

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125472Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

BLA#: [125472](#) Supplement Number: \_\_\_ NDA Supplement Type (e.g. SE5):

Division Name: [DPARP](#) PDUFA Goal Date: [10/21/13](#) Stamp Date: [12/21/12](#)

Proprietary Name: [Actemra](#)

Established/Generic Name: [tocilizumab](#)

Dosage Form: Solution for subcutaneous injection (Pre-filled Syringe)

Applicant/Sponsor: [Genentech, Inc.](#)

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

- (1) [Rheumatoid Arthritis](#)
- (2) [Systemic Juvenile Idiopathic Arthritis](#)
- (3) [Polyarticular Juvenile Idiopathic Arthritis](#)
- (4)

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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:** [Rheumatoid Arthritis](#)

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

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: 1

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

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

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

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

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

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

**Q3:** Does this indication have orphan designation?

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

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

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

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

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

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

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

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

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

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

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	<u>0</u> yr. __ mo.	<u>2</u> yr. __ mo.	<input checked="" 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).

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

## † 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.

*Polyarticular JIA (PJIA) has been identified as the relevant pediatric disease to study in agents seeking approval for adult RA. PJIA rarely occurs in children less than 2 years of age, therefore necessary studies are impossible or highly impractical because the number of pediatric patients in this age group is small.*

*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 checked="" type="checkbox"/>	Other	<u>2</u> yr. __ mo.	<u>17</u> yr. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" 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): <u>May 31, 2018</u>							

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

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

\* Other Reason: \_\_\_\_\_

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

(Revised: 6/2008)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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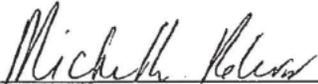
/s/  
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PHILANTHA M BOWEN  
10/15/2013

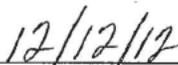
**1.3.3 Debarment Certification**

Genentech, 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 Biologic License Application.

Signed by:



Michelle H. Rohrer, Ph.D.  
Vice President, Regulatory Affairs  
Genentech, Inc.

  
Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
BLA # <a href="#">125472</a>	BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: <a href="#">Actemra</a> Established/Proper Name: <a href="#">tocilizumab</a> Dosage Form: <a href="#">prefilled syringe</a>		Applicant: <a href="#">Genentech, Inc.</a> Agent for Applicant (if applicable):
RPM: <a href="#">Philantha Bowen</a>		Division: <a href="#">DPARP</a>
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2) Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>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.</b></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <a href="#">October 21, 2013</a></li> </ul>	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>	<input checked="" type="checkbox"/> None	

<sup>1</sup> 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.

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

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)  Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)  Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input checked="" type="checkbox"/> MedGuide  <input checked="" type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input checked="" type="checkbox"/> Yes, dates 10/18/13; 10-16-13</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<p><input checked="" type="checkbox"/> None  <input type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input type="checkbox"/> Other</p>

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

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

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

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

Yes     No

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

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

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

Yes     No

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

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

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

Yes     No

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

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

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

Yes     No

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

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

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

❖ Copy of this Action Package Checklist <sup>4</sup>	October 21, 2013
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) AP: October 21, 2013
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	October 18, 2013
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	12/21/12
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ 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>)</li> </ul>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	10/10/13 – MG & IFU
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	12/21/12
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	September 26, 2013
<ul style="list-style-type: none"> <li>❖ Proprietary Name               <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	Review: 8/9/13 Letter: 8/9/13
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 2/19/13 <input checked="" type="checkbox"/> DMEPA 9/19/13; 10/8/13 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 9/30/13 <input checked="" type="checkbox"/> ODPD (DDMAC) 10/1/13 <input checked="" type="checkbox"/> SEALD 10/16/13 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews OBP-9/10/13; PMHS – 8-23-13
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	2/4/13
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> Not a (b)(2) <input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP               <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)               <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>8/28/13</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ 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, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	10/18/13; 10/17/13; 10/11/13, 10/10/13, 10/9/13, 10/8/13, 10/3/13, 10/1/13 (2), 9/20/13, 9/18/13, 8/12/13, 8/7/13, 7/15/13, 7/12/13, 7/1/13, 6/26/13, 6/20/13, 6/4/13, 5/24/13, 5/20/13, 5/10/13, 5/9/13, 4/10/13, 2/19/13, 1/31/13, 1/3/13
❖ Internal memoranda, telecons, etc.	6/13/13, 1/3/13
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 10/31/12 (under IND 11972)
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/21/13
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 9/30/13
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 2
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	See concurrence primary review
• Clinical review(s) ( <i>indicate date for each review</i> )	9/16/13, 2/13/13
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Clinical Review: 9/16/13, pg 20
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None  CDRH/ODE – HF 9/23/13, 2/15/13 CDRH/ODE – Device 10/10/13, 2/14/13

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ 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"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>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>)</li> </ul>	10/17/13; 10/14/13, 10/10/13, 10/3/13 Memo – 10/16/13 <input type="checkbox"/> None Reviews - 10/17/13; 9/27/13
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None See concurrence on primary review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None See concurrence on primary review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 9/9/13, 2/12/13
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None See concurrence on primary review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 9/16/13, 1/29/13
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None See concurrence on primary review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 9/9/13, 1/23/13
❖ 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
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
<b>❖ Product Quality Discipline Reviews</b>	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 9/16/13
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 9/10/13, 2/5/13
<b>❖ Microbiology Reviews</b>	<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 (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	10/11/13, 9/16/13, 2/12/13
<b>❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer</b> <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
<b>❖ Environmental Assessment (check one) (original and supplemental applications)</b>	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	3/20/13
<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>	
<b>❖ Facilities Review/Inspection</b>	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup>)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: 10/18/13 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<b>❖ NDAs: Methods Validation</b> <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)

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

## Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

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/s/  
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PHILANTHA M BOWEN  
10/21/2013

## Bowen, Philantha

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**Subject:** FW: BLA 125276/92 and BLA 125472 - FDA Request for Label Revisions

---

**From:** Bowen, Philantha  
**Sent:** Friday, October 18, 2013 1:53 PM  
**To:** 'Stuart Heminway'  
**Cc:** 'Hilary Henshaw'  
**Subject:** BLA 125276/92 and BLA 125472 - FDA Request for Label Revisions

Hello,

Your submissions dated October 17, 2013, containing a prior approval supplement and revised labeling to sBLA 125276/92 and BLA 125472, respectively, are currently under review. We have the following request for label revisions for the package insert:

Revise the product title in the Highlights Section as follows:

**Actemra (tocilizumab)  
injection, for intravenous use  
injection, for subcutaneous use**

Submit an official response to the sBLA and BLA by COB today, October 18, 2013. Provide a clean and tracked version of the label. Forward a courtesy copy to me via email.

If you have questions, let me know.

*Sincerely,  
Philantha*

---

**Philantha M. Bowen, MPH, BSN, RN**  
CDR, U.S. Public Health Service  
Sr. Program Management Officer  
Food and Drug Administration  
Center for Drug Evaluation and Research/ODEII  
Division of Pulmonary, Allergy, and Rheumatology Products  
10905 New Hampshire Ave., Bldg 22, Room 5526  
Silver Spring, MD 20993  
☎ 301-796-2466  
☎ 301-796-9718  
✉ philantha.bowen@fda.hhs.gov

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/s/  
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PHILANTHA M BOWEN  
10/21/2013

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Dear Mr. Heminway:

Your submission dated October 8, 2013, to BLA 125472 containing a revised package insert (PI) is currently under review and we have a request for labeling revisions. The FDA-proposed insertions for the PI are underlined and deletions are in strike-out. These revisions are not final and we may have additional comments and/or requests as we continue our review of the label.

Submit revised draft labeling incorporating the revisions outlined in the attached label. Provide a clean copy and a tracked-change version of the package insert by 12 NN, Friday, October 18, 2013, to the BLA. In addition, forward a courtesy copy via email to [philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov).

If you have any questions, contact me at 301-796-2466.

*{See appended electronic signature page}*

---

Philantha Montgomery Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Drafted: Bowen/10-17-13

Clearance: Jafari/10-17-13  
Karimi-Shah/10-17-13

Finalized: Bowen/10-17-13

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

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/s/  
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PHILANTHA M BOWEN  
10/17/2013

**BLA 125472**  
**Tocilizumab (Prefilled Syringe)**  
**Genentech, Inc.**

Dear Mr. Heminway:

Your submission dated October 10, 2013, to BLA 125472 containing a revised proposed REMS modification and appended REMS materials are currently under review. We have the following comments and requests for information:

1. Since the journal pieces will be available on the REMS website, edit the description of demyelinating disorders in Attachment G: Journal Information Piece for Neurologists and Attachment F: Journal Information Piece for Internists and Internal Medicine Subspecialists, as below:

**Demyelinating disorders:** The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies of adults with RA. *Monitor* patients [REDACTED] (b) (4) [REDACTED] for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

2. Revise the REMS document to note that the dissemination of the non-oncology journal pieces is for 3 years following the original approval of the Actemra REMS.
3. Revise any REMS materials as needed to ensure consistency with the most-recent labeling.

*General Comments*

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Actemra with the attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

Submit a revised REMS incorporating the comments and revisions by 10 AM EST Tuesday, October 15, 2013. Forward a courtesy copy via email to [philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov).

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

If you have any questions, contact me at 301-796-2466.

*{See appended electronic signature page}*

---

Philantha Montgomery Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Drafted: Bowen/10-11-13

Clearance: Paterniti/10-11-13  
Seymour/10-11-13  
Jafari/10-11-13

Finalized: Bowen/10-11-13

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/s/  
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PHILANTHA M BOWEN  
10/11/2013

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Dear Mr. Heminway:

Your submission dated October 8, 2013, to BLA 125472 containing revised labeling is currently under review and we have a request for labeling revisions. The enclosed label contains FDA comments regarding some of the changes made to the label. The FDA-proposed insertions are underlined and deletions are in strike-out. These revisions are not final and we may have additional comments and/or requests as we continue our review of the label.

Submit revised draft labeling incorporating the revisions outlined in the enclosed label. Provide a clean copy and a tracked-change version of the MG and IFU by 12 NN, Friday, October 11, 2013, to the BLA. In addition, forward a courtesy copy via email to [philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov).

If you have any questions, contact me at 301-796-2466.

*{See appended electronic signature page}*

---

Philantha Montgomery Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Drafted: Bowen/10-10-13

Clearance: Jafari/10-10-13

Finalized: Bowen/10-10-13

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/s/  
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PHILANTHA M BOWEN  
10/10/2013

**BLA 125472**  
**Tocilizumab (Prefilled Syringe)**  
**Genentech, Inc.**

Dear Mr. Heminway:

Your submission dated October 3, 2013, to BLA 125472 containing a revised proposed REMS modification and appended REMS materials are currently under review. We have the following comments and requests for information. In our comments below, deletions are identified as strikethrough and insertions/additions are underlined.

1)  (b) (4)

2) To be consistent with the USPI, *remove* the word  (b) (4) for the description of SJIA hypersensitivity in the Dear Healthcare Provider Letter, as below:

In the SJIA controlled trial with intravenous ACTEMRA, 1 out of 112 patients (0.9%) experienced  (b) (4) hypersensitivity reactions that required treatment discontinuation.

3) In the Dear Healthcare Provider Letter, we agree with *removing* the word  (b) (4) in regards to monitoring for signs and symptoms of potentially indicative of demyelinating disorders, as below:

***Potential Risk of Demyelinating Disorders***

- The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies of adults with RA. Monitor patients  (b) (4) for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

4) To be consistent with the USPI, make the following changes in the prescriber education slide deck:

a) Warnings and precautions slide for  (b) (4) (1 of 2): *add* “intravenous” in the postmarketing setting description as below:

 (b) (4)

b) Warnings and precautions slide for (b) (4) (2 of 2): **add** the following statement to relay information regarding the subcutaneous route of administration:

(b) (4)

*General Comments*

**Resubmission Requirements and Instructions:** Submit the revised proposed REMS for Actemra with the attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

**Format Request:** Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

Submit a revised REMS incorporating the comments and revisions by 10 AM EST Thursday, October 10, 2013. Forward a courtesy copy via email to [philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov).

If you have any questions, contact me at 301-796-2466.

