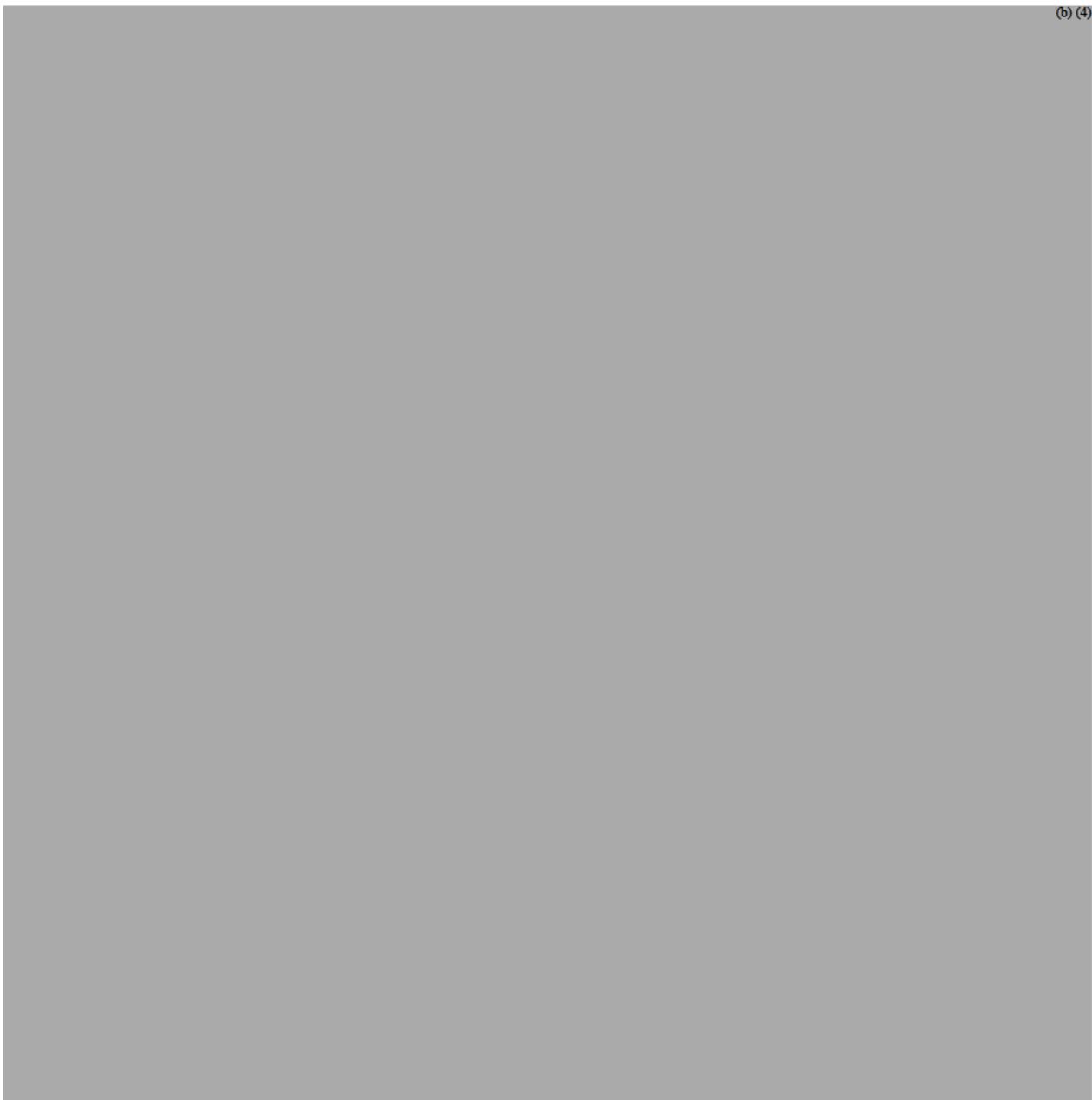
would require submission of a supplement supporting a new LIVCA prior to product release and should not be administered only through a general established deviation procedure and Regeneron's QA release process.

d. Section 3.2.S.2.4.1 (p. 11) states that "IPCs with limited predictive power will be removed from consideration." The IPCs identified in section 3.2.S.2.2 should not be removed without the proper submissions to the BLA.

5. For DS process validation:

(b) (4)





d. Regarding hold time:

i. Provide data supporting the hold time validation acceptance criteria.

ii. Submit results (raw data) from IEF testing for the samples that did not meet acceptance criteria for hold time validation.



v. Table 13 in section 2.3.S.2 lists the completion status of processing hold times as “concurrent validation.” Please clarify your intentions. Until validation of hold times is complete and data are submitted to the BLA, the hold times may not be considered part of the approved BLA process.

vi. For (b) (4) hold times, it is stated that microbial results met their acceptance criteria “demonstrating that the evaluated hold times are acceptable for this process” (section 3.2.S.2.5.7 p. 108). However, product quality assessment was included in the study design and testing is “currently in progress.” Therefore, the hold time validations are not complete, and the hold times will not be acceptable as part of the approved BLA process.

vii. Regarding media hold times (Table 78, section 3.2.S.2.5.7, p. 109), bioburden acceptance criteria are presented; however, footnote “a” states that “a bioburden specification is not applicable.” The media and media solution hold studies are performed to ensure that the hold times and conditions are appropriate with respect to the quality of the solutions for use in manufacture; bioburden is a critical parameter for media and solutions, and therefore should be included in these hold studies. Hold times should be based on materials prepared and stored as they would be for use in manufacturing. Therefore, the media and solutions should be filtered and stored under conditions comparable to those used during the manufacturing process, and appropriate bioburden criteria should be set and met. Provide appropriate media and solutions hold times and validation data to justify these times.

f. The section on Leachates from Contact Surfaces (3.2.S.2.5.9) does not provide any information on the assessments made for the components used and gives the impression that this assessment has not yet been done for the current process. Identify whether assessment of leachates for contact surfaces has been finalized and include the evaluation results for those products/steps requiring further evaluation based on your decision process.

g. Regarding the production-scale conformance batches:

i. Provide the validation protocols, including acceptance criteria.

ii. Provide the genealogy for all batches from C07003 through C07006. (b) (4)

iii. Provide data justifying the use of (b) (4) SD outside of the historical average for those situations where (b) (4) SD was u

iv. Provide all the validation data, including all operating parameters, performance values, and quality assessments. Include a column containing the historical ranges for each.

v. The action limits for operation and performance values were not discussed; identify any results that were outside the action limits that were identified in section 3.2.S.2.4.

vi. Regeneron's conclusion of the performance results for DS intermediate (section 3.2.S.2.5.11.1, p. 125) is that "in total, the outlying performance results comprised less than (b) (4) of the total results evaluated. These data suggests that the performance of the aflibercept manufacturing process is highly consistent." This statement is not supported by the information provided as this is not the total of the outlying performance results but is the performance results with particular results excluded. Two paragraphs earlier, it is stated that "in total, 123 of 2472 performance results (72 of 616 performance parameters) fell outside the (b) (4) standard deviation historical limits." Therefore, the actual outlying performance results comprised (b) (4) of the total results evaluated. No data were provided to allow an assessment of the results that were excluded by Regeneron. In your response to item g(iii), identify those datapoints that were excluded. For each of these datapoints, provide a justification for the validity of its exclusion.

vii. Clarify why there is a minimum load requirement for the (b) (4)

(b) (4) (section 3.2.S.2.5.10.2, p. 133).

viii. Provide good quality reproductions of the IEF gels and individual band quantitation data for the conformance lots and any additional lots from which data will be used for setting specification acceptance criteria.

6. Regarding DS characterization:

a. Provide data for characterization of higher order (secondary/tertiary) structure in addition to the disulfide bonding assessment obtained using peptide mapping.

b. Regarding MALLS analyses:

i. Provide justification of (b) (4) for performing an assessment to detect high molecular weight species. Include any data identifying if there are HMW species that are no longer detected (b) (4)

ii. Provide enlargements of the entire chromatograph for SEC-MALLS (b) (4)

c. Regarding MS analysis:

i. Provide results from a blank run.

ii. Provide an enlarged view of the spectra surrounding the main aflibercept peaks and clarification of the “satellite” peaks/deconvolution artifacts.

(b) (4)

e. Provide relative percentage data for (b) (4) for each of the lots assessed.

f. Provide the complete integrated peak area analyses for (b) (4). In addition, there are unidentified peaks with percent areas that appear to be greater than (b) (4) (based on the apparent size of (b) (4) identification of such peaks should have been determined. Submit data on all these peaks and the complete integrated peak area analysis to the BLA.

g. Provide the VEGF165 binding stoichiometry data for lot C08001M440.

h. (b) (4) and (b) (4) should be assessed as process related impurities; there is no discussion of either of these cell culture components in either the validation section or the impurities section. Provide data regarding the amount present in drug substance or validate clearance of these process related impurities by the purification process.