*{See appended electronic signature page}*

---

Philantha Montgomery Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Drafted: Bowen/10-8-13

Clearance: Yancey/10-8-13  
Worthy/10-8-13  
Jafari/10-9-13  
Paterniti/10-9-13  
Seymour/10-9-13

Finalized: Bowen/10-9-13

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/s/  
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PHILANTHA M BOWEN  
10/09/2013

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Dear Mr. Heminway:

Your submission dated September 30, 2013, to BLA 125472 containing revised labeling is currently under review and we have a request for labeling revisions to the package insert (PI), Medication Guide (MG), and Instructions for Use (IFU). The enclosed label contains FDA comments regarding some of the changes made to the label, as well as requests for revisions. The FDA-proposed insertions are underlined and deletions are in strike-out. These revisions are not final and we may have additional comments and/or requests as we continue our review of the label.

Submit revised draft labeling incorporating the revisions outlined in the enclosed label. Provide a clean copy and a tracked-change version of the PI, MG, and IFU as soon as possible or by COB, Monday, October 7, 2013, to the BLA. In addition, forward a courtesy copy via email to [philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov).

If you have any questions, contact me at 301-796-2466.

*{See appended electronic signature page}*

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Philantha Montgomery Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Drafted: Bowen/10-3-13

Clearance: Jafari/10-3-13

Finalized: Bowen/10-3-13

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/s/  
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PHILANTHA M BOWEN  
10/03/2013

**BLA 125472**  
**Tocilizumab (Prefilled Syringe)**  
**Genentech, Inc.**

Dear Mr. Heminway:

Your submission dated August 12, 2013, to BLA 125472 containing a REMS modification is currently under review. We have the following comments and requests for information, as well as revisions for the **Attachments**.

1. The REMS Document, insert the “Most Recent Modification” date as October/2013 in the second-line, left-side of the header. Delete “June” and the DD portion of the date.
2. Insert “and BLA 125-472” in the center header before “ACTEMRA® (tocilizumab)”
3. In the appended REMS materials in the communication plan:
  - a. For all the REMS materials, update the hypersensitivity language as shown in track changes in the attached Dear Healthcare Provider Letter.
  - b. *Prescriber Education Slide Deck*
    - i. Insert an updated “version date” in the lower-left corner of each slide
    - ii. Update the slide deck with the SC dosing information
    - iii. Update the slide deck to reflect the modified laboratory monitoring as revised in labeling
  - c. *Dear HealthCare Provider letter*
    - i. Insert an updated “version date” at the bottom of the final page of this letter.
    - ii. Delete all references to the product website, [www.ACTEMRA.com](http://www.ACTEMRA.com). Only reference to the REMS website, [www.ACTEMRAREMS.com](http://www.ACTEMRAREMS.com), should appear in appended REMS materials. The exception is in the journal information pieces where you appropriately direct providers to the product website, [www.ACTEMRA.com](http://www.ACTEMRA.com), for access the Prescribing Information and Medication Guide.
    - iii. Insert text in 1st bullet point, “for intravenous (IV) or every other week or weekly for subcutaneous (SC) administration.”
    - iv. Insert text in 3<sup>rd</sup> bullet point to read, “Children 2 years of age and older with active systemic Juvenile Idiopathic Arthritis (SJIA) with a recommended ACTEMRA dosing interval of every 2 weeks for IV administration.”
    - v. Insert text under “Hypersensitivity Reactions, Including Anaphylaxis” that is shown in track changes to align with revisions to Actemra labeling.

- vi. Insert text under “Potential Risk of Demyelinating Disorders” as noted in minor track changes.
  - vii. Insert text under “Important Information on Laboratory Abnormalities” to align with revisions to the Actemra labeling.
- d. *Journal Information Pieces*
- i. Insert the same track changes (as they apply to the specialty provider) in each journal information piece that are cited in track changes to the *DHCP letter*.
4. Timetable for Submission of Assessments
- a. There are no changes to the approved timetable for submission of assessments.
5. REMS Assessment Plan  
The REMS assessment plan is acceptable as approved.
6. You are reminded that the REMS Supporting Document must be consistent with the revised REMS Document.

#### *General Comments*

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Actemra with the attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

Submit a revised REMS incorporating the comments and revisions in the Attachments by Wednesday, October 3, 2013. Forward a courtesy copy via email to [philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov).

If you have any questions, contact me at 301-796-2466.

*{See appended electronic signature page}*

---

Philantha Montgomery Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Drafted: Bowen/9-30-13

Clearance: Jafari/9-30-13  
Seymour/10-1-13

Finalized: Bowen/10-1-13

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/s/  
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PHILANTHA M BOWEN  
10/01/2013

**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

Dear Ms. Cook:

Your submission dated December 21, 2012, to BLA 125472 is currently under review and we have the following request for information:

In the submission, you provided Certificates of Conformity for the (b) (4) syringe 1ml Long 27G ½”, colorless (b) (4) glass barrel with 27G ½” stainless steel needle. These certificates indicate that your device has conformed to certain standards and testing and meets the criteria. You have not provided any performance test protocols, reports, or results for the (b) (4) syringe. Provide complete performance test reports for our review in accordance to:

- ISO 11040-4: Prefilled Syringes-Part 4: Glass barrels for injectables.
- ISO 9626: Stainless steel needle tubing for manufacture of medical devices.

We request that you submit a response officially to the BLA by October 3, 2013. In addition, forward a courtesy copy to me via email ([philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov)).

If you have any questions, contact me at 301-796-2466.

Sincerely,

*{See appended electronic signature page}*

---

Philantha Montgomery Bowen  
Sr. Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

Drafted: Bowen/9-26-13

Clearance: Jafari/9-26-13

Finalized: Bowen/9-26-13

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/s/  
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PHILANTHA M BOWEN  
10/01/2013

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Dear Mr. Heminway:

Your submission dated December 21, 2012, to BLA 125472 is currently under review and we have a request for revisions to the instructions for use (IFU) and the carton/container labeling. These revisions are not final and we may have additional comments and/or requests as we continue our review of the label.

**Instructions for Use**

The IFU in your submission is not the same as the IFU tested in the summative human factors study. The IFU does not contain the bolded paragraph and instructional headings. Bold all paragraph and instructional headings so that the reader can clearly reference each paragraph and instruction step.

(b) (4)

(b) (4)

**Carton Labeling and Container Labels**

1. The dosage form has been omitted. Revise the labels and labeling to read as follows:  
Actemra  
(tocilizumab)  
Injection
2. Increase the font size of the “For Subcutaneous Injection Only” statement to increase its prominence.
3. The container label and the carton labeling for proposed strength is not adequately differentiated from the marketed 80 mg/4 mL strength. The trade dress colors used for the label are similar (b) (4) across both these strengths thereby minimizing the strength differentiation. To prevent selection errors, revise this label to provide more color contrast between all strengths within this product line.

*Carton Labeling*

4. Add the following statement to appear after the route of administration statement on the principal display panel:

Single Dose Prefilled Syringe – Discard Unused Portion

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

*Container Labeling*

5. Revise the statement (b) (4) to read “Single Dose – Discard Unused Portion”.

Submit a response by COB, Thursday, September 26, 2013, to the BLA. In addition, forward a courtesy copy via email to [philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov).

If you have any questions, contact me at 301-796-2466.

*{See appended electronic signature page}*

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Philantha Montgomery Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Drafted: Bowen/9-10-13

Clearance: Hill for Jafari/9-20-13  
McMillan/9-20-13  
Merchant/9-20-13

Finalized: Bowen/9-20-13

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/s/  
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PHILANTHA M BOWEN  
09/20/2013

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Dear Mr. Heminway:

Your submission dated May 28, 2013, to BLA 125472 containing revised labeling is currently under review and we have a request for labeling revisions to the package insert (PI). The enclosed label contains FDA comments regarding some of the changes made in the PI. In the enclosed PI, the FDA-proposed insertions are underlined and deletions are in strike-out. These revisions are not final and we may have additional comments and/or requests as we continue our review of the label. The following comments provide some general labeling recommendations for the Package Insert:

1. Ensure that cross-references are accurate throughout the package insert.
2. Ensure that the section and subsection titles in the Table of Contents match those in the Full Prescribing Information.

Submit revised draft labeling incorporating the revisions outlined in the enclosed label, as well as the recommendations provided above. Provide a clean copy and a tracked-change version of the package insert as soon as possible or by COB, September 25, 2013, to the BLA. In addition, forward a courtesy copy via email to [philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov).

If you have any questions, contact me at 301-796-2466.

*{See appended electronic signature page}*

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Philantha Montgomery Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Drafted: Bowen/9-17-13

Clearance: Hill for Jafari/9-17-13  
Paterniti/9-18-13  
Karimi-Shah/9-18-13

Finalized: Bowen/9-18-13

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/s/  
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PHILANTHA M BOWEN  
09/18/2013

## Bowen, Philantha

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**From:** Greeley, George  
**Sent:** Friday, August 30, 2013 12:45 PM  
**To:** Bowen, Philantha; Hanan, Elisabeth; Davi, Christopher; Williams, Dawn; Sullivan, Matthew; Bugin, Kevin; Dewey, Maureen; Chung, Christine; Darkwah, Mavis; Jackson, Colette  
**Cc:** Inglese, Jane  
**Subject:** Draft PeRC Minutes - August 28, 2013

**Importance:** High

**Attachments:** 8-28-13 PeRC BPCA Subcommittee Minutes.doc; 8-28-13 PeRC PREA Subcommittee Minutes.doc

All,

Draft PeRC minutes from August 28th meeting are attached for your review and reference as measure of informing you of the results of your product review. The minutes are internal documents and are not to be disseminated externally or uploaded into DARRTS. Once the final review of the minutes has been completed by the Committee we will finalize and upload to DARRTS.

Additional recommendations may have been offered for some products. Pediatric records will be modified based on PeRC recommendations.

Thanks!  
George



3-28-13 PeRC BPCA3-28-13 PeRC PREA  
Subcommittee... Subcommittee...

**PeRC PREA Subcommittee Meeting Minutes  
August 28, 2013**

**PeRC Members Attending:**

Lynne Yao  
Wiley Chambers  
Tom Smith  
William J. Rodriguez  
Peter Starke  
Rosemary Addy  
Dionna Green  
Martha Nguyen  
Jane Inglese  
Coleen LoCicero  
Shrikant Pagay  
George Greeley  
Melissa Tassinari  
Hari Cheryl Sachs  
Andrew Mosholder

**Guests Attending:**

Erica Radden (PMHS)	Gilbert Burckart (OCP)
Nichella Simms (PMHS)	Terrie Crescenzi (OPT)
Mavis Darkwah (DAAAP)	Philantha Bowen (DPARP)
Renan Bonnel (OPT)	Lori Gorski (PMHS)
Suchitra Balakrishnan (DMEP)	Gerald Tran (OCP)
Elisabeth Hanan (DMEP)	Jaya Vaidyanathan (OCP)
Zhihong Li (OCP)	Christopher Davi (DAIP)
Hala Shamsuddin (DAIP)	Karen Mahoney (DMEP)
Steven Lemery (DOP2)	Melinda McCord (DDDP)
Gordana Diglisic (DDDP)	Danita Gromel-Woods (CMC)
Miya Paterniti (DPARP)	Nikolay Nikolov (DPARP)
Raj Nair (DPARP)	Banu Karimi-Shah (DPARP)

**Agenda**

BLA 125472 Actemra (tocilizumab) Partial Waiver/Deferral/Plan

NDA

NDA

NDA

BLA

NDA

**Actemra Partial Waiver/Deferral/Plan**

- BLA 125472, Actemra (tocilizumab) solution for subcutaneous injection, is indicated for the treatment of rheumatoid arthritis.
- The application was submitted on December 21, 2012 and has a PDUFA goal date of October 21, 2013.
- The application triggered PREA as new dosing regimen and new route of administration.
- The sponsor submitted a partial waiver request for children ages birth through twenty three months because there are too few children with disease/condition to study.
- *Sponsor Waiver Justification:*
- Polyarticular JIA (PJIA) has been identified as the relevant pediatric disease to study in agents seeking approval for adult RA. PJIA rarely occurs in children less than 2 years of age, therefore necessary studies are impossible or highly impractical because the number of pediatric patients in this age group is small.
- The sponsor submitted a deferral request in pediatric patients ages 2-17 years because the product is ready for approval in adults.

*PeRC Recommendations:*

- The PeRC agreed with the Division to grant a partial waiver in patients ages birth to less than 2 years of age and to a deferral in patients 2-17 years.

*Additional PeRC Discussion*

- These studies are already underway as part of a Written Request.

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**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Dear Mr. Heminway:

Your submission dated December 21, 2012, to BLA 125472 is currently under review. We have the following comment and request for information:

In your pediatric deferral request for the subcutaneous use of Actemra in patients 2 to 17 years of age, you provided a final report submission date of May 31, 2018. We are requesting that you also specify the protocol and study completion dates.

Submit a response officially to the BLA. In your response, use the following format for providing the requested information.

- Protocol Submission Date
- Study Completion Date
- Final Report Submission Date

Submit the requested information by 10AM Wednesday, August 14, 2013. Forward a courtesy copy via email to [philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov).

If you have any questions, contact me at 301-796-2466.

*{See appended electronic signature page}*

---

Philantha Montgomery Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Drafted: Bowen/8-12-13

Clearance: Jafari/8-12-13

Finalized: Bowen/8-12-13

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/s/  
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PHILANTHA M BOWEN  
08/12/2013



BLA 125472

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Genentech, Inc.  
1 DNA Way  
South San Francisco, CA 94080

ATTENTION:       Stuart Heminway  
                          Regulatory Program Director

Dear Mr. Heminway:

Please refer to your Biologics License Application (BLA) dated December 21, 2012, received December 21, 2012, submitted under section 351 of the Public Health Service Act, for Tocilizumab, 162 mg/0.9 mL.

We also refer to your May 16, 2013, correspondence, received May 16, 2013, requesting review of your proposed proprietary name, Actemra. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Actemra, 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 May 16, 2013 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 Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Philantha Bowen, at (301) 796-2466.

Sincerely,

*{See appended electronic signature page}*

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

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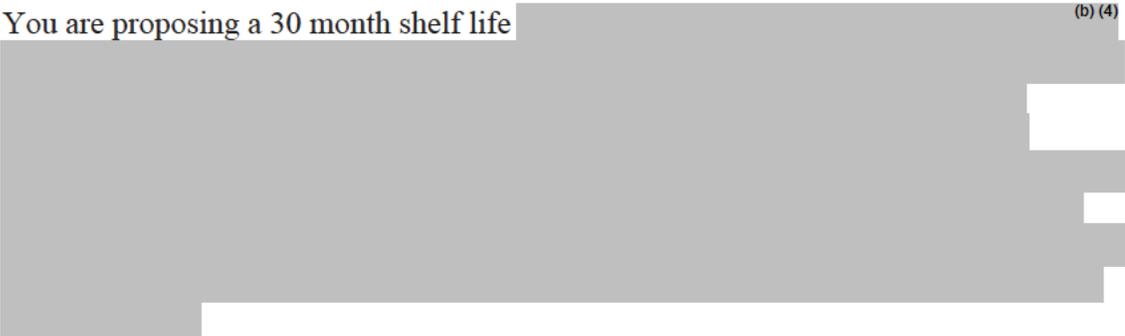
/s/  
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CAROL A HOLQUIST  
08/09/2013

**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

Dear Ms. Cook:

Your submission dated December 21, 2012, to BLA 125472 is currently under review and we have the following request for CMC information:

You are proposing a 30 month shelf life (b) (4)  


We request that you submit a response officially to the BLA by August 13, 2013. In addition, forward a courtesy copy to me via email ([philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov)).

If you have any questions, contact me at 301-796-2466.

Sincerely,  
*{See appended electronic signature page}*

---

Philantha Montgomery Bowen  
Sr. Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

Drafted: Bowen/8-7-13

Clearance: Jafari/8-7-13  
Feldman/8-7-13  
Shapiro/8-7-13

Finalized: Bowen/8-7-13

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/s/  
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PHILANTHA M BOWEN  
08/07/2013

Dear Ms Cook:

Reference is made to your submission dated December 21, 2012, to BLA 125472 and the FDA information request dated June 20, 2013. Your response dated July 1, 2013, to our request is currently under review.

We have the following comments and requests for information in response to the data provided in your July 1, 2013, amendment for the elements listed below:

**Process Validation and/or Evaluation - Qualification Runs**

1. Study reports 300-PRD01-PQH-020 and 300-PRD01-PQH-021 do not contain information about growth promotion studies. Submit growth promotion study reports for the minimal media used to validate integrity of the (b) (4). Indicate organisms and spike used, positive and negative controls, and temperature and incubation conditions. Justify any growth promotion incubation time longer than the incubation time used in the hold study (56 hours). Alternatively, validate maximum hold times of (b) (4) using worst-case conditions.

**Stability**

2. Clarify why it may be necessary to store BDS (b) (4)

(b) (4) **Validation - Microbial Retention Test**

3. (b) (4)  
Validate microbial retention of (b) (4)  
using Actmra SC DP solution (b) (4) and for bacterial  
inoculation and submit validation summary data and the validation report. Validation should be conducted using three different (b) (4) lots, and include microbial count at beginning and end of challenge, results of the (b) (4) integrity test before and after use, and a description of (b) (4). Refer to PDA Technical Report 26 section 6.8.1 for guidance on product use at reduced exposure times. In addition, using a higher initial concentration of the challenge organism may improve viability over the duration of the study.

(b) (4) **Validation - (b) (4) Integrity Test**

4. The troubleshooting approach for retesting (b) (4) integrity in PDA Technical Report 26 is not intended to be used as an alternative to process consistency. Determine the volume of

**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

(b) (4) necessary to provide (b) (4) Establish  
acceptance criteria for the (b) (4) using the determined (b) (4)

We request that you submit a response by July 25, 2013, officially to the BLA. Forward a courtesy copy to me via email. If you have any questions, contact me at 301-796-2466.

Sincerely,  
*{See appended electronic signature page}*

---

Philantha Montgomery Bowen  
Sr. Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

Drafted: Bowen/7-12-13

Clearance: Jafari/7-12-13  
Candauchacon/7-12-13  
CThomas for Hughes/7-12-13

Finalized: Bowen/7-15-13

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/s/  
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PHILANTHA M BOWEN  
07/15/2013

**BLA 125472**  
**Tocilizumab (Prefilled Syringe)**  
**Genentech, Inc.**

Dear Mr. Heminway:

Your submission dated December 21, 2012, to BLA 125472 is currently under review. We have the following requests for information:

- Provide a rationale for using a different decay time in the supplemental human factors study, 20831D103.
- The [REDACTED] (b) (4) and the Information for Use were tested in study NA25656B. However, only the Instructions for Use was tested in study 20831D103. Clarify your intent for the [REDACTED] (b) (4) and provide a rationale for not testing the [REDACTED] (b) (4) in study 20831D103.

Submit the requested information by Thursday, July 18, 2013. Forward a courtesy copy via email to [philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov).

If you have any questions, contact me at 301-796-2466.

*{See appended electronic signature page}*

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Philantha Montgomery Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Drafted: Bowen/7-12-13

Clearance: Jafari/7-12-13  
Mcmillan/7-12-13  
Merchant/7-12-13

Finalized: Bowen/7-12-13

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/s/  
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PHILANTHA M BOWEN  
07/12/2013

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Dear Mr. Heminway:

Your submission dated December 21, 2012, to BLA 125472 is currently under review. We have the following request for information regarding the data set and Sharp scores for study NA25220:

In our review of your submission, it appears that the only response variable in the XRAY data set is the change from baseline in Sharp scores. In addition, we could not locate the baseline Sharp scores or, in the case of escaped subjects, the score used in conjunction with the baseline score to impute a score at 24 weeks. Submit a revised data set that includes all Sharp scores, including those of subjects who completed the trial.

Submit the requested information by Wednesday, July 10, 2013. Forward a courtesy copy via email to [philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov).

If you have any questions, contact me at 301-796-2466.

*{See appended electronic signature page}*

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Philantha Montgomery Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**

**Tocilizumab (*Prefilled Syringe*)**

**Genentech, Inc.**

Drafted: Bowen/6-27-13

Clearance: Jafari/6-27-13  
Hoberman/6-27-13  
Buenconsejo/6-28-13

Finalized: Bowen/7-1-13

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/s/  
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PHILANTHA M BOWEN  
07/01/2013

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Dear Mr. Heminway:

Your submission dated December 21, 2012, to BLA 125472 is currently under review. We have the following request for statistical information:

We noted in your product label that you proposed to include the results from the analyses of SF-36 summary scores i.e., physical component score (PCS) and mental component score (MCS) in the Clinical Studies Section (Section 14). Because the SF-36 summary scores were developed on data from a general population of subjects, provide a justification for the use of the PCS and MCS in rheumatoid arthritis patients. This justification should discuss the appropriateness of using the PCS and MCS scoring algorithms in rheumatoid arthritis patients. In particular, the similarity of the factor structure of the eight scale scores for RA patients to that seen for subjects used to create the original scoring algorithm should be discussed. Include copies of all the references you plan to cite.

Submit the requested information by Monday, July 10, 2013, officially to the BLA, or you may propose a timeline for submitting the requested information.

If you have any questions, contact me at 301-796-2466.

*{See appended electronic signature page}*

---

Philantha Montgomery Bowen, MPH, RN  
Sr. Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Drafted: Bowen/6-24-13

Clearance: Jafari/6-24-13  
Buenconsejo/6-25-13  
Komo/6-24-13

Finalized: Bowen/6-26-13

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/s/  
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PHILANTHA M BOWEN  
06/26/2013

**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

Dear Ms Cook:

Reference is made to your submission dated December 21, 2012, to BLA 125472 and the FDA information request dated April 10, 2013. Your response dated April 23, 2013, to our request is currently under review.

We have the following requests for additional microbial quality information:

**Process Validation and/or Evaluation - Qualification Runs**

1. Justify the use of (b) (4) for the microbial quality hold times validation of (b) (4). Provide growth promotion studies conducted for the (b) (4) used in the study.

**Stability**

2. Storage of BDS at (b) (4) is supported by microbial quality results. Storage of BDS at (b) (4) by (b) (4) microbial quality results. Therefore, storage of BDS should be limited to (b) (4). Longer storage times at (b) (4) should be supported by microbial quality results. In addition clarify under which circumstances DBS would be stored at (b) (4).
3. DP sterility during worst airfreight conditions is not ensured by integrity of the container closure after shipping. The plunger, displaced to a non-sterile part of the barrel during low pressure conditions, may return to its initial position at the end of shipping under atmospheric pressure, compromising sterility without breaching integrity of the container closure. Provide data showing that plunger movement during worst-case shipping will not compromise sterility of the DP.

**Control of Critical Steps and Intermediates**

4. Submit endotoxin alert and action limits at the monitoring step prior to the (b) (4).

(b) (4) **Validation - Microbial Retention Test**

5. Your response is inadequate because characteristics other than osmolarity and pH may impact the microbial retention capacity (b) (4). Validate the microbial retention (b) (4) using Actemra SC DP and worst-case (b) (4) conditions. Reduced exposure of *B. diminuta* to Actemra may be used to increase survival. Include microbial count and the beginning and end of the test and challenge level per cm<sup>2</sup>.

(b) (4) **Validation - (b) (4) Integrity Test**

6. Determine the volume (b) (4) necessary to provide a (b) (4) int of the (b) (4). Establish acceptance criteria for the (b) (4) test using the determined (b) (4).

**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

(b) (4) **Stoppers and Process Equipment**

- 7.
- a) (b) (4)
  - b)
  - c)

**Batch Analysis**

8. Conduct the endotoxin recovery study in a container of the same material as the PFS (glass).

We request that you submit a response by June 24, 2013, officially to the BLA. If you have any questions, contact me at 301-796-2466.