(b) (4)

j. Regarding product size-related impurities:

i. It is stated in section 3.2.S.3.2.3.1.2 (p. 26) that all (b) (4) (including (b) (4)) were “determined to possess the correct, predicted N-terminal sequence of aflibercept.” However, Table 13 of that section states that the N-terminal sequence of (b) (4) was “not determined.” Clarify this discrepancy.

ii. Table 13 lists only 3 N-terminal sequences for the non-reduced (b) (4) species (b) (4) while an additional sequence with truncation at (b) (4) is listed in Table 12. It is not clear which species corresponds to the structure depicted for the (b) (4) species. Please clarify.

iii. Provide information regarding the locations of the truncations for species that initiate at the N-terminus.

iv. Provide to section 3.2.S.3.2.3.2 Table 14 the results for % aggregate for all lots, as these data should be available, and update the aggregation range to include the additional data.

(b) (4) There appear to be HMW bands in the reduced SDS-PAGE gel shown in Figure 7 (section 3.2.S.3.2.3.1.2). However, in section 3.2.S.3.2.3.2 (p. 34), it is stated that “the lack of high molecular weight species in SDS-PAGE analysis suggests that aflibercept aggregates formed under stress conditions are reversible in SDS-PAGE and non-covalent in nature.” It appears that there are discrepancies in the identification of the nature of the aflibercept aggregates; in addition, SDS-PAGE analyses of material stored under stress conditions are not described in this section. Clarify the apparent discrepancies and include data supporting the statements and conclusions made.

k. ISOQUANT analysis was used for the characterization of deamidation. Given that deamidation of asparagine can result in non-isomerized aspartate, and, therefore, that

this assay would not monitor all potential deamidation reactions, provide information on non-isomerized forms of deamidated species that may be present.

7. Regarding specifications:

a. Provide justification for a proposed bioassay acceptance criterion of (b) (4) for DS intermediate, when the proposed acceptance criterion for DS is (b) (4)

b. Provide justification for a proposed charge heterogeneity acceptance criterion of 70% for DS intermediate, when the proposed acceptance criterion for DS is (b) (4)

c. Provide justification for the proposed DS protein concentration acceptance criterion (b) (4)

(b) (4)

d. Describe and justify the use of stability data for setting proposed acceptance criteria for release (section 3.2.S.4.5.1). Include an assessment of how release at extremes that are supported by stability data would not allow for failure of aflibercept by the expiration timeline.

8. Regarding analytical procedures:

a. Clarify the statement that appearance and color and pH methods are “based on” USP and Ph. Eur. If different from the compendial method, provide information on the changes from compendia and the validation data where appropriate.

b. Provide data supporting the use of material diluted to 1 mg/ml for the SEC assay that is intended to monitor levels of aggregate.

9. Provide batch analysis data for all DS intermediate lots and equivalent lots used as (b) (4)

(b) (4)

10. Regarding reference standard (RS):

a. In section 3.2.S.5.1.2 Regeneron states that Qualification of future lots of reference standard will be performed using the commercial specifications. Please be aware that qualification of a RS based on the lot release acceptance criteria is not necessarily acceptable. Criteria must be in place to prevent drift in product quality. For example, assays that use RS as a comparator, such as the potency assay, would require a new RS to be very similar to the existing reference standard, and those requirements should be reflected in the protocol for qualification of a new RS. Please note that release of new RS would require submission of the protocol and data to the BLA for approval prior to use.

b. Characterization results for the current RS lot (b) (4) at qualification and data from earlier RS lots at the 24 month stability time point (section 3.2.S.5.1.3, Table 3)

show that the molecular weights for HMW species and main species determined by SEC-MALLS were significantly lower for the 24 month stability samples than for the fresh qualification sample, indicating that there could have been an (b) (4) change in each monomer during storage. Address the apparent instability of the RS under its storage condition of -80°C.

11. Regarding DS container closure:

a. Regarding the microbial aerosol challenge (section 3.2.S.6.1.7.3), identify the manufacturing steps involving (b) (4) and justify the use of (b) (4) during container closure integrity testing. Clarify if step 18.3.2 of batch record document number MR1054, describing (b) (4) is the same as the (b) (4)

b. Justify the use of the (b) (4) leachable/extractable testing (section 3.2.S.6.1.4, Table 2).

c. Clarify the calculation of (b) (4) (3.2.S.6.1.4.2, p. 7), as the FTIR results listed in Table 4 are significantly higher than (b) (4)

d. Justify the methods used for concentration of samples from extractables testing, given that the concentration methods could lead to loss of some types of extractables.

12. Regarding DS stability:

a. For SDS-PAGE and IEF testing, provide good quality reproductions of the gels containing the first and last available timepoints for all lots on stability.

b. Provide freeze-thaw stability data for DS intermediate and DS. Alternatively, provide the controls that are in place to prevent thawed DS intermediate or DS from being refrozen and thawed again for use in future manufacturing.

13. Regarding post-approval stability protocol and stability commitment:

a. Regeneron states in both section 3.2.S.7.2 and in the overall quality summary that one lot of drug substance will be placed on stability annually and that any failures will be reported. (b) (4)

b. We note that drug substance stability allows a (b) (4) Identify the causes for this change in protein concentration. We also note that color and appearance are not tested to the same criteria at stability as at release. Please justify these differences.

14. Provide stability data for all formulated bulk lots tested. Include data for all timepoints available and provide good quality reproductions of SDS-PAGE and IEF gels for the first and last available timepoints for each of the lots.

Drug Product (DP):

15. Regeneron's formulation development studies to support upper and lower ranges and effect on product quality is ongoing. Very limited data were submitted to the BLA in section 3.2.P.2.1.4. Conclusions made based on these limited data need further justification:

a. Provide updated stability data and justification of conclusions made based on only 2 months of real time data. The submitted 1st and 2nd month timepoints for the "proven acceptable range" studies have no potency assessments for any of the completed portions of the study or for any available time point for the real time or accelerated portions of the study, no SDS-PAGE or IEF assessments for the real time or accelerated portions of the study, and no instron, imaged microscopy, FTIR assessments. Provide updated data to this section.

b. The studies for assessment of effects of (b) (4) on product quality are not complete. Provide updated data to this section. In addition, provide justification for the filtering of data to exclude (b) (4)

(b) (4)

c. Update the data from the studies assessing effects of (b) (4) on product quality.

d. Update the data from the studies assessing the effects of manufacturing steps on product quality.

e. Regarding the assessment of effects of exposure to (b) (4) on stability, section 3.2.P.2.2.1.7.3 states that the control was DP that was "not exposed to (b) (4)." Clarify this statement; i.e. was DP manufactured without the use of (b) (4) or was there no additional exposure to (b) (4)

16. Regarding manufacturing process development:

a. On the subject of comparability:

i. The comparative stability study was not complete at the time of BLA submission. (b) (4)