Sincerely,  
*{See appended electronic signature page}*

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Philantha Montgomery Bowen  
Sr. Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

Drafted: Bowen/6-17-13

Clearance: Jafari/6-18-13  
Candauchacon/6-18-13  
Hughes/6-19-13

Finalized: Bowen/6-20-13

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/s/  
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PHILANTHA M BOWEN  
06/20/2013

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

**Date:** May 29, 2013

**From:** Reyes Candau-Chacon, Ph.D., OC/OMPQ/DGMPA/BMAB  
Gerald Feldman, Ph.D., OPS/OBP/DMA

**To:** BLA File, STN 125472/0

**Through:** Patricia Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB

**Subject:** Inspection Waiver

**Applicant:** Genentech, Inc.

**Facility:** [REDACTED] (b) (4)

**Product:** Tocilizumab (Actemra® SC PFS)

**Dosage:** Prefilled syringe containing a sterile, preservative-free liquid solution containing 162 mg/0.9 mL tocilizumab for subcutaneous injection

**Indication:** Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs)

**Waiver Recommendation**

Based on the compliance history of the firm, the current GMP status, and the fact that [REDACTED] (b) (4) [REDACTED] has been approved to manufacture other licensed products using similar manufacturing processes, we recommend that the pre-license inspection of [REDACTED] (b) (4) [REDACTED] drug product manufacturing facility in [REDACTED] (b) (4) [REDACTED] be waived for STN 125472/0 (action date October 21, 2013).

**Summary**

BLA 125472 was submitted by Genentech, Inc. to license Actmra PFS for subcutaneous injection. Actmra SC PFS drug product is manufactured at [REDACTED] (b) (4) [REDACTED], a contract facility located in [REDACTED] (b) (4) [REDACTED].

Actmra SC PFS is a recombinant humanized anti-human monoclonal antibody that inhibits function of IL-6. Actmra SC PFS is indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). Actmra is currently approved as a concentrate solution to be diluted prior to IV infusion. BLA 125472 seeks approval of a subcutaneous dosage formulation and regimen using a single-use PFS for the treatment of adult PA patients.

Facility Information

The supplement proposes the use of [REDACTED] (b) (4) [REDACTED]

(b) (4)

(b) (4)

Supporting Information for the inspection waiver:

The following information is provided in support of waiving the pre-license inspection:

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

(b) (4)

2. *FDA has not inspected the establishment in the last 2 years.*

The establishment was inspected by FDA IOG on (b) (4).

3. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

The inspection was classified VAI with acceptable GMP status.

4. *The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities / buildings / areas.*

(b) (4)

5. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment. The manufacturing process for Actmera SC PFS is similar to other drug product manufacturing processes used in the same facility.*

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/s/  
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REYES CANDAU-CHACON  
05/29/2013

PATRICIA F HUGHES TROOST  
05/30/2013

GERALD M FELDMAN  
05/30/2013

KATHLEEN A CLOUSE STREBEL  
05/31/2013

JOSEPH D DOLESKI  
06/13/2013



**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

8. Provide the “homogeneity of slopes” analysis previously described (3.2.S.7.1) that was performed to compare the (b) (4).

**Drug Product:**

9. In Module 3.2.P.2.4 Container Closure, it states “The extractables profiles obtained were used to support the identification of potential leachables in the filled SIN PFSs”, however the “extractables profiles” are not provided. Provide the full report describing identification of extractables and leachables from the PFS.
10. In Table P.5.6-2 you describe the use of (b) (4). Provide the statistical assessment used for this purpose.
11. You describe the (b) (4) the glass barrels, but do not mention any analysis performed post filling. Provide data assessing levels of (b) (4) in the tocilizumab drug product and the impact that levels of (b) (4) may have on tocilizumab drug product quality.
12. We note that testing for visible particles is conducted (b) (4). Explain why removal of tocilizumab drug product from the PFS+NSD for particulate testing would not be appropriate.
13. We note that Injection Force is listed (b) (4) test with an acceptance criterion of (b) (4) N. Provide the Injection Force test results for the 4 validation as well as any subsequent commercial lots manufactured. Provide a justification as to why Injection Force should be an acceptable test method in lieu of Breakloose and Extrusion. Ordinarily, Breakloose and Extrusion would be considered release specifications rather than (b) (4) tests, and thus a component of the Certificate of Analysis. Modify your batch release testing paradigm accordingly.
14. To support your proposed expiration dating period, provide a “simple stability update” for both Drug Substance and Drug Product. A "simple stability update" is defined as follows: Stability data and analyses performed under the same conditions and for the same batches in the same container closure system(s) as described in the stability protocol provided in the original submission. Provide these data using the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any). Simple stability updates submitted up to month 7 for a standard submission will be reviewed and considered in shelf life determinations.

Submit a response officially to the BLA. In addition, forward a courtesy copy to me via email ([philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov)).

**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

If you have any questions, contact me at 301-796-2466.

Sincerely,  
*{See appended electronic signature page}*

---

Philantha Montgomery Bowen  
Sr. Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

Drafted: Bowen/5-31-13

Clearance: Jafari/5-31-13  
Shapiro/6-4-13

Finalized: Bowen/6-4-13

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PHILANTHA M BOWEN  
06/04/2013

**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

Dear Mr. Heminway:

Your submission dated December 21, 2012, is currently under review and we have the following request for clarification of DMF information in the BLA:

- Table P.7-1 (section 3.2.P.7) indicates that the DMF numbers for (b) (4) are (b) (4) and (b) (4). However, the LOA indicates that the DMF numbers for (b) (4) are (b) (4). Amend the BLA to provide the correct DMF numbers for (b) (4) in Table P.7.1.

If you have any questions, contact me at 301-796-2466.

Sincerely,  
*{See appended electronic signature page}*

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Philantha Montgomery Bowen  
Sr. Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

Drafted: Bowen/5-23-13

Clearance: Jafari/5-23-12  
Hughes/5-24-13

Finalized: Bowen/5-24-13

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PHILANTHA M BOWEN  
05/24/2013

## **Rashid, Nichelle E**

---

**From:** Rashid, Nichelle E  
**Sent:** Friday, May 10, 2013 5:20 PM  
**To:** heminway.stuart@gene.com  
**Cc:** Rashid, Nichelle E; Bradley, Sean  
**Subject:** Information Request/ BLA 125472/ Tocilizumab

Good Afternoon Mr. Heminway,

Your submission for BLA 125472 submitted on December 21, 2012 is currently under review. We have the following request:

Please submit a Request for Proprietary Name Review for Actemra. Since this is a new BLA and a different route of administration, we would need to complete a Proprietary Name Review for this application.

Please provide the requested information no later than noon, Friday, May 17, 2013. If you have any questions, please contact me via email or at (301) 796-3904.

Thanks,

**Nichelle E. Rashid**  
Safety Regulatory Project Manager  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
**Tel: (301) 796-3904**  
Fax: (301) 796-9725  
[nichelle.rashid@fda.hhs.gov](mailto:nichelle.rashid@fda.hhs.gov)

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/s/  
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NICHELE E RASHID  
05/22/2013

**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

Dear Mr. Heminway:

Your submissions dated December 21, 2012, and May 15, 2013, to BLA 125472 are currently under review and we have the following comments regarding your proposed label.

1. Provide justification for the [REDACTED] <sup>(b) (4)</sup> you propose in Section 5.3 - Warnings and Precautions of the label. Include data for both subcutaneous and intravenous formulations of tocilizumab since the changes would apply to both formulations.
2. In Section 14 - Clinical Studies, group all data pertaining to the subcutaneous formulation together, similar to the grouping in Section 6.

Submit revised labeling incorporating requests outlined above for the Package Insert. Provide a clean copy and a tracked-change version of the Package Insert and Medication Guide by May 28, 2013, for item 2 and June 10, 2013, for item 1 to the BLA. In addition, please forward a courtesy copy to me via email.

If you have any questions, contact me at 301-796-2466.

Sincerely,

*{See appended electronic signature page}*

---

Philantha Montgomery Bowen  
Sr. Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Actemra (tocilizumab) SC**  
**Genentech**

Drafted: MPaterniti/5-16-13

Clearance: Jafari/5-16-13  
Paterniti/5-20-13  
Yim/5-20-13

Finalized: Bowen/5-20-13

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PHILANTHA M BOWEN  
05/20/2013

## Bowen, Philantha

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**From:** Bowen, Philantha  
**Sent:** Thursday, May 09, 2013 1:23 PM  
**To:** 'Stuart Heminway'  
**Cc:** Hilary Henshaw  
**Subject:** BLA 125472 (Actemra) SC - FDA Request for Updated Labeling

Hi Stuart,

Your submission dated December 21, 2012, to BLA 125472 is currently under review. Reference is made to the approval letter dated April 29, 2013, for the pJIA indication. We request that you submit updated labeling to BLA 125472 to include the pJIA indication. Submit a clean and tracked version of the updated label to the BLA by May 15, 2013. Forward a courtesy copy to me via email.

Sincerely,

*Philantha*

---

**Philantha M. Bowen, MPH, BSN, RN**  
**CDR, U.S. Public Health Service**  
**Sr. Program Management Officer**  
Food and Drug Administration  
Center for Drug Evaluation and Research/ODEII  
Division of Pulmonary, Allergy, and Rheumatology Products  
10905 New Hampshire Ave, Bldg 22, Room 3326  
Silver Spring, MD 20993  
☎ 301-796-2466  
☎ 301-796-9718  
✉ [philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov)

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PHILANTHA M BOWEN  
05/09/2013

**BLA 125472**  
**Tocilizumab (Prefilled Syringe)**  
**Genentech, Inc.**

Dear Ms. Cook:

Your submission dated December 21, 2012, to BLA 125472 is currently under review. We have the following information requests and/or comments:

**Drug Substance, Microbial Quality**

**1. Description of the Manufacturing Process and Process Controls**

Provide shipping information of tocilizumab DS from Genentech Oceanside to (b) (4)

**2. Control of Critical Steps and Intermediaries**

Clarify if (b) (4) bioburden and endotoxin samples are taken (b) (4)

**3. Process Validation and/or Evaluation - Qualification Runs**

Clarify if (b) (4) hold times have been validated for microbial quality at commercial scale. Clarify if (b) (4)

**4. Process Validation and/or Evaluation - Shipping Validation**

Clarify if the shipping validation in supplement 125276/50 included DS shipments from Genentech Oceanside to (b) (4).

**5. Specifications**

Clarify if bioburden for DS release specifications are (b) (4) CFU/100 mL (section 3.2.S.4.1) or (b) (4) CFU/100 mL and exclusion of *E. coli*, *Enterobacteriaceae*, *P. aeruginosa*, *S. aureus*, and *Salmonella sp.* (section 3.2.S.4.4) and amend the BLA to provide the correct specifications.

**6. Validation of Analytical Procedures - Endotoxin**

- a) Endotoxin specification according to 3.2.S.4.1 is (b) (4) EU/mL; clarify why an endotoxin limit of (b) (4) EU/mL was used to calculate the endotoxin MVD.
- b) Provide endotoxin concentrations used for the standard curve.
- c) Clarify if (b) (4) EU/mL were used in the determination of non-inhibitory concentration.
- d) Summarize deviation MVP-0554-120109-BFSSC.
- e) Clarify if determination of method suitability has been performed for (b) (4)

**7. Validation of Analytical Procedures - Bioburden**

- a) Provide incubation conditions used for bioburden test qualification and for routine bioburden samples.
- b) Clarify if growth promotion for each lot of media is routinely performed.

**8. Batch Analysis**

Amend section 3.2.S.4.4 of the BLA to include the correct endotoxin specifications of (b) (4) EU/mL.

**9. Stability**

Provide data in support of microbial quality of DS stored for the maximum allowed time at (b) (4).

**Drug Product, Microbial Quality**

**10. General**

Amend the BLA to include description and validation of the PFS CCIT in section 3.2.P.2 (currently is in 3.2.P.8.3), and shipping validation in section 3.2.P.3.5 (currently is in 3.2.R).

**11. Container Closure Integrity Test**

- a) Clarify if the Helium Leak Test is feasible in the PFS assembled with the NSD and plunger rod.
- b) Clarify if the syringes used for the Actmera DP were used in the media-filled CCIT. If the test was conducted using different syringes, justify their use for the test.
- c) Media fill of the PFS assembled with the NSD and plunger rod may not be sufficient to demonstrate CCI. CCI of the assembled syringes should be determined using the Helium Leak Test or, if the test is not feasible, by subjecting the media-filled [PFS + NSD] to microbial ingress challenge. Alternatively, assembled [PFS + NSD] can be tested for CCI by any other test that has been correlated to microbial ingress.
- d) Indicate the sample size that will be tested for CCI in the stability program.