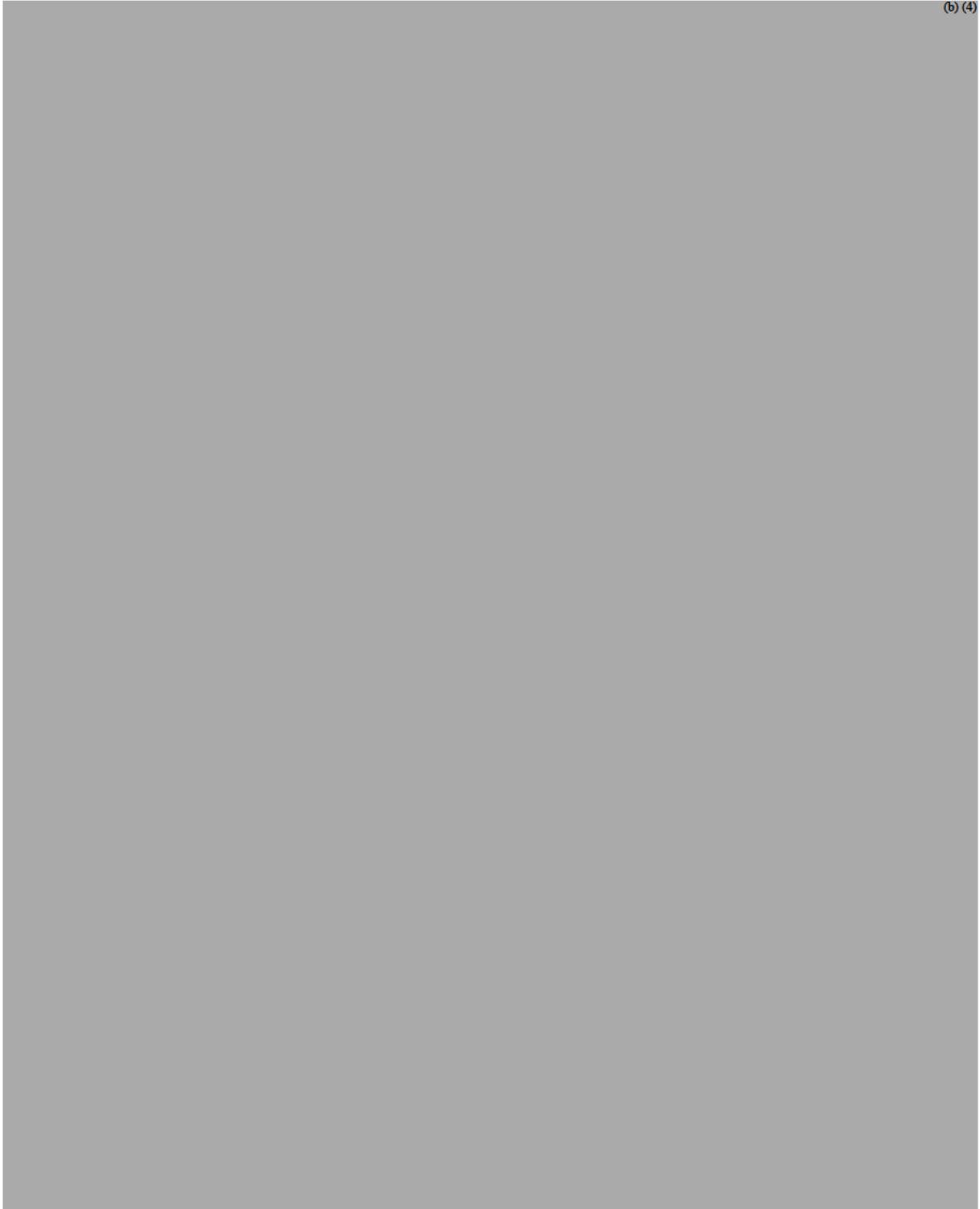
(b) (4)

(b) (4)

Regarding the decay profiles, as no primary data were provided, the degradation profile of individual aspects (e.g. the identity of HMW variants, LMW variants, charge variants that are generated) cannot be assessed; provide appropriate data to the BLA for review.

iii. Provide assessments of rates of degradation for the stressed (45°C) stability comparability studies based on statistical analyses.

iv. Provide data with respect to charge variants supporting the comparability of stability of DP in vials (b) (4)



(b) (4)

17. There are inconsistencies among the quality overall summary (2.3.I) Table 1, the manufacturer information in sections 2.3.P and 3.2.P, and the attachment to FDA Form 356h regarding manufacturers and the activities occurring at each manufacturing site. Update all of the sections to reflect the correct manufacturing and testing activities occurring at each site for each of the drug product presentations.

19. Regarding controls of critical steps and intermediates:

a. Submit formulated bulk stability data for all lots placed on stability. Include all time points available.

b. In sections 3.2.P.3.4, it is not clear what type(s) of limit are associated with the given parameters and criteria. The limits are listed as action limits in section 3.2.P.3.3. Clarify and discuss the action taken. (b) (4)

20. Regarding process validation

a. Formulated bulk – (b) (4):

(b) (4)

v. While section 3.2.P.3.5.1.1 (p.3) states that a validation study designed to establish process hold times is currently in progress, section 3.2.P.3.5.1.3 indicates that this validation is complete. Clarify this discrepancy and submit the full validation results to the BLA. Although some results are listed in section 3.2.P.3.5.1.3 table 5, it is not clear whether this is the final completed validation data or some interim data while validation is in progress.

vi. Evaluate the hold time for effects on product quality and submit the data to the BLA. We note that there was some assessment of a hold in (b) (4)

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ix. The (b) (4) vial and (b) (4) validation protocols and reports (PVP-R-MA-VITV-3.0, PVR-R-MA-VITV-3.0/4.0/7.0, respectively) state that “the time and distance covered by this route also validates shipments between any other locations within this shipping distance.” Provide justification for this statement, as the time/distance could allow for shipping to locations outside this climate zone, and validation of the shipper’s ability to hold the 2-8°C temperature under high temperature conditions or without access to a power supply has not been provided. Alternatively, identify how deviations due to such variables are controlled by your process.

x. Provide an assessment of potential adverse effects on product quality caused by the (b) (4) based on the pre-sterilization values, not the lot release acceptance criteria as shown in sections 3.2.P.3.5.1.2 (Table 7) and 3.2.P.3.5.1.2 (Table 4). The fact that test results that are still within release specification acceptance criteria do not indicate that the sterilization process did not affect the product.

21. Regarding control of drug product:



(b) (4)



22. According to the container closure section for ^{(b) (4)} vials (3.2.P.7 p.5), the secondary packaging contains one vial, one filtration needle, and one package insert; there is no mention of a syringe or delivery needle. Clarify the contents of the final packaging.

(b) (4)



(b) (4)



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f l l i t h i

Puglisi, Michael

From: Puglisi, Michael
Sent: Tuesday, May 31, 2011 10:58 AM
To: 'Laura Pologe'
Subject: Micro Information Request for BLA 125387

Hi Laura,

Below please find a request for additional information from the micro reviewer for BLA 125387. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comment:

Please provide the bioburden and endotoxin release specifications for the aflibercept formulated bulk drug substance.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

IND 012462
BLA 125387

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

ATTENTION: Laura Pologe, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Pologe:

Please refer to your Investigational New Drug Application (IND), submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act, and to your Biologics License Application (BLA) dated February 17, 2011, received February 18, 2011, submitted under section 351 of the Public Health Service Act for Afilbercept Injection, 40 mg/ml.

We also refer to your December 9, 2010, IND correspondence, received December 10, 2010, and to your February 28, 2011, BLA correspondence, received March 1, 2011, requesting review of your proposed proprietary name, Eylea. We have completed our review of the proposed proprietary name, Eylea, and have concluded that it is acceptable.

The proposed proprietary name, Eylea, 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 17, 2011, 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 Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Michael Puglisi at (301) 796-0791.

Sincerely,

Carol Holquist 5-25-2011

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

Puglisi, Michael

From: Puglisi, Michael
Sent: Friday, May 06, 2011 3:14 PM
To: 'Laura Pologe'
Subject: Stats Information Request for BLA 125387

Hi Laura,

Below please find an information request from our statistician for BLA 125387. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comments:

In our review, we plan to conduct a sensitivity analysis using multiple imputation approach for missing data. Please provide the same for the following two endpoints:

- 1. Proportion of Subjects who Maintained Vision at Week 52*
- 2. Change from baseline in BCVA as measured by ETDRS letter score*

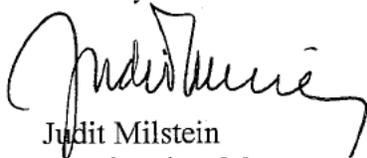
STN 125387 Aflibercept
Receipt date: February 18, 2011

Dear Dr. Pologe,

In order to continue with the timely review of your application, we request you submit the following information no later than May 27, 2011.

1. Please explain the actions taken for bioburden and endotoxin excursions above the specified action limits for the (b) (4)
2. Please clarify why the endotoxin release criterion for the drug substance intermediate (Table 5, section 3.2.S.2.4) is different from action limits specified for the drug substance intermediate (b) (4). Please indicate if (b) (4) was used to test the drug substance intermediate. If the (b) (4) was used, provide qualification data for the (b) (4) and indicate the process steps where this assay is used.
3. Please explain how bioburden is introduced into the process at (b) (4) and why the bioburden action limit (b) (4)
4. Please provide bioburden and endotoxin monitoring data (initial and end of hold) from full scale hold studies for 3 batches of media, buffer, and solutions. Please provide a justification for the bioburden acceptance criterion (b) (4) in the hold studies.

Thank you



Judit Milstein
Chief Project Management Staff
Division of Transplant and Ophthalmology Products
Center for Drug Evaluation and Research



Our STN: BL 125387/0

FILING COMMUNICATION

April 15, 2011

Regeneron Pharmaceuticals, Inc.
Attention: Laura Pologe, Ph.D.
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, New York 10591-6707

Dear Dr. Pologe:

This letter is in regard to your biologics license application (BLA), dated February 17, 2011, received February 18, 2011, submitted under section 351 of the Public Health Service Act, for Aflibercept Ophthalmic Injection.

We also refer to your submissions dated February 28, March 10, 18, 24, and April 1, 4, 8, 11 (two), and 13 (two), 2011.

We have completed an initial review of your application to determine its acceptability for filing. Under 21 CFR 601.2(a), we will file your application on April 19, 2011. The review classification for this application is Priority. Therefore, the user fee goal date is August 20, 2011. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

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, mid-cycle, 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 commitment requests by July 23, 2011.

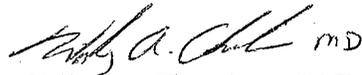
At this time, we have not identified any potential review issues. Our filing review is only a preliminary review, and deficiencies may be identified during substantive review of your application.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

Handwritten signature of Wiley A. Chambers, M.D. in cursive script.

Wiley A. Chambers, M.D.

Acting Director

Division of Anti-Infective and Ophthalmology Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

Puglisi, Michael

From: Puglisi, Michael
Sent: Friday, April 01, 2011 4:05 PM
To: 'Laura Pologe'
Subject: Micro Reviewer's Comments re: BLA 125387

Hi Laura,

Below please find an information request from our micro reviewer concerning BLA 125387. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comments:

Please refer to the 27-Sep-2010 pre-BLA CMC meeting minutes and the guidance document referenced therein for additional guidance on Agency expectations regarding submission of product quality information for original BLAs.

(b) (4)

Regarding vial manufacturing at (b) (4), please resubmit section 3.2.P.3.5 with the following product quality microbiology data included and links to the requested reports:

11. Provide validation summaries and data for the (b) (4) to sterilize product contact surfaces, parts, and closures. List and compare parameters and loads used for validation to those used for routine production.
12. Provide validation summaries and data for vial washing and sterilization/depyrogenation. List and compare parameters and loads used for validation to those used for routine production.
13. Provide validation summaries and data for SIP of any surfaces that contact sterile product, if applicable. List and compare SIP parameters used for validation to those used for routine SIP.
14. Provide the process parameters for the (b) (4), including the time limit (b) (4) and explain how the validation studies support these parameters. Provide the (b) (4) reports for the microbial retention and product bubble point determination studies.
15. Provide additional information regarding media fills, including environmental monitoring data collected during the fills. Describe media fill procedures and explain how media fill conditions are considered worst-case compared to routine production.

Please provide the following additional information regarding vial manufacturing at (b) (4)

16. Provide validation summaries and data for the microbial ingress and dye ingress container closure integrity tests.
17. The hold time validation data presented in Table 6 of section 3.2.P.3.5 does not include bioburden and endotoxin data for each lot at the end of hold. Provide at-scale bioburden and endotoxin data from three lots of material supporting the hold time acceptance criteria as listed in Table 6.
18. Clarify the vial size used at (b) (4)
19. Clarify whether a bulk sterility test is performed. If not, submit a formal request to waive the bulk sterility test requirement (21 CFR 610.9).

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MEMORANDUM OF TELECONFERENCE

MEETING DATE: March 25, 2011
TIME: 1:45 pm
LOCATION: WO22-6336
APPLICATION: BLA 125387
DRUG NAME: Eylea (aflibercept injection)
SPONSOR: Regeneron Pharmaceuticals, Inc.

FDA ATTENDEES:

Michael Puglisi/ Project Manager
William Boyd/Clinical Team Leader
Wiley Chambers/ Deputy Division Director

EXTERNAL CONSTITUENT ATTENDEES:

Laura Pologe/ Regulatory Affairs
William Roberts/ Regulatory Affairs
Ned Braunstein/ Executive Director, Regulatory Affairs

DISCUSSION POINTS:

The Sponsor requested this telecon to ask the Agency for advice in preparation for the June 17, 2011, Advisory Committee Meeting. The Agency informed the Sponsor that we intend to focus on the safety and efficacy of the two Phase 3 studies, VIEW 1 and VIEW 2.

The Sponsor asked if they could provide the Agency any information to help prepare for the meeting. The Agency stated that we do not need any additional information at this time.

The Agency asked the Sponsor if they intend to pursue [REDACTED] ^{(b) (4)} the 2 mg doses. The Sponsor stated that the intended dose is the 2 mg, Q8-weeks dose. The Sponsor stated they would [REDACTED] ^{(b) (4)} depending on the outcome of the review of the BLA.

Michael Puglisi 3/30/11

Michael Puglisi
Regulatory Project Manager

Puglisi, Michael

From: Puglisi, Michael
Sent: Thursday, March 24, 2011 1:52 PM
To: 'Laura Pologe'
Subject: Statistics Reviewer's Comments re: BLA 125387

Hi Laura,

Below please find an information request from our statistics reviewer concerning BLA 125387. Please confirm that you have received these comments and let me know if you have any questions about them. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comments:

- 1. The datasets and programs used to support the integrated analyses of efficacy and safety (ISE and ISS) cannot be located. Please advise if you have submitted them. If not, please submit them as soon as possible to help us conduct a more efficient review.*
- 2. A total of 36 subjects in Study VGFT-OD-0618 were classified as screening failures in analysis dataset (ADSL) and their randomization numbers were set to blank even though they were randomized and assigned a randomization number. It is understood that subjects were not randomized until their eligibility was confirmed. Please explain why these subjects were classified as screening failures.*
- 3. It is expected that unique randomization numbers are to be consistently presented in the datasets and conform to the numbers in IVRS system. However, we noted the inconsistency in presenting the randomization number in Study VGFT-OD-0605. The annotated CRF indicates that the randomization number could have 6 digits. But the randomization number in datasets RAND01 and TREAT01 has 7 digits; and in the analysis datasets, the randomization number has 4 digits.
Please clarify the format of the randomization number in IVRS and data manipulation involved to create the randomization number variable in these datasets.*

Puglisi, Michael

From: Puglisi, Michael
Sent: Wednesday, March 23, 2011 4:14 PM
To: 'Laura Pologe'
Subject: Quality Micro Information Request for BLA 125387

Hi Laura,

Below please find an information request from our quality micro reviewer for BLA 125387. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Information Request:

1. Please provide qualification data for the bioburden and endotoxin test methods used for testing in process

(b) (4) Summary data from 3 lots of each in process (b) (4).

(b) (4)

2. Please provide the bioburden testing procedure for (b) (4)

3. Please provide the in process intermediate hold time study protocol. In addition, provide a table with bioburden and endotoxin data along with in process intermediate hold times (each step) for all batches manufactured using the (b) (4).

4. In Section 3.2.S.2.2 "Description of manufacturing process and process control", Tables 6, 7, 9, 10, 12, 13, and 14, show time of production for each step which do not correlate with the proposed in process intermediate hold times. Please explain the discrepancies.

5. Please explain if the shipping method used in the shipping validation study for drug substance is applicable to all drug product sites (b) (4). If not, please explain the differences.

Puglisi, Michael

From: Puglisi, Michael
Sent: Friday, March 18, 2011 12:43 PM
To: 'Laura Pologe'
Subject: Product Quality Information Request for BLA 125387

Hi Laura,

Below please find comments from our Product Quality reviewer concerning BLA 125387 for Aflibercept. Please confirm you have received these comments and let me know if you have any questions about them. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comments:

Filing Issues:

1. Regarding batch records (3.2.R):

- a. The executed batch records currently included in section 3.2.R.1.1 begin with the (b) (4) records for a single lot (b) (4). Submit a complete set of executed batch records for a single lot (b) (4).

(b) (4)

(b) (4)

- d. Submit English translations of batch records executed in a foreign language (e.g. 3.2.R.1.3, 3.2.R.1.4). Alternatively, English translations of the master batch records may be submitted.

2. Submit Letters of Authorization to reference DMFs for all container closure components. Currently, the submission includes authorization to reference DMFs for (b) (4) the submission should include a letter of authorization to cross reference DMFs for all components of the container closure systems to be used in the to be marketed product (b) (4) (b) (4)

(b) (4) (b) (4)

3. A rabbit pyrogen test should be performed at least once to demonstrate that your product does not contain

pyrogenic substances other than bacterial endotoxin.

Provide information and summary data for the rabbit pyrogen test of aflibercept in conformance to 21CFR610.13(b).