**12. Description of Manufacturing Process and Process Controls**

- a) (b) (4)
- b)
- c)

- d)
- e)
- f)

(b) (4)

### 13. Control of Critical Steps and Intermediates

- a) Provide measures in case the acceptance limits for bioburden are exceeded.
- b) Include endotoxin monitoring as part of microbial quality in-process controls prior to (b) (4).
- c) We recommend including bioburden and endotoxin alert limits based on historical trend data as part of the microbial control strategy.

### 14. Validation Batches [PFS + NSD] Roche Kaiseraugst

- a) List any differences between the equipment used for process validation batches and PFS production manufacture and justify the use of the different equipment.
- b) Validation of [PFS + NSD] assembly may impact container closure integrity and should be supported by results from CCIT in assembled [PFS + NSD] devices. Refer to IR-11c.

### 15. (b) (4) Validation - Microbial Retention Test

- a) Indicate the size of your routine production (b) (4)
- b) Indicate how (b) (4) area in Table P.3.5-14 was calculated.
- c) Clarify the test volumes used in the validation: Table P.3.5-14 indicates that the (b) (4) area is (b) (4) mL/cm<sup>2</sup> but Table P.3.5-15 indicates an average of (b) (4) cm .
- d) Submit study showing microbial challenge survival to DP using different exposure times.
- e) Since the composition of (b) (4) is very different form the DP composition, justify its use as surrogate and indicate if other alternatives to the use of surrogate have been explored, for example reduced exposure of the challenge to the DP as per PDA Technical Report No. 26.
- f) Indicate microbial count at beginning and end of challenge.
- g) Indicate if (b) (4) elements used in the bacterial retention studies were subjected to (b) (4) integrity test before and after use and submit results.
- h) Indicate if three different lots of (b) (4) elements were used for the test.
- i) Describe how (b) (4)

**16. (b) (4) Validation - (b) (4) Integrity Test**

Submit report for the validation of the (b) (4) integrity test and indicate if the test is performed with WFI or with product. If the integrity test is performed with WFI, provide data demonstrating that the (b) (4) process is thorough and results in consistent (b) (4) test results. If the integrity test is performed with product, provide determination of the product-specific (b) (4).

**17. Hold Times**

Clarify if intermediate holds have been validated for microbial quality. (b) (4)  
(b) (4) should be validated for microbial quality at commercial scale by conducting hold studies for the maximum processing times and sampling for bioburden and endotoxin at the end of hold.

**18. Environmental Monitoring and (b) (4)**

- a) (b) (4)
- b) (b) (4)
- c) (b) (4)
- d) (b) (4)
- e) Indicate how locations for environmental monitoring are selected.
- f) Indicate measures followed in the event that environmental monitoring limits are exceeded.
- g) Submit an environmental monitoring summary report for the last (b) (4) simulations. Indicate if alert and action limits were exceeded and provide the identity of microorganisms isolated if limits were exceeded.

**19. Shipping Validation**

- a) Submit shipping validation report for all shipping studies performed to validate transport of PFS and [PFS + NSD].
- b) Provide a summary description and results of mechanical tests and/or airfreight simulations performed for each shipping validation study.
- c) Provide summary description and results of the CCIT used to validate integrity of the PFS and [PFS + NSD] during each shipping validation study (note that media fill units not subject to microbial challenge conditions are not sufficient to demonstrate CCI (refer to IR-11).
- d) Indicate if [PFS + NSD] shipping validation in the final packaging configuration includes CCIT and justify your answer.

20. (b) (4) **Stoppers and Process Equipment**

- a) (b) (4)
- b) (b) (4)

**21. Specifications for Release and End of Shelf-life**

Conduct CCIT in the [PFS + NSD] at the end of shelf life. Alternatively, provide data supporting that the NSD assembly does not impact integrity of the PFS (refer to IR-11c and IR-14b).

**22. Validation of Analytical Procedures – Sterility**

Provide a brief description on how the sterility suitability test was performed, including (b) (4)

**23. Validation of Analytical Procedures – Endotoxin**

- a) Clarify why an endotoxin limit of (b) (4) EU/mL was used to calculate the endotoxin MVD.
- b) Describe the type and amount of endotoxin spike used in the inhibition/enhancement studies.
- c) Presence of (b) (4) may result in an underestimation of endotoxin over time. Provide evidence ensuring endotoxin recovery is not underestimated by conducting endotoxin spiking and recovery studies over time.
- d) Submit validation report for the rabbit pyrogen test.

**24. Batch Analysis**

- a) Endotoxin acceptance criterion is (b) (4) EU/mL according to Table P.5.4-2 and to the validation batches CofA, and (b) (4) EU/mL according to specifications in section P.5.1 and P.5.6. Amend the BLA and the validation batches CoA to reflect the correct endotoxin limits.
- b) Process validation batches CAAK104, CAAK106, and CAAK107 are not assembled into the final product [PFS + NSD] in the BLA submission. Indicate if those batches have been currently assembled. We recommend performing CCIT in final product of process validation batches to validate integrity of the finish product after assembly into the [PFS + NSD].

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

**25. Stability**

- a) Indicate the proposed shelf life for Actmera SC [PFS + NSD].
- b) Refer to IR-21 regarding CCIT in the PFS *vs.* [PFS + NSD] at the end of shelf-life.

Submit the requested information officially to the BLA by Tuesday, April 23, 2013. Forward a courtesy copy via email to [philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov).

If you have any questions, contact me at 301-796-2466.

*{See appended electronic signature page}*

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Philantha Montgomery Bowen, MPH, RN  
Sr. Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Drafted: Bowen/3-9-13

Clearance: Jafari/3-9-13  
Candauchaon/3-9-13  
Hughes/3-10-13

Finalized: Bowen/3-10-13

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/s/  
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PHILANTHA M BOWEN  
04/10/2013



BLA 125472

## FILING COMMUNICATION

Genentech, Inc.  
A Member of the Roche Group  
1 DNA Way  
South San Francisco, CA 94080

Attention: Stuart Heminway, Program Director  
Regulatory Affairs

Dear Mr. Heminway:

Please refer to your Biologics License Application (BLA) dated December 21, 2012, received December 21, 2012, submitted under section 351(a) of the Public Health Service Act for Actemra (tocilizumab).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 21, 2013.

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 September 23, 2013.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

**Highlights**

1. The Highlights Section of Prescribing Information must be limited to no more than one-half page. Submit a waiver for this requirement.
2. The following verbatim statement <sup>(b) (4)</sup> **PATIENT COUNSELING INFORMATION** <sup>(b) (4)</sup> must appear at the end of this section. Deletions are strike-through.

**Full Prescribing Information (FPI):**

3. For the recent major changes listed in the Highlights, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

We request that you resubmit labeling (Microsoft Word format) that addresses these issues by March 12, 2013. The resubmitted labeling will be used for further labeling discussions.

**PROMOTIONAL MATERIAL**

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

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

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

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

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application in patients 0 to 2 years of age. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application in patients 2 to 17 years of age. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Philantha Montgomery Bowen, Senior Regulatory Project Management Officer, at (301) 796-2466.

Sincerely,

*{See appended electronic signature page}*

Sarah Yim, M.D.  
Associate Director  
Division of Pulmonary, Allergy, and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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SARAH K YIM  
02/19/2013

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Dear Mr. Heminway:

Your submission dated December 21, 2012, to BLA 125472 is currently under review. We have the following request for statistics information regarding Study WA22762:

1. Submit the formulas used to compute the weighted differences in proportions and the variance used to produce the confidence intervals. Also indicate how you treated any "zero" cells in the stratified analysis.
2. There are 3 subjects listed as having withdrawn from the trial, but are listed as ACR20 responders: 203556\_55005 (SC), 203557\_55209 (SC), and 203490\_45412 (IV). Our understanding is that withdrawn subjects should be counted as non-responders for the ACR20. Provide an explanation.
3. There are 5 subjects who may have been assigned to incorrect strata for purposes of the stratified analysis. For example, subject 202898\_38201 in Europe is listed as in stratum 1, but the weight is 60 kg, so presumably would have been listed in stratum 2. The others are 202055\_42002, 203781\_17807, 203133\_29008, and 202785\_10803. Review the assignment of these subjects in the strata and provide clarification.
4. We have been unsuccessful in using your instructions for sub-setting the full dataset to arrive at the Per Protocol population using SAS 9.1. Provide further explanation on how this can be accomplished.
5. In the full data set, we calculate that there are 57 SC subjects and 66 IV subjects who are ACR20 non-responders due to withdrawal. However, on page 61 of the report, the Table 5 shows 59 and 67 respectively as "total withdrawn from treatment." Explain the discrepancy and clarify whether or not withdrawn from treatment is the same as being withdrawn from the trial for the purpose of counting ACR20 non-responders.

Submit the requested information by Thursday, February 14, 2013, at 10 AM EST. Forward a courtesy copy via email to [philantha.bowen@fda.hhs.gov](mailto:philantha.bowen@fda.hhs.gov).

If you have any questions, contact me at 301-796-2466.

*{See appended electronic signature page}*

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Philantha Montgomery Bowen, MPH, RN  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**BLA 125472**  
**Tocilizumab (*Prefilled Syringe*)**  
**Genentech, Inc.**

Drafted: Bowen/1-29-13

Clearance: Jafari/1-29-13  
Hoberman/1-29-13  
Buenconsejo/1-31-13

Finalized: Bowen/1-31-13

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PHILANTHA M BOWEN  
01/31/2013

## Biologic Licensing Application (BLA) and Supplements (sBLA) Review Committee (Review Team) Assignment Memorandum

- Initial assignment  
 Change (only list deletions &/or additions)

**STN:** 125472/0

**Applicant:** Genentech, Inc. - A Member of the Roche Group

**Product:** Tocilizumab (TCZ)

**Date:** January 3, 2013

### Addition/Change of Review Committee Members (Review Team):

Name	Reviewer Type (Role)	Job Types (Discipline)	Assignment Type (New/Added/Deleted)
Theresa Michele	Chairperson	CDTL	New
Philantha Bowen	Reg. Project Manager	Admin/Regulatory	New
Miya Paterniti	Primary Reviewer	Clinical	New
Gerald Feldman	Primary Reviewer	Product	New
	Primary Reviewer	Facility	Assignment type
	Reviewer	Clinical Pharmacology	Assignment type
Asoke Mukjerhee	Reviewer	Pharm/Tox	New
David Hoberman	Reviewer	Biostatistics	New
	Reviewer	BIMO (OSI)	Assignment type
	Consultant Reviewer	Other (Safety Evaluator)	Assignment type
	Reviewer	Other	Assignment type
	Reviewer	Labeling	Assignment type
	Collaborative Reviewer	Promotional Materials	Assignment type
	Other Reviewer	Inspector	Assignment type

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PHILANTHA M BOWEN  
01/03/2013



BLA 125472/0

**BLA ACKNOWLEDGEMENT**

Genentech, Inc.  
A Member of the Roche Group  
1 DNA Way  
South San Francisco, CA 94080

Attention: Stuart Heminway, Program Director  
Regulatory Affairs

Dear Mr. Heminway:

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

**Name of Biological Product:** Actemra (tocilizumab[TCZ])

**Date of Application:** December 21, 2012

**Date of Receipt:** December 21, 2012

**Our Secondary Tracking Number (STN):** BLA 125472

**Proposed Use:** The subcutaneous use of tocilizumab, via a pre-filled syringe, for the treatment of adult patients with Rheumatoid Arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs.

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

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Pulmonary, Allergy, and Rheumatology Products  
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.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-2466.

Sincerely,

*{See appended electronic signature page}*

Philantha M. Bowen, M.P.H., RN  
Senior Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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PHILANTHA M BOWEN  
01/03/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 11972

**MEETING MINUTES**

Hoffmann-LaRoche, Inc.  
340 Kingsland Street  
Nutley, NJ 07110

Attention: Kristine L. Ogozalek, Program Director  
Regulatory Program Management

Dear Ms. Ogozalek:

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

We also refer to the telecon between representatives of your firm and the FDA on October 31, 2012. The purpose of the meeting was to discuss the format and content of your proposed supplemental BLAs for subcutaneous administration via a pre-filled syringe (b) (4) for the treatment of rheumatoid arthritis.