Request for clarification:

The Package Insert included in the submission lists only 40 mg/ml dosage forms of the vial (b) (4)

(b) (4) Please verify your intention to commercialize only the 40 mg/ml dosage forms. If only the 40 mg/ml dosage forms are currently intended for licensure (b) (4)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125387/0

BLA ACKNOWLEDGEMENT

March 8, 2011

Regeneron Pharmaceuticals, Inc.
Attention: Laura Pologe, Ph.D.
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, New York 10591-6707

Dear Dr. Pologe:

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: Aflibercept Ophthalmic Injection

Date of Application: February 17, 2011

Date of Receipt: February 18, 2011

Our Submission Tracking Number (STN): BL 125387/0

Proposed Use: Neovascular (Wet) Age-Related Macular Degeneration

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
Therapeutic Biological Products Document Room
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 Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,



/Maureen P. Dillon-Parker/

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Puglisi, Michael

From: Puglisi, Michael
Sent: Monday, March 07, 2011 2:31 PM
To: Laura Pologe
Subject: Clinical Pharmacology Information Request - BLA 125387

Hi Laura,

Below please find an information request from the ClinPharm reviewer for BLA 125387. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Reviewer's Comments:

Regarding the datasets supporting the clinical pharmacology studies in BLA 125387, please submit the individual pharmacokinetic data (free and bound plasma VEGF- Trap concentration-time data and pharmacokinetic parameters) for each study in an easily accessible format (e.g. .xpt, .xls, etc.). If these datasets have already been submitted electronically, please provide the location in the electronic submission where these files can be found.

Puglisi, Michael

From: Puglisi, Michael
Sent: Thursday, February 24, 2011 1:45 PM
To: 'Laura Pologe'
Subject: Information Request for BLA 125387

Hi Laura,

Below please find an information request from our clinical reviewer for BLA 125387. Please confirm you have received this request and let me know if you have any questions about it. Thanks.

Mike Puglisi
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and
Ophthalmology Products
phone - 301-796-0791
fax - 301-796-9881

Regarding BLA 125387 for aflibercept:

1) *We are unable to locate the number of subjects enrolled per investigational site for two trials, VGFT-OD-0605/14393 (VIEW 1) and VGFT-OD-0702/14262.*

Please provide the location of this information within the BLA submission or provide tables with the Investigator name, ID number, and number of enrolled subjects at that site.

2) *Regarding 311523 (VIEW 2): please clarify if the "Number of Subjects" in the List of Investigators and Subinvestigators provided on page 8920 of 51624 of the CSR refers to the number of subjects randomized, number enrolled, or number completed.*



IND 12,462

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Laura G. Pologe, Ph.D.
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, New York 10591-6707

Dear Dr. Pologe:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VEGF Trap-Eye (aflibercept ophthalmic solution).

We also refer to the Pre-BLA CMC Meeting between representatives of your firm and the FDA on September 27, 2010.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Michael Puglisi, Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective
and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure



MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 27, 2010
MEETING TIME: 1:00 pm

APPLICATION (DRUG): IND 12,462
VEGF Trap-Eye (aflibercept ophthalmic solution)

SPONSOR: Regeneron Pharmaceuticals, Inc. (Regeneron)

TYPE OF MEETING: Type-B, Pre-BLA CMC Meeting

MEETING CHAIR: Wiley A. Chambers, M.D.

MEETING RECORDER: Michael Puglisi

FDA PARTICIPANTS: Division of Anti-Infective and Ophthalmology Products (Agency)

Wiley Chambers/ Acting Director
William Boyd/ Clinical Team Leader
Jennifer Harris/ Medical Officer
Bo Chi/ Quality Microbiology
Patricia Hughes/ Team Leader, Quality Microbiology
Sarah Kennett/ Quality/CMC Reviewer
Chana Fuchs/ Quality/CMC Team Leader
Michael Puglisi/ Project Manager

INDUSTRY PARTICIPANTS:

Representing Regeneron Pharmaceuticals, Inc. (Regeneron)

Laura Pologe/ Regulatory Affairs
William Roberts/ Regulatory Affairs and Medical Development
Chris Szustkiewicz/ Regulatory Affairs
Ned Braunstein/ Executive Director, Regulatory Affairs
Sunkwei Huang/ CMC Regulatory Affairs
Amy Jones/ CMC Project Manager
William Trompeter/ CMC Regulatory and Process Sciences
Gerald Underwood/ Vice President, Technical Operations
Venkat Yelma/ Global Regulatory Affairs

MEETING OBJECTIVE: To discuss CMC issues concerning the planned BLA submission for VEGF Trap-Eye for the treatment of Age-Related Macular Degeneration (AMD).

SUMMARY OF DISCUSSION:

Agency responses to the questions outlined in the August 12, 2010, background package were provided to Regeneron in an email sent on September 22, 2010 (see text in italics below). This meeting served to clarify those responses.

Questions for the Agency:

Sterility testing

Question 1: Does the Agency agree that sterility testing of the outer surface of the syringes (and needles) will be carried out by submerging the syringes in nutrient media (direct inoculation method)?

FDA Response: The proposed approach appears acceptable. Include in the BLA submission a description of the procedure for testing the outer surface of syringes and needles for sterility and the results of method suitability studies specific to the items tested. The number of units to be tested will depend on the proposed commercial batch size.

Meeting Comments:

(b) (4)
(b) (4)

Blister integrity

(b) (4)

FDA Response:

(b) (4)
(b) (4)

(b) (4) *Include in the BLA a description of the specific method used and results of validation studies. In addition, include in the BLA a description of the procedures and configurations for shipping*

Provide shipping validation studies to demonstrate integrity and temperature control of final product during shipping.

Meeting Comments:

(b) (4)
(b) (4)

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Analytical Validation/Qualification

Question 6: Three analytical assay methods were used in the characterization and comparability studies, which are not in the routine release and stability testing. Regeneron is intended to perform validation/qualification on these assays. Is it acceptable to submit these reports during the review period?

***FDA Response:** Yes, but only for the extended characterization methods. All validation reports for release and stability assays should be included in the original BLA submission. These reports would need to be submitted with sufficient time remaining to perform a review of the validation/qualification; a commitment to the timeframe for the submission of these reports should be made at the time of the BLA submission. Note that any submission of a significant amount of data within 3 months of the end of the review cycle could be considered a major amendment.*

Comment: There was no further discussion of this matter.

(b) (4)

Comment: There was no further discussion of this matter.

Anti-Drug Antibody Assay

Question 8: Regeneron has developed an antibody assay to monitor the amount of anti-drug antibody which may be formed in human blood serum after IVT injections and has used this assay in the clinical trials. Does the Agency agree that this anti-drug antibody assay is sufficient?

FDA Response: *Based on the data presented in the meeting package, the screening assay appears to be appropriate. The validation report should be included in the BLA submission, and the acceptability of the validated assay will be a review issue once all the relevant information has been assessed. Please include in the BLA a justification and supporting data for using* (b) (4)

An assay for detection of neutralizing antibodies should have also been developed and used to assess any samples that tested positive for anti-drug antibody in the screening assay. Include the validation report for this assay s in the BLA.

Comment: There was no further discussion of this matter.

Table of Contents for Module 3

Question 9: The draft Table of Contents (TOC) for the DP section in Module 3 of the BLA that Regeneron plans to submit in March 2011 is provided in Appendix 8. Does the Agency agree with the proposed TOC?

FDA Response: *The Table of Contents appears to be acceptable as a format for including data on the various presentations;. As this is a complex submission, please make clear in the BLA which information in module 3 is the same and which is different between or among the different drug product presentations.*

Comment: There was no further discussion of this matter.

ADDITIONAL FDA COMMENTS:

Validation data summaries should be submitted in the BLA for the (b) (4) processes for vials and syringes and the (b) (4) Refer to the November 1994 FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072171.pdf>) for information to be provided in the BLA.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:

- Monitoring of bioburden and endotoxin levels at critical manufacturing steps using qualified bioburden and endotoxin tests. The pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful consecutive product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- [REDACTED] (b) (4)
- Bioburden and endotoxin data obtained during manufacture of the three conformance lots (3.2.S.2.5).
- Data summaries of shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications.

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the [REDACTED] (b) (4). For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products. Test methods and validation data summaries for the container closure integrity test and preservative effectiveness test (if applicable) should be submitted in Section 3.2.P.2.5 of the submission.

Provide the study protocols and validation data summaries in Section 3.2.P.3.5 for the following:

- [REDACTED] (b) (4)
- Sterilization and depyrogenation of sterile product-contact equipment and components, and equipment requalification program. Letters of authorization to applicable CDER DMFs for validation data [REDACTED] (b) (4) [REDACTED] (b) (4) also acceptable.
- In-process controls and hold times.
- Three successful consecutive media fill runs, including a summary of environmental monitoring results obtained during the runs.
- A description of the routine environmental monitoring program.