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

If you have any questions, call me at (301) 796-2466.

Sincerely,

*{See appended electronic signature page}*

Philantha M. Bowen, M.P.H., RN  
Senior Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** (b) (4) Pre-Filled Syringe (b) (4)  
**Meeting Date and Time:** October 31, 2012; 3:00 – 4:00 EST  
**Meeting Location:** Teleconference  
**Application Number:** 11972  
**Product Name:** Tocilizumab  
**Indication:** Rheumatoid Arthritis  
**Sponsor/Applicant Name:** Hoffmann-LaRoche  
**Meeting Chair:** Badrul A. Chowdhury, M.D., Ph.D., Division Director  
**Meeting Recorder:** Philantha Bowen, M.P.H., RN, Sr. Program Manager

**FDA ATTENDEES**

Office of Drug Evaluation II

Badrul A. Chowdhury, M.D., Ph.D., Division Director, Division of Pulmonary, Allergy, and Rheumatology Products, Office of Drug Evaluation II

Sarah Yim, M.D., Supervisory Associate Director, Division of Pulmonary, Allergy, and Rheumatology Products

Philantha Bowen, M.P.H., RN, Senior Regulatory Management Officer, Division of Pulmonary, Allergy, and Rheumatology Products

Larissa Lapteva, Acting Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

Nikolay Nikolov, M.D., Clinical Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products

Office of Clinical Pharmacology

Liang Zhao, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II

Office of Translational Sciences

Joan Buenconsejo, Ph.D., Statistical Team Leader, Office of Biometrics, Division of Biometrics II

Office of Pharmaceutical Sciences/Office of Biotechnology Products

Marjorie Shapiro, Chief, Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies

Gerald Feldman, Ph.D., Product Quality Reviewer, Division of Monoclonal Antibodies

Office of Surveillance and Epidemiology

Carolyn L. Yancey, M.D., Medical Officer, Division of Risk Management

Lubna Merchant, M.S., Pharm. D., Team Leader, Division of Medication Error Prevention and Analysis, Office of Medication Error Prevention and Risk Management

Center for Devices and Radiographic Health

Jacqueline Ryan, M.D., Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices, Office of Device Evaluation

Quynh Nhu Nguyen, B.S., Biomedical Engineer/Human Factors Reviewer, Human Factors Pre-Market Evaluation Team, Office of Device Evaluation

**SPONSOR ATTENDEES**

Mark Chipperfield, PhD, Device Development Head, Pharma Technical Development

Desiree Crisolo, Senior Associate, Pharma Technical Regulatory

Wendy Douglass, PhD, Clinical Scientist

Cornelia Kruettli, PhD, Team Leader, Pharma Technical Development

Robert Lichtneckert, PhD, Group Leader, Pharma Technical Regulatory

Matt Meldorf, PhD, Global Development Lead

Jennifer Mercer, Director, Pharma Technical Regulatory

Kristine Ogozalek, Program Director, Regulatory Affairs

Florian Wildenhahn, PhD, Device Team Leader, Pharma Technical Development

Lee Wood, PhD, Human Factors Engineer, Pharma Technical Development

Stephen Wright, MD, Senior Medical Director

## 1.0 BACKGROUND

Actemra is a recombinant, humanized, anti-human IL-6R monoclonal antibody currently marketed for intravenous infusion and approved for rheumatoid arthritis.

The purpose of this meeting is to obtain agreement on the content and format of the proposed supplemental BLAs for subcutaneous administration via a pre-filled syringe (PFS) (b) (4) (b) (4) for the treatment of rheumatoid arthritis (RA).

The expected outcome of this (b) (4) BLA meeting is to obtain FDA guidance on the acceptability of the following:

- Data from the pivotal Phase 3 studies WA22762 and NA25220 to support (b) (4) amending the Dosing and Administration section of the Actemra
- The proposed change to the package insert to include the new dosage form and route of administration utilizing a PFS (b) (4) in adults with RA.
- The proposed structure and content to support filing and review (b) (4)
- The proposed contents of the Risk Evaluation and Mitigation Strategy (REMS).

## 2. DISCUSSION

### 2.1 CLINICAL

***Question 1:*** *The Sponsor believes that the clinical data from the pivotal studies WA22762 and NA25220 are sufficient to support the filing (b) (4) for the SC dosage form of TCZ with administration utilizing a PFS (b) (4) for adults with RA.*

*a) Does the Agency agree that the data support a (b) (4) filing for the SC dosage form with the PFS?*

*b)* (b) (4)

*FDA Response to Question 1:*

*The safety and efficacy data summarized in the briefing package appear to be adequate to support filing of an application for SC formulation of tocilizumab with the prefilled syringe (PFS). However, determination of the approvability of the application will be contingent upon review of the (b) (4)*

(b) (4)

[Redacted] (b) (4)

Discussion:

Roche verbalized understanding of the Agency's concern regarding the human factor validation study for the pre-filled syringe (PFS) [Redacted] (b) (4) discussed at the previous type C meeting on 10.24.12. Roche further asked if the information provided, excluding [Redacted] (b) (4) would be sufficient to support filing. The FDA stated that [Redacted] (b) (4) no comment could be made until the complete PFS submission is reviewed.

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] Roche acknowledged the FDA's position.

*Post-Meeting Comment:*

Be advised that the proposed application should be submitted as a separate original BLA, [Redacted] (b) (4) (refer to the post-meeting comments in questions 10 and 17).

## 2.2 CLINICAL

***Question 2:*** *Given the safety and efficacy data presented herein, does the Agency agree that for patients weighing less than 100 kg the starting dose for TCZ is 162 mg SC q2w (which can be increased to qw based upon clinical response), and for patients weighing 100 kg or more the starting dose for TCZ is 162 mg SC qw?*

*FDA Response to Question 2:*

*We will not be able to determine whether you have provided adequate safety and efficacy data to support your proposed dosing regimens until we have reviewed the data in your (b) (4) submission.*

*Regarding your proposed analyses of the exposure-response relationship using Phase 3 data, perform exposure-response analyses both with SC and IV data, combined or separately, whichever is appropriate. For the analysis with IV data, also include the IV data from the original BLA125276 submission. If it is not feasible to perform an exposure-response analysis using data from all studies, a separate exploratory exposure-response analysis of the data previously submitted in the original BLA may be sufficient.*

*Discussion:*

There was no discussion on question 2.

## 2.3 CLINICAL

***Question 3:*** *The planned submission will include data from the pivotal studies WA22762 and NA25220 of TCZ SC in combination with DMARDs, as well as from the Chugai-sponsored Japanese studies MRA227JP and MRA229JP of TCZ SC as monotherapy. The Sponsor believes that these data support the addition of the SC dosage form to the current Dosing and Administration section of the Actemra USPI, including the use either as monotherapy or concomitantly with MTX or other DMARDs. Does the Agency agree?*

*FDA Response to Question 3:*

*The adequacy of the safety and efficacy data to support the proposed addition of the SC dosage form to the current Dosing and Administration section of the Actemra USPI, including the use either as monotherapy or concomitantly with MTX or other DMARDs, will be contingent upon review of the data.*

*You may propose labeling that adds information about the SC formulation to the current USPI. We will evaluate whether your rationale is adequate and whether the risk-benefit balance of doing so would be favorable. It would be prudent to have separate SC labeling prepared in case there are major differences between the products, e.g. if the SC formulation does not have adequate data to support*

*monotherapy use or if there are major differences in efficacy or safety between the IV and SC formulations.*

Discussion:

Roche acknowledged the FDA recommendations and comments provided during the type C meeting held on October 24, 2012, and plan to submit the PFS (b) (4) (b) (4)

Roche requested that the FDA share any concerns regarding the Japanese studies (i.e. study design, population). Roche does not plan to submit the data sets for these studies. Additionally, Roche asked if the study reports would be acceptable for the data quality. The FDA commented that the Japanese studies will be viewed as supportive, since summaries will be provided versus the actual data. No commitment can be made to include this data as part of the monotherapy claim. The FDA explained that there are differences in the Japanese studies versus the pivotal subcutaneous (SC) studies. A decision will be made based on the totality of data as to whether the Japanese studies would be sufficient to support of the inclusion of the SC within the intravenous (IV) labeling. As part of this decision, the Agency will need to determine if there are concerns with increased immunogenicity with the SC route of administration, and this will be determined upon review. The FDA clarified that Roche will need to provide a clinical report describing the analysis of the Japanese trials. Lastly, the FDA stated that no agreement could be made regarding the data quality in the absence of reviewing the financial disclosures.

Roche and the FDA agreed that:

- No data sets will be submitted for the Japanese studies; Roche will provide the analysis plans and the actual analyses that were conducted for these trials; and
- Depending upon review of the data, the Japanese trials may support a determination of inclusion of the SC formulation within the intravenous (IV) labeling.

## 2.4 CLINICAL

Question 4:

*a) As discussed with the FDA in a meeting held on 2 September 2010, the Sponsor included radiographic assessments at 6 months in Study NA25220. Does the Agency agree that the data are sufficient to file and support inclusion of data in the label for effect of structural damage outcome?*

*b) Does the Agency agree that the data for HAQ-DI are sufficient to file and support inclusion in the label?*

FDA Response to Question 4:

*The efficacy data on the radiographic and HAQ-DI assessments summarized in the briefing package appear adequate to include in your submission. Whether these data are adequate to include in labeling will be determined upon review (b) (4)*

*Also refer to the FDA responses to Question 3 above.*

Discussion:

There was no discussion on question 4.

## 2.5 CLINICAL

**Question 5:** *As indicated in written advice from the Agency on the SC program dated 8 March 2009, the Sponsor has incorporated an Ease-of-Use (EoU) sub-study for the PFS and AI in the long-term extension (LTE) portion of Study NA25220. Data from PFS users (HCP, patients or caregivers) and AI users will be summarized in the EoU Report at the time of filing. Does the Agency agree that the amount of EoU data, in combination with the clinical data and the human factors simulated use data (to be summarized in Module 3) are adequate for review (b) (4)*

FDA Response to Question 5:

*Refer to our response to Question 1.*

Discussion:

There was no discussion on question 5.

## 2.6 NON-CLINICAL

**Question 6:** *Roche has conducted a 9-week Monkey SC bridging toxicity study. In the letter dated 9 March 2009, Roche received feedback on the design of this study. Does the Agency agree that this study adequately addresses the Agency's feedback?*

FDA Response to Question 6:

*Yes, we agree that the 9-week SC bridging study is adequate.*

Discussion:

There was no discussion on question 6.

## 2.7 RISK EVALUATION AND MITIGATION STRATEGY

***Question 7: The Sponsor believes the risks of TCZ SC in the adult RA patient population are consistent with those seen with TCZ IV and can be managed with the existing Actemra REMS (including SC dosing regimen revisions to the communication plan materials). To date, no additional risks have been identified in this population that would warrant new REMS elements. Does the Agency agree with this plan?***

FDA Response to Question 7:

*At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a REMS Modification including revision to the approved elements will be necessary to ensure that the benefits of ACTEMRA outweigh the risks. We will determine the need for a REMS Modification during the review of your application.*

Discussion:

There was no discussion on question 7.

## 2.8 RISK EVALUATION AND MITIGATION STRATEGY

***Question 8: The Sponsor seeks guidance from the Agency on whether a REMS assessment is needed for this efficacy supplement. Can the Agency comment if an assessment is needed, and if it is, whether reference to the 18-month assessment will be sufficient to satisfy this requirement?***

FDA Response to Question 8:

*An assessment of the most recent REMS Modification for ACTMERA, dated October 11, 2012, is not required based on submission of a new efficacy supplement. The Office of New Drugs and the Office of Surveillance and Epidemiology require that you submit the ACTEMRA REMS assessments based on the approved timetable for submission of assessments as stated in the most recent REMS Modification.*

Discussion:

There was no discussion on question 8. We have the following post meeting comment pertaining to the REMS assessment for your BLA submission.

*Post-Meeting Comment:*

An assessment of the most recent REMS Modification for ACTMERA, dated October 11, 2012, will not be required based on submission of a new original BLA.