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. Manufacturing facility information should be included in the BLA as background information for the pre-license inspections.

A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the BLA submission to facilitate the planning of the pre-license inspections during the review cycle.

Please inform us about your manufacturing and process validation plans with timelines as there will be Agency inspections to coordinate for this BLA. The inspections must be conducted during the review cycle and while the manufacturing sites are producing the subject drug substance and drug product, and within a timeframe to allow for resolution of deficiencies.

An option of pre-submitting portions of an application is available. With so many manufacturing sites and processes submitted in one BLA, Regeneron may want to consider submitting the CMC module prior to submission of the other BLA modules to allow for the additional time that would be needed for activities related to the pre-approval inspections. (see also the January 2006 Guidance for Industry - Fast Track Drug Development Programs - Designation, Development, and Application Review)

Meeting Comments: The Agency stated that in-process bioburden limits typically range from 1-100 CFU/mL. Limits should be based on product impact, manufacturing capability and the ability of the material to support microbial growth. Tighter limits are expected for higher-risk steps and for steps that are closer to the end of the process. Validation of hold steps within the process is required to demonstrate control of the process and to set time limits. Routine monitoring is required to show ongoing control. Ongoing monitoring is required because equipment or cleaning/sterilization may malfunction with respect to bioburden levels.

The Agency stated that routine monitoring and process hold studies are needed for proper microbial control. Hold time studies on 3 separate lots should be completed at the time of BLA submission.

The Agency stated that only complete drug substance and/or drug product sections can be pre-submitted for review. Regeneron agreed to submit a proposal before any pre-submissions.

Action Items:

The Agency agreed to issue minutes of this meeting within 30 days.

Minutes Prepared by: *{See appended electronic signature page}*

Michael Puglisi
Project Manager

Concurrence by: *{See appended electronic signature page}*

Wiley A. Chambers, M.D.
Acting Division Director

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/s/

WILEY A CHAMBERS
10/26/2010



IND 12,462

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Laura G. Pologe, Ph.D.
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, New York 10591-6707

Dear Dr. Pologe:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VEGF Trap-Eye.

We also refer to the Pre-BLA Clinical Meeting between representatives of your firm and the FDA on September 8, 2010.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Michael Puglisi, Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective
and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure



MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 8, 2010
MEETING TIME: 12:00 noon

APPLICATION (DRUG): IND 12,462
VEGF Trap-Eye (aflibercept ophthalmic solution)

SPONSOR: Regeneron Pharmaceuticals, Inc. (Regeneron)

TYPE OF MEETING: Type-B, Pre-BLA Clinical Meeting

MEETING CHAIR: Wiley A. Chambers, M.D.

MEETING RECORDER: Michael Puglisi

FDA PARTICIPANTS: Division of Anti-Infective and Ophthalmology Products (Agency)

Wiley Chambers/ Acting Director
William Boyd/ Clinical Team Leader
Lucious Lim/ Medical Officer
Martin Nevitt/ Medical Officer
Mushfiquir Rashid/ Statistics Reviewer
Yan Wang/ Statistics Team Leader
Yongheng Zhang/ Clinical Pharmacology Reviewer
Charles Bonapace/ Clinical Pharmacology Team Leader
Michael Puglisi/ Project Manager

INDUSTRY PARTICIPANTS:

Representing Regeneron Pharmaceuticals, Inc. (Regeneron)

Laura Pologe/ Regulatory Affairs
Ned Braunstein/ Regulatory Affairs
William Roberts/ Regulatory Affairs and Medical Development
Chris Szustkiewicz/
Robert Vitti/ Clinical Development
Thomas Daly/ Preclinical Development
Yuhwen Soo/ Biostatistics and Data Management
Georg Groetzbach/ Clinical Development

MEETING OBJECTIVE: To discuss clinical issues concerning the planned BLA submission for VEGF Trap-Eye for treatment of Age-Related Macular Degeneration.

SUMMARY OF DISCUSSION:

Agency responses to the questions outlined in the August 3, 2010, background package were provided to the Sponsor in an email sent on August 31, 2010 (see text in italics below). This meeting served to clarify those responses.

Questions for the Agency:

CLINICAL PHARMACOLOGY

Question 1: We propose to provide in the BLA the following pharmacokinetic (PK) data from the IVT clinical studies listed below and detailed in Section 8.3.

- Data and a summary of PK from relatively frequent blood sampling of 6 patients after a single IVT administration of 2 mg in study VGFT-OD-0702.PK,
- Corroborative data on blood levels after IVT administration from Phase 1 and Phase 2 studies (VGFT-OD-0502, VGFT-OD-0508 and VGFT-OD-0603), and
- Trough blood levels from approximately 100 patients/arm during chronic IVT dosing in the PK substudy to the VIEW 2 Phase 3 study

Does the Agency agree that the proposed PK data would be sufficient for filing and review of the application?

***FDA Response:** Agree. However, other than PK data from the IVT clinical studies, the sponsor should also submit the relevant data following IV administrations for in vivo bioavailability assessment in this BLA submission.*

Meeting Comment: The Agency requested that Regeneron submit all available PK data including those from the oncology and healthy volunteer studies.

Question 2: A summary of the proposed clinical pharmacology data to be provided in module 2.7.2 of the BLA is described in Section 8.3. The summary will present data on blood levels and relevant PK parameters (C_{max}, T_{max}) in patients after IVT injection and will relate those levels to the observations in preclinical species. In addition, this section will include correlative data on the pharmacodynamic effect of reducing retinal thickness with increasing IVT doses. The summary will address the potential for accumulation of systemic drug levels with repeated dosing at dose regimens under consideration for licensure, and the potential influence of demographic (ethnicity) and other factors (compromised renal function, concomitant medications) on systemic drug levels based on population PK assessments of European and Japanese patients in the Phase 3 study, VIEW 2.

Does the Agency agree with the proposed clinical pharmacology module 2.7.2?

FDA Response: *The content in the proposed clinical pharmacology module appears to be acceptable. The sponsor should also include additional information in the submission, as specified in the response to Question 1.*

Comment: There was no further discussion of this matter.

CLINICAL EFFICACY

Content of the SCE

Question 3: We propose that the SCE for the BLA will include the following key studies and analyses?

- The 1-year analyses of the two Phase 3 studies (VIEW 1 and VIEW 2),
- The pooled analysis of the 1-year data from the two Phase 3 studies, and
- Results of the dose/dose interval ranging Phase 2 study, VGFT-OD-0508

For a more detailed description of the content of the SCE, please see Sections 8.4.1 and 8.4.2.

Does the Agency agree?

FDA Response: *The proposed plan is acceptable.*

Comment: There was no further discussion of this matter.

Subgroup Analysis

Question 4: In accordance with 21CFR314.50(c)(5)v, we propose to present effectiveness data by gender, age and racial subgroup, as well as other subgroups appropriate to the neovascular AMD population. The proposed subgroups are summarized in Section 8.4.6.

Does the Agency agree with the proposed evaluation of efficacy subgroups?

FDA Response: *The subgroup analyses should be performed for each individual Phase 3 study (VIEW 1 and VIEW 2) and included in their respective CSR in Module 5. We have no objection to including an additional pooled subgroup analysis of the Phase 3 studies.*

Meeting Comments: Regeneron proposed performing subgroup analyses for the primary endpoint (loss of <15 letters) and for the secondary endpoints of mean change in visual acuity and the number of patients gaining 3 lines or more. The Agency agreed that performing subgroup analyses on only visual acuity endpoints would be acceptable. In addition, Regeneron should perform subgroup analyses for any endpoints they want considered for labeling.

CLINICAL SAFETY

Question 5: We propose to [REDACTED]

(b) (4)

[REDACTED]
(b) (4)

Does the Agency agree?

FDA Response: *No. The safety data submitted in the NDA should include results from all studies regardless of the route of administration [REDACTED] the intravenous studies conducted with aflibercept.*

(b) (4)

Meeting Comments: The Agency stated that, by regulation all available safety data, irrespective of the route of administration or indication, must be provided. The Agency stated that all the data from the systemic studies could be grouped together and submitted separately from the ophthalmology data.

Question 6a: With respect to the data referenced in Question 5, we propose to include the following specific content in Module 5 of the BLA?

[REDACTED]
(b) (4)

Does the Agency agree?

FDA Response: *No. The safety data submitted in the NDA should also include results from the intravenous studies conducted with aflibercept [REDACTED] ophthalmic (Table 3, page 28 of Regeneron briefing document).*

(b) (4)

Module 5 should contain the CSR for the Phase 2 Study, VGFT-OD-0508. Module 5 should also contain the individual 1-year analyses CSR for the two Phase 3 Studies (VIEW 1 and VIEW 2).