## 2.9 CLINICAL

***Question 9:*** *Does the Agency agree with the plans the Sponsor has outlined to support home administration of the SC dosage form with the PFS (b) (4) including updates to the Medication Guide? Does the Agency agree that, following appropriate training and assessment by a HCP, TCZ can be prescribed for home administration?*

*FDA Response to Question 9:*

*The acceptability of your proposed plan to support home administration will be determined upon review of the data. The safety of home self-administration is predicated on a very low potential for anaphylaxis and an individual's access to emergent medical care. In your submission, provide an estimate of the risk of anaphylaxis and details on how you will assure expeditious medical attention for patients experiencing hypersensitivity and anaphylaxis with home administration. We recommend you use the defined clinical criteria to identify patients with anaphylaxis, as described by Sampson et al. [J Clin Immunol 2006; 117:391-7].*

*Also refer to FDA preliminary comments dated October 22, 2012, for the Type C meeting held on October 24, 2012, regarding the human factor studies (b) (4)*

*Discussion:*

There was no discussion on question 9.

## 2.10 REGULATORY / PROPOSED CONTENT

***Question 10:***

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

Discussion:

There was no discussion on question 10. However, as agreed in these preliminary comments and the meeting minutes for the type C meeting held on October 24, 2012, FDA is providing the following post-meeting comment regarding user fees, as well as submission information regarding the proposed application: (b) (4)

*Post-Meeting Comment:*

(b) (4)

The submission of an original BLA will require a full user fee. If you have additional user fee and/or bundling policy questions, we refer you to Mr. Michael Jones in the User Fee Office at 301-796-3602.

We refer you to Section 3.0 of the meeting minutes for additional information pertaining to an original BLA submission.

## 2.11 REGULATORY / PROPOSED CONTENT

***Question 11:*** *The Sponsor plans to include the SC dosage form of TCZ, for the treatment of RA, within the current TCZ IV US Package Insert (USPI). Does the Agency agree?*

*FDA Response to Question 11:*

*Refer to our response to Question 3.*

Discussion:

There was no discussion on question 11.

## 2.12 REGULATORY / PROPOSED CONTENT

***Question 12:*** *Does the Agency agree that the proposed contents of Module 1 (b) (4) are sufficient for filing and review? In particular:*

*a) The Sponsor intends to provide financial disclosure certification for Studies WA22762 and NA25220. The Sponsor does not plan to submit financial disclosure information for the Phase*

***I studies and Chugai Japanese studies (MRA227JP and MRA229JP) as these studies do not fit the definition of “covered studies” and this information was not collected. Does the Agency agree?***

FDA Response to Question 12 (a):

*Yes, we agree that your proposal to not provide updated financial disclosure information for the Phase I studies and Chugai Japanese studies, since they do not qualify as covered studies, is acceptable.*

Discussion:

There was no discussion on question 12(a).

***b) The Sponsor plans to request a pediatric waiver for pediatric Juvenile Idiopathic Arthritis (pJIA) in children under 2 years old, and a deferral for pJIA in children 2 years or older for the SC formulation of TCZ. Does the Agency agree?***

FDA Response to Question 12 (b):

*Yes, we agree that your proposal is acceptable.*

Discussion:

There was no discussion on question 12(b).

## **2.13 REGULATORY / PROPOSED CONTENT**

***Question 13: Does the Agency agree with the planned content and format of Module 2, particularly the clinical pharmacology, clinical efficacy, and clinical safety summaries?***

FDA Response Question 13:

*The proposed content and format of Module 2 appears acceptable.*

Discussion:

There was no discussion on question 13.

## **2.14 REGULATORY / PROPOSED CONTENT**

**Question 14: Does the Agency agree with the planned content and format of the Module 4 Non-clinical components (b)(4)**

FDA Response to Question 14:

Yes, we agree. All nonclinical study reports as listed in the meeting package should be included in your (b)(4) submissions.

Discussion:

There was no discussion on question 14.

## 2.15 REGULATORY / PROPOSED CONTENT

**Question 15: Does the Agency agree with the planned content and format of Module 5? Specifically:**

- a) *The Sponsor will provide patient narratives for the following categories: Deaths, SAEs, and AEs leading to withdrawal. Does the Agency agree with the plan for submission of patient narratives?*
- b) *Is the proposed plan for the submission of Case Report Forms (CRFs, including images) and SAS datasets, acceptable to the Agency?*
- c) *The ease of use (EoU) data from study NA25220 will be summarized in a separate report (appended to CSR NA25220 LTE in 5.3.5.1), with the dataset and individual questionnaires available on request. Does the Agency agree with this plan?*

FDA Response to Question 15 a, b, and c:

Yes, we agree. This proposal is generally acceptable.

Discussion:

There was no discussion on questions 15 a, b or c.

Additional FDA Comment:

*In the briefing package, the Company position, on page 50 states:*

*"No separate text portion of the integrated summaries of efficacy and safety (ISE and ISS) will be provided in Section 5.3.5.3; cross-reference will be made to the clinical summaries of efficacy and safety (Sections 2.7.3 and 2.7.4)."*

*Your proposal is acceptable, provided that you perform and submit the integrated analyses required in an ISS, as required by 21 CFR 314.50(d)(5)(v)-(vi), and not simply provide summaries. The Module 2 summaries were not intended to contain the level of detail expected for an ISS or ISE. Therefore, we recommend you submit the required integrated analyses in Section 5.3.5.3. However, if the narrative portions of the ISE or ISS are suitable for use in Module 2.7.3 or Module 2.7.4, you may place these once in Module 2.7.3 and Module 2.7.4 and reference them in Section 5.3.5.3. For further detail regarding placement of the ISS and ISE in the electronic common technical document (eCTD) refer to the information at the following link:*

*<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm163558.htm>*

*The approach to the analyses of safety should take into account the complexity of the trial design (e.g. cross-over and escape provisions).*

*For the pooled LTE population analyses, use the total exposure time on drug and not only the exposure while in LTE studies.*

*Additionally, clarify in your (b) (4) submission what attribution windows you are proposing to use for the safety analyses. For patients on placebo, it makes sense that attribution stops immediately upon escape, change in therapy, or discontinuation from study. However, for patients on tocilizumab, it is more appropriate to include a period of time after treatment has stopped during which time adverse events will be attributed to tocilizumab.*

#### Discussion:

There was no discussion on the additional FDA comment.

## **2.16 REGULATORY / PROPOSED CONTENT**

**Question 16:** *The Sponsor intends to provide*

(b) (4)

(b) (4)

(b) (4) *Does the Agency agree with this*

*proposal?*

FDA Response to Question 16:

*We do not agree with your plan (b) (4) We remind you that the application should be complete on submission, meaning that all efficacy and safety data that you consider necessary for approval should be included with the initial submission. The format of the 4 month safety update listings and summary tables should be consistent with the format of the initial submission.*

Discussion:

Roche commented [REDACTED] (b) (4)

[REDACTED] (b) (4)  
(b) (4) FDA disagreed with Roche's proposal and reiterated that the [REDACTED] (b) (4) must be complete for assessment of the risk-benefit at the time of the original submission, and must include all the relevant safety and efficacy data. FDA pointed out that [REDACTED] (b) (4)

**2.17 REGULATORY / PROPOSED CONTENT**

**Question 17:** The Sponsor intends to submit the file [REDACTED] (b) (4) **BLA 125276.** (b) (4)

FDA Response to Question 17:

[REDACTED] (b) (4)

Discussion:

There was no discussion on question 17. However, the FDA has the following post-meeting comment pertaining to the standard review cycle for the original BLA application:

*Post-Meeting Comment:*

Refer to our post-meeting comment in question 10, regarding the need to submit a separate original BLA, [REDACTED] (b) (4)

The submission of an original application will be subject to "The Program" goals under PDUFA V. The review clock will begin upon submission of the application. However, the PDUFA action date will be determined upon a decision to file the application.

**2.18 REGULATORY / PROPOSED CONTENT**

**Question 18:** *Does the Agency anticipate reviewing the data at an Advisory Committee?*

FDA Response to Question 18:

Based on the (b) (4) meeting package information, it is unlikely that an Advisory Committee meeting will be convened to discuss the data to be provided in support of (b) (4). However, the decision about Advisory Committee meeting will be made upon submission and initial review of the (b) (4).

Discussion:

There was no discussion on question 18.

## 2.19 REGULATORY / PROPOSED CONTENT

**Question 19:** *Would the Agency like the Sponsor to provide a face-to-face technical walkthrough of (b) (4) to help orient the Division to the application following its submission? Specifically, we would provide the Agency with:*

- *A Table of Contents with document descriptions as needed.*
- *A walkthrough of the submission in Global Submit, with particular attention to specific constructs in the filing that may be unique.*

FDA Response to Question 19:

No, a technical walkthrough (b) (4) will not be necessary. However, you may submit a reviewer guide to highlight any unique aspects you think might require clarification.

Discussion:

There was no discussion on question 19.

## 3.0 GENERAL INFORMATION

### DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Refer to the discussion sections for questions 1 and 16. The complete applications must include the human factors data, as well data to support the risk-benefit assessment and safety and efficacy at the time of submission.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was not held since it was stated that the need for a REMS Modification would be determined during the review of the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. There are no agreements for late submission of application components.

### **PREA PEDIATRIC STUDY PLAN**

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov).

### **PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

**4.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

**5.0 ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts for the meeting minutes.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PHILANTHA M BOWEN  
11/30/2012



IND 11972

**MEETING MINUTES**

Pharma Technical Regulatory  
Genentech, Inc.  
Member of the Roche Group  
1 DNA Way, MS# 241B  
South San Francisco, CA 94080-4990

Attention: Catherine Sarmiento, Senior Associate

Dear Ms. Sarmiento:

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

We also refer to the meeting between representatives of your firm and the FDA on October 24, 2012. The purpose of the meeting was to obtain agreement on the adequacy of the human factors validation studies for the pre-filled syringe needle safe device (PFS-NSD) [REDACTED] (b)(4) as well as agreement on the proposed organization and structure of the device content in support [REDACTED] (b)(4)

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

If you have any questions, call me at (301) 796-2466.

Sincerely,

*{See appended electronic signature page}*

Philantha M. Bowen, M.P.H., RN  
Senior Program Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** C  
**Meeting Category:** Guidance: Pre-Filled Syringe (b) (4)  
**Meeting Date and Time:** October 24, 2012; 11:00 AM – 12:00 NN EST  
**Meeting Location:** White Oak, Conference Room 1417  
**Application Number:** IND 11972  
**Product Name:** Tocilizumab  
**Indication:** Rheumatoid Arthritis  
**Sponsor/Applicant Name:** Genentech, Inc., Member of the Roche Group  
**Meeting Chair:** Badrul Chowdhury, M.D., Ph.D., Division Director  
**Meeting Recorder:** Philantha Bowen, M.P.H., RN, Sr. Regulatory Project Manager

**FDA ATTENDEES**

Office of Drug Evaluation II

Badrul A. Chowdhury, M.D., Ph.D., Division Director, Division of Pulmonary, Allergy, and Rheumatology Products, Office of Drug Evaluation II

Philantha Bowen, M.P.H., RN, Senior Regulatory Management Officer, Division of Pulmonary, Allergy, and Rheumatology Products

Sarah Yim, M.D., Supervisory Associate Director, Division of Pulmonary, Allergy, and Rheumatology Products

Larissa Lapteva, Acting Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

Nikolay Nikolov, M.D., Clinical Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products

Office of Surveillance and Epidemiology

Nichelle Rashid, B.S., Safety Regulatory Project Manager

Lubna Merchant, M.S., Pharm.D., Team Leader, Division of Medication Error Prevention and Analysis, Office of Medication Error Prevention and Risk Management

Teresa McMillian, Reviewer, Division of Medication Error Prevention and Analysis, Office of Medication Error Prevention and Risk Management

Jane Gilbert, M.D., Medical Officer, Division of Pharmacovigilance I

Center for Devices and Radiographic Health

Jacqueline Ryan, M.D., Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices, Office of Device Evaluation

QuynhNhu Nguyen, B.S., Biomedical Engineer/Human Factors Reviewer, Human Factors Pre-Market Evaluation Team, Office of Device Evaluation

**SPONSOR ATTENDEES**

Mark Chipperfield, PhD, Device Development Head, Pharma Technical Development

Desiree Crisolo, Senior Associate, Pharma Technical Regulatory

Wendy Douglass, PhD, Clinical Scientist

Cornelia Kruettli, PhD, Team Leader, Pharma Technical Development

Robert Lichtneckert, PhD, Group Leader, Pharma Technical Regulatory

Matt Meldorf, PhD, Global Development Lead

Jennifer Mercer, Director, Pharma Technical Regulatory

Kristine Ogozalek, Program Director, Regulatory Affairs

Florian Wildenhahn, PhD, Device Team Leader, Pharma Technical Development

Lee Wood, PhD, Human Factors Engineer, Pharma Technical Development

Stephen Wright, MD, Senior Medical Director

## 1.0 BACKGROUND

Actemra is a recombinant, humanized, anti-human IL-6R monoclonal antibody currently marketed for intravenous infusion and approved for rheumatoid arthritis.