Any Summary of SAEs should specifically separate the events by individual study.

Meeting Comment: The Agency stated that it is acceptable to provide masked safety data from the pharmacovigilance database from the ongoing studies.

Question 6b:

(b) (4)

(b) (4)

Does the agency agree?

FDA Response: *No. The CRFs should be submitted to the NDA. In addition to the CRFs for subjects experiencing death and/or a significant adverse event or who did not complete a trial because of an adverse event, you should submit the CRFs for all Phase 3 discontinued patients, regardless of reason for discontinuation.*

Meeting Comments: The Agency clarified that it considers “significant adverse events” those which are serious, unexpected (i.e not listed in the Investigator’s Brochure), and related to the study. The Agency clarified that it expects CRFs for all completed studies.

POOLING OF SAFETY DATA

Question 7: For the ISS, we propose to present pooled safety analyses only within Pooled Sets 1 and 2, and to present the analyses of the other safety data as separate studies. Specifically, we propose that the Pooled Set 1 will include patients from the Phase 3 neovascular AMD studies, VIEW 1 and VIEW 2. We propose that Pooled Set 2 will include data up to one year from patients in Phase 1 and 2 neovascular AMD studies. Data beyond one year in neovascular AMD and data from other ophthalmology indications will be presented from the respective individual studies. The datasets that we propose to pool for the integrated analysis of safety and the datasets from each study that we propose to analyze and display separately in the ISS are described in Section 8.5.4.

Does the Agency agree?

FDA Response: *Agree.*

Comment: There was no further discussion of this matter.

SUBGROUP ANALYSIS

Question 8: We propose

(b) (4)

(b) (4)

Does the Agency agree?

FDA Response: No. The subgroup analyses should be performed for each individual Phase 3 study (VIEW 1 and VIEW 2) and included in their respective CSR in Module 5. We have no objection to including an additional pooled subgroup analysis of the Phase 3 studies.

Comment: There was no further discussion of this matter.

DATASETS

Question 9: We propose to provide both analysis datasets (ADS) and study data tabulation model (SDTM) datasets only for VIEW 1 and VIEW 2 in the BLA. These datasets will be provided in SAS transport (.xpt) format unless otherwise requested.

Does the Agency agree that provision of the ADS and SDTM datasets for the Phase 3 studies in AMD (VIEW 1 and VIEW 2) are sufficient?

FDA Response: Module 5 should include a folder named 'datasets'. This folder should have the following subfolders for each study:

- a. Raw datasets (Tabulations) along with the defined document.
- b. Derived (analysis) datasets used to generate the study results along with the defined document; for the primary and secondary endpoints, please provide one variable for the observed data and one variable for the LOCF imputed data.
- c. SAS programs used to produce the derived datasets along with the defined document.
- d. SAS programs used to produce the summary tables, figures and listings for the study report along with the defined document.

We highly recommend that the format of the dataset be compliant with the CDISC requirements.

Meeting Comment: The Agency stated it is acceptable to provide datasets for the Phase 2 and Phase 3 studies in AMD. The Agency clarified that it is acceptable to provide SAS programs to reproduce the derived datasets only for the primary and secondary endpoints. In addition, SAS programs should be submitted for any endpoint that Regeneron wants considered for labeling.

The Agency clarified that it is acceptable to provide SAS programs to reproduce the results that are presented in the summary tables and not the programs to reproduce the tables themselves.

VIEW 1 AND INTEGRATED STATISTICAL ANALYSIS PLANS (SAPs)

Question 10: The statistical analysis plan (SAP) for the VIEW 1 study and the integrated SAP are provided in Attachment 2 and Attachment 3, respectively.

Does the Agency agree with the analytic plans?

FDA Response: *Your proposed analysis plans are acceptable. However, we have the following comments:*

- 1) We expect that the primary efficacy results based on the Per Protocol Set are corroborated by those based on the Full Analysis Set. If they are not consistent, the study report needs to provide explanations.*
- 2) Besides LOCF to impute missing data, other imputation methods (e.g. worst observation carried forward, multiple imputation method, etc.) should be performed as sensitivity analyses.*

Meeting Comments: The Agency stated it expects ITT with LOCF and Per Protocol with observed cases only analyses to be provided. Sensitivity analyses for the primary endpoint and secondary endpoint of mean change in visual acuity are acceptable. Sensitivity analyses should also be provided for any other endpoints that Regeneron wants considered for labeling.

FOUR-MONTH SAFETY UPDATE REPORT

Question 11: We propose that the 4-month safety update report will include the following content as described in detail in Section 8.7:

- Summary and Listings of updated and new masked SAEs (unmasked from the open-label study 0910) from ongoing studies from the time of the initial BLA cut-off date of approximately September 15, 2010 through an approximate cut-off date of March 1, 2011
- Summary of clean unmasked data up to a cut-off of approximately March 1, 2011 for Study VGFT-OD-0702 comparing the safety of aflibercept iso-osmotic ophthalmic in vials vs in PFS

(b) (4)

Does the Agency agree with the proposed content for the 4-month SUR?

FDA Response: *In addition to the pooled analysis for VIEW 1 and VIEW 2, individual analyses for each trial should be submitted.*

Meeting Comment: The Agency agreed with Regeneron's proposal to provide reports for newly completed studies, (b) (4), in the 120-Day Safety Update. Reports of serious adverse events in the ongoing studies should be included in the update.

Question 12: The data to be provided in the initial BLA will include the 1-year efficacy and safety data from the two nearly identical Phase 3 non-inferiority studies of aflibercept iso-osmotic ophthalmic compared to ranibizumab as previously agreed with the Agency (Special Protocol Assessment, letter from FDA of July 13, 2007). In order to provide useful information regarding the long-term safety and efficacy of aflibercept iso-osmotic ophthalmic for the Agency's consideration in labeling that could be informative for physician's contemplating longer term use beyond one year, Regeneron is considering that the 4-month safety update report would include a pooled analysis of locked data for all patients from the ongoing VIEW 1 and VIEW 2 studies, who have completed year 2 by an approximate cut-off date of January, 2011. This pooled analysis would include approximately 1100 patients. The VIEW 1 and VIEW 2 studies will continue and final CSRs will be provided upon their completion.

If we are able to provide the proposed pooled analysis of approximately 1100 patients from VIEW 1 and VIEW 2 who completed year 2 by the cut-off date, would the Agency accept and review those data for consideration for labeling?

FDA Response: *Amendments to the statistical plan should be submitted and discussed prior to implementation, including an interim analysis of the two year data. The results of any analyses should be submitted to the BLA when available. Labeling is a review issue requiring review of the complete submitted BLA. It is expected that any study results intended for the labeling should be submitted at the time of the BLA submission.*

Meeting Comments: The Agency agreed that two year data from the VIEW 1 and VIEW 2 studies could be submitted as part of the 120-Day Safety Update. Regeneron agreed to pre-specify the statistical analyses and submit the SAP to the Agency for review. The Agency stated that submitting the two year data as part of the 120-Day Safety Update would not extend the review clock. There is, however no guarantee that data submitted after the time of the original BLA submission will be reviewed during the first review cycle.

(b) (4)

REGULATORY

Question 15: We propose to submit the BLA either on a DVD or an external hard drive. Will this be an acceptable medium for submission of the BLA?

FDA Response: *The Food and Drug Administration (FDA) Electronic Submissions Gateway (ESG) is responsible for accepting electronic regulatory submissions. We suggest you contact them directly to ensure all aspects of your electronic application will be acceptable:*
<http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>

Comment: There was no further discussion of this matter.

Question 16:

(b) (4)

(b) (4)

Does the Agency agree?

FDA Response: *No, we do not agree. We strongly recommend that any changes to the statistical analysis plan be submitted and discussed with the Agency prior to implementation.*

Comment: There was no further discussion of this matter.

Question 17: The international non-proprietary name (INN) for VEGF Trap is aflibercept.

(b) (4)

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Minutes Prepared by: *{See appended electronic signature page}*
Michael Puglisi
Project Manager

Concurrence by: *{See appended electronic signature page}*
Wiley A. Chambers, M.D.
Acting Division Director

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/s/

WILEY A CHAMBERS
09/30/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 12,462

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Laura G. Pologe, Ph.D.
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, New York 10591-6707

Dear Dr. Pologe:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VEGF Trap-Eye.

We also refer to the teleconference between representatives of your firm and the FDA on September 15, 2009.

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

If you have any questions, call Michael Puglisi, Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective
and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: September 15, 2009

MEETING TIME: 10:00 am

APPLICATION (DRUG): IND 12,462
VEGF Trap-Eye

SPONSOR: Regeneron Pharmaceuticals, Inc. (Regeneron)

TYPE OF MEETING: Type-C, Clinical, Chemistry, and Microbiology Guidance

MEETING CHAIR: William Boyd, M.D.

MEETING RECORDER: Michael Puglisi

FDA PARTICIPANTS: Division of Anti-Infective and Ophthalmology Products

William Boyd/ Clinical Team Leader
Lucious Lim/ Medical Officer
Martin Nevitt/ Medical Officer
Rhea Lloyd/ Medical Officer
Sarah Kennett/ Product Quality Reviewer
Chana Fuchs/ Product Quality Team Leader
Anastasia Lolas/ Microbiology Reviewer
Patricia F. Hughes/ Microbiology Team Leader
Denise A. Miller/ Microbiology Reviewer
Michael Puglisi/ Project Manager

INDUSTRY PARTICIPANTS:

Representing Regeneron Pharmaceuticals, Inc.

Laura Pologe/ Regulatory Affairs
Ned Braunstein/ Regulatory Affairs
William Roberts/ Regulatory Affairs and Medical Development
Sunkwei Huang/ CMC Regulatory Affairs
Avner Ingerman/ Clinical Development
William Trompeter/ Process and Analytical Sciences
Amy Jones/ CMC Product Planning and Logistics

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(b) (4)

Additional Comments for the BLA Submission:

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for both the drug substance and drug product should be provided at least a month prior to the BLA submission to facilitate the planning of the pre-license inspections during the review cycle. Manufacturing facility information should be included in the BLA as background information for the pre-license inspections. The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:

- Monitoring of bioburden and endotoxin levels at critical manufacturing steps using qualified bioburden and endotoxin tests. The pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful consecutive product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- [REDACTED] (b) (4)
- Bioburden and endotoxin data obtained during manufacture of the three conformance lots (3.2.S.2.5).
- Data summaries of shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications. The bioburden limit should be < 1 CFU/10 mL for bulk materials allowed to be stored for extended periods of time at refrigerated temperatures (3.2.S.4).

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the [REDACTED] (b) (4). For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products. Test methods and validation data summaries for the container closure integrity test and preservative effectiveness test (if applicable) should be submitted in Section 3.2.P.2.5 of the submission.

Provide the study protocols and validation data summaries in Section 3.2.P.3.5 for the following:

- [REDACTED] (b) (4)
- Sterilization and depyrogenation of sterile product-contact equipment and components, and equipment requalification program,
- In-process controls and hold times,

- *Three successful consecutive media fill runs, including a summary of environmental monitoring results obtained during the runs, and*
- *A description of the routine environmental monitoring program.*

Comment: There was no discussion of this matter during the meeting.

Action Items:

The Agency agreed to issue minutes of this meeting within 30 days.

Minutes Prepared by: *{See appended electronic signature page}*
Michael Puglisi
Project Manager

Concurrence by: *{See appended electronic signature page}*
Wiley A. Chambers, M.D.
Acting Division Director

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-12462	GI-1	REGENERON PHARMACEUTICA LS INC	Vascular Endothelial Growth Factor Fc Fusion Protein (human, recombinant, CHO cells, Regeneron)

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/s/

WILEY A CHAMBERS
10/15/2009



IND 12,462

(b) (4)

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Laura G. Pologe, Ph.D.
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, New York 10591-6707

Dear Dr. Pologe:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VEGF Trap.

We also refer to the teleconference between representatives of your firm and the FDA on June 1, 2009.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the teleconference outcomes.

If you have any questions, call Michael Puglisi, Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective
and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure



MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: June 1, 2009

MEETING TIME: 11:30 am

APPLICATION (DRUG): IND 12,462
(b) (4)
VEGF Trap

SPONSOR: Regeneron Pharmaceuticals, Inc.

TYPE OF MEETING: Type-C, Preclinical Guidance

MEETING CHAIR: Wiley A. Chambers, M.D.

MEETING RECORDER: Michael Puglisi

FDA PARTICIPANTS: Division of Anti-Infective and Ophthalmology Products

William Boyd/ Clinical Team Leader
Martin Nevitt/ Medical Officer
James Wild/ Pharmacology/Toxicology Reviewer
Wendy Schmidt/ Pharmacology/Toxicology Team Leader
Michael Puglisi/ Project Manager

**INDUSTRY PARTICIPANTS:
Representing Regeneron Pharmaceuticals, Inc.**

Laura Pologe/ Regulatory
William Roberts/ Regulatory and Medical Safety
Avner Ingerman/ Clinical
Thomas Daly/ Preclinical Development
Jacob Lesniak/ Toxicology
Edward Zimmer/ Toxicology
Kimberly Broadwell/ Toxicology
Kirstin Meyer/ Toxicology

MEETING OBJECTIVE: To discuss the Sponsor's preclinical program for VEGF Trap for the treatment of Age-related Macular Degeneration (IND 12,462) (b) (4)

SUMMARY OF DISCUSSION:

Agency responses to the questions outlined in the April 1, 2009, background package were provided to the Sponsor in a fax dated May 29, 2009 (see text in italics below). This meeting served to clarify those responses, as follows:

Questions for the Agency:

1. Does the Agency agree that the pharmacology/toxicology program is adequate to support product marketing approval for VEGF Trap-Eye in the intended marketed formulation for the treatment of male and female patients with AMD (b) (4) (See Appendix 1 for a complete listing of all pharmacology/toxicology studies that will support the initial registration.)

***FDA Response:** The scope of the program appears to be consistent with current guidance documents, and appears to be sufficient for the indications of AMD (b) (4) as long as there are no findings which warrant further study. Please justify the use of a single species in the chronic ocular toxicity studies.*

Currently, final study reports have not been submitted for the 8-month repeated-dose study in Monkeys (VGFT-TX-05011) the monkey reproduction study (VGFT-TX-05009), and the rabbit embryo-fetal development studies (VGFT-TX-06001; VGFT-TX-06002). The adequacy of the data to support safety for product marketing approval will be determined upon review of the data.

Meeting Comments: Regeneron agreed to submit an amendment to the IND with a justification for the use of a single species in the chronic ocular toxicity studies.

2. Does the Agency agree that the 8-month ITV monkey toxicology study is appropriate with respect to species, treatment period, dose levels, dosing interval, and endpoints to support product marketing approval at doses of up to 2 mg/eye administered at ≥ 4 -week intervals (See Section 10.1)?

***FDA Response:** The 8-month ITV monkey toxicology study (VGFT-TX-05011) as it has been summarized in the April 1, 2009, submission appears to be appropriately designed to support clinical administration at doses of ≤ 2 mg/eye administered at ≥ 4 week intervals. Examination of a wide range of endpoints including toxicokinetics, bone plate effects, kidney and adrenal damage are needed to demonstrate safety. A final report has not been submitted for this study, and the adequacy of the data to support safety for product market approval will be determined upon review of the data.*

Comment: There was no discussion of this matter during the teleconference.

3. Does the Agency agree that since the AMD patient population is elderly and unlikely to be of child-bearing potential, that additional pre- and post-natal development studies are not necessary to support registration of VEGF Trap-Eye

in AMD? Likewise, does the Agency agree that additional studies are not necessary to support registration in (b) (4)

***FDA Response:** Additional pre- and post-natal development studies are not required to support VEGF Trap-Eye in AMD (b) (4). Based on the documented adverse reproductive and developmental effects of VEGF-Trap and other pharmacological blockers of VEGF signaling, any eventual label will include qualifying statements/and or categorization restrictions regarding compound effects on fertility and pregnancy.*

Comment: There was no discussion of this matter during the teleconference.

(b) (4)

(b) (4)

(b) (4)

6. International Conference on Harmonisation (ICH) guidance S6 states that “The range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed.” It also states “Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals.” Does the Agency agree that, in accordance with ICH guidance S6, genotoxicity and carcinogenicity studies of VEGF Trap-Eye are not required? (Sections 11, 12)

FDA Response: *Agreed.*

Comment: There was no discussion of this matter during the teleconference.

Minutes Prepared by: *{See appended electronic signature page}*
Michael Puglisi
Project Manager

Concurrence by: *{See appended electronic signature page}*
Wiley A. Chambers, M.D.
Acting Division Director

Linked Applications

Sponsor Name

Drug Name / Subject

IND 12462

REGENERON
PHARMACEUTICALS
INC

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

(b) (4)

REGENERON
PHARMACEUTICALS
INC

VEGF Trap

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

/s/

WILEY A CHAMBERS

06/30/2009