Presently, Actemra is under development for subcutaneous (SC) administration via a pre-filled syringe needle safe device (PFS-NSD) (b) (4) for the treatment of rheumatoid arthritis (RA). The sponsor has performed several nonclinical and clinical studies. The Phase 3 program includes two ongoing pivotal global studies (WA22762 and NA25220) that are being conducted with the PFS-NSD.

Human factors simulated use validation studies have been conducted for the PFS-NSD (b) (4) to confirm that the device (b) (4) can be used safely and correctly by the intended users in the intended end use environment.

The purpose of this meeting is to obtain agreement on the adequacy of the human factors validation studies for the pre-filled syringe needle safe device (PFS-NSD) (b) (4) as well as agreement on the proposed organization and structure of the device content in support of a (b) (4)

## 2. DISCUSSION

### FDA INTRODUCTORY COMMENTS

1.



2. *Additionally, we note your intent* [REDACTED] (b) (4)

[REDACTED] (b) (4)

*Below are the preliminary responses to your questions.*

## **2.1. Human Factors**

### **Question 1:**

*Does the Agency agree* [REDACTED] (b) (4)

[REDACTED] (b) (4)

### **CDRH Response to Question 1:**

*No, we do not agree. We believe that the use errors seen in the study indicate that the instructions for use (IFU) and training should be further optimized. For example, you reported the following:*

- (1) Two participants who had hand impairment were not able to perform their first injection. Ensure that this difficulty for hand impaired users is communicated to healthcare providers so that the patient's caregivers will understand the need to assist the patients in performing the injection at home.*
- (2) Some participants failed essential tasks necessary to insure proper injection. Of most importance were:*
  - pinching the skin*
  - injecting at a 45 degree angle*
  - completely depressing the plunger*
  - visually checking the drug and the syringe*
  - waiting for the drug to come to room temperature and*
  - releasing the plunger.*

*Review of the IFU and training indicates that these tasks were not well addressed and that improvements are necessary to improve user performance. In addition, instructions should include warnings that describe the negative outcome when these steps are not performed adequately.*

Discussion:

Referring to slide 5 (*see Section 5.0 – Attachments and Handouts of the meeting minutes*) Roche acknowledged the FDA's comments regarding the use errors and recommendations for improving training and PFS IFU to enhance user performance and outlined their proposals to address those concerns. In response to the FDA's synopsis of the failed essential tasks required to ensure proper injection, Roche described the task failures and proposed mitigations to reduce the identified use errors (*refer to slides 6, 7, 8, and 9 for full details*). In short, Roche explained that the results demonstrated a 95% usability among patients to complete a full injection, although a small number of errors were noted. Additionally, Roche discussed the following task failures (use errors), to include the overall success and root cause: 1) pinching the skin 2) injecting at a 45 degree angle 3) completely depressing the plunger 4) visually checking the drug and the syringe 5) waiting for the drug to come to room temperature, and 6) releasing the plunger. Roche sought FDA agreement on whether appropriate revisions to instructions with IFU use would be sufficient to address the FDA's concern. These instructions may include outlining the consequences for not adhering/following the instruction to ensure a complete injection, and the inclusion of health professional supervision and consultation for certain tasks.

The FDA responded that Roche has provided a reasonable approach, however, revisions to the PFS IFU will require a validation study in order to verify that the revisions to the IFU do improve user performance and do not add any additional use errors. The FDA explained that the changes to the IFU are critical to ensuring delivery of a complete full dose. It is difficult to conclude, in the absence of a study, that the changes will effectively minimize use errors and no new risks have been introduced. The FDA recommended that Roche conduct a small supplemental study of at least 15 participants.

(b) (4)

The FDA reiterated that a validation study will be necessary to conclude that the PFS IFU revisions are acceptable. The study may focus on the specific changes that Roche has proposed to IFU. Roche asked whether the study should only include aspects of the IFU that will change. The FDA stated that the study should include patients reviewing the instructions and performing the injection. Moreover, the FDA commented that the self-injection steps are two-fold, knowledge-base and performance, thus both need to be assessed. Roche requested further clarification on the critical elements that need to be addressed within the validation study. The FDA recommended that Roche submit a draft protocol for review and comment.

4 Page(s) have been Withheld in Full as b4 (CCI/tS) immediately following this page

Roche summarized the meeting discussion regarding the device use errors (b) (4) (b) (4) follows:

- Update the IFU to address the use errors with the PFS and ensure that the mitigations will not introduce any new errors;
- A small validation study is needed to support the PFS IFU updates/revisions which should include at least 15 distinct patients from the RA population. Roche may have a small disease variation among the selected population; and

**Question 3:**

*Does the Agency agree with the Sponsor's proposal to do the following regarding the organization of the device content (b) (4)*

- *Present combination product information (i.e., integrated Drug Product and device information) in the CTD structure*
- *Present device-specific (drug-independent) information in the regional section of the CTD (3.2.R) based upon the principles of the traditional 510(k) structure and content and in accordance with the draft FDA guidance (b) (4)*

**CDRH Response to Question 3:**

Your proposal regarding the organization of the device content (b) (4) is generally acceptable. Also refer to FDA Introductory Comment 2 above.

**Additional Device Comments:**

- In your (b) (4) submission include data demonstrating that tocilizumab drug product is not subjected to excess shear forces when extruded through the 27 gauge syringe needle, (b) (4)

**Discussion:**

Roche provided a response to the FDA's introductory comment noted in this question on slide 20. There was no further discussion on question 3. The FDA deferred further explanation and clarification to the (b) (4) meeting scheduled for October 31, 2012.

### 3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further meeting discussion at this time.

### 4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Draft protocol to address the IFU revisions for the use errors for CDRH review	Roche	When available

### 5.0 ATTACHMENTS AND HANDOUTS

To facilitate the meeting discussion, Roche provided the FDA with the following slide presentation:

## Type C FDA Meeting Actemra® (tocilizumab)

Hoffmann La Roche  
October 24, 2012

## Roche Attendees

Name	Title
Mark Chipperfield	Device Development Head, Pharma Technical Development
Desiree Crisolo	Senior Associate, Pharma Technical Regulatory
Wendy Douglass, PhD	Clinical Scientist
Cornelia Kruettli	Team Leader, Pharma Technical Development
Robert Lichtneckert, PhD	Group Leader, Pharma Technical Regulatory
Matt Meldorf, M.D.	Global Development Lead
Jennifer Mercer	Director, Pharma Technical Regulatory
Kristine Ogozalek	Program Director, Regulatory Affairs
Florian Wildenhahn	Device Team Leader, Pharma Technical Development
Lee Wood	HF Engineer, Pharma Technical Development
Stephen Wright, M.D.	Senior Medical Director

11/19/2020

11/19/2020

## Meeting Objective

- The objective of this CMC Type C meeting is to obtain agreement on:
  - Design validation for the PFS + NSD (b) (4)
  - The organization and structure of the device content within the (b) (4) biologics License Application.

11/19/2020

11/19/2020

## Agenda

- The Sponsor would like to thank the Agency for the preliminary comments and would like to use this meeting to provide a response and additional clarification.
- Questions for discussion:
  - Question 1: PFS+NSD Design Validation
  - Question 2 (b) and 2 (c): [REDACTED] (b) (4)
  - If time permits:
    - Question 3 and additional FDA comments [REDACTED] (b) (4)
    - [REDACTED] (b) (4)

## Question 1: Sponsor Response

- The Agency's comments regarding use errors and the recommendation to modify the IFU and training is acknowledged.
  - Potential use errors will be communicated as part of the training materials provided to HCPs, and the
  - IFU will be reviewed and updated to include warnings to describe the negative outcomes associated with higher risk tasks.
  - The USPI will be updated as described.

## Important task failures and mitigations proposed to reduce use errors (1)

Task Failure	Success	Root Cause Assessment	Risk Mitigation and Benefit
Failure to Pinch Skin (Injection pad in study)	81.8% (14/77)	<p>Failure to pinch skin was the most frequently occurring error with potential impact.</p> <ul style="list-style-type: none"> <li>The most frequent cause of the use error (7 of the 14, 50%) was forgetting to pinch and not referring to the instructions for use</li> <li>4 of the 14 (28.6%) errors were determined to be due to the experimental setting (e.g. participants did not understand that they could treat the injection pad as their skin)</li> <li>A small proportion (2 users) stated they didn't pinch because they didn't understand why they needed to (doesn't seem important) or they currently don't do it (negative transfer)</li> <li>Healthcare professionals did not make this error</li> </ul>	<p><b>Risk Mitigation:</b> Update the instructions for use to include consequence for not pinching the skin.</p> <p><b>Benefit:</b> Providing information to the patient will ensure they understand why pinching the skin is important.</p>
Fails to completely depress plunger	97.4% (2/77)	<ul style="list-style-type: none"> <li>The two subjects who did not fully depress the plunger are estimated to have pushed 290% of the plunger down based upon visual analysis, however both users did not depress fully to engage the NSD indicating a non-complete depression.</li> <li>Both participants who made this error used their index finger to depress the plunger. Both believed that they had fully pressed the plunger</li> </ul>	<p><b>Risk Mitigation:</b> Update the instructions for use to include consequence for not completely depressing the plunger</p> <p><b>Benefit:</b> Providing information to the patient will ensure they understand why completely depressing the plunger rod important</p>

## Important task failures and mitigations proposed to reduce use errors (2)

Task Failure	Success	Root Cause Assessment	Risk Mitigation and Benefit
Injects at less than a 45 degree angle	96.1% (3/77)	<p>Three users injected at less than 45 degrees into the pad because:</p> <ul style="list-style-type: none"> <li>1 user (needle naive) explained they had forgotten the injection angle was supposed to be at greater than 45degrees.</li> <li>2 needle-experienced patients intentionally inject at less than 45degrees with their current injections as they consider it not to hurt as much. For these users, injecting at less than 45degrees is a well-meant optimization.</li> </ul>	<p><b>Risk Mitigation:</b> Update the instructions for use to include consequence for injecting at less than 45 degree angle</p> <p><b>Benefit:</b> Providing information to the patient will ensure they understand why injection at the instructed angles is important</p>
Fails to release plunger rod after completing injection	100% (0/77)	No failures observed	N/A

## Important task failures and mitigations proposed to reduce use errors (3)

Task failure	Success	Root cause assessment	Risk Mitigation and Benefit
Visually inspect syringe (for damage)	78.2% (61/78)	<ul style="list-style-type: none"> <li>• Forgot to check/ not use IFU (=70%)</li> <li>• Experimental artifact (=24%)</li> <li>• Assumes product from pharmacy is not damaged (=6%)</li> </ul>	<p><b>Risk Mitigation:</b> Update the instructions for use to include consequence of not visually inspecting the syringe</p> <p><b>Benefit:</b> Providing information to the patient will ensure they understand why visual inspection of the syringe is important</p>
Visually inspect syringe (contents)	76.9% (60/78)	<ul style="list-style-type: none"> <li>• Forgot to check/ not use IFU (=72%)</li> <li>• Experimental artifact (=22%)</li> <li>• Assumes product from is not damaged (=6%)</li> </ul>	<p><b>Risk Mitigation:</b> Update the instructions for use to include consequence of not visually inspecting the syringe contents</p> <p><b>Benefit:</b> Providing information to the patient will ensure they understand why visual inspection of the syringe content is important</p>
Wait for the PFS with NSD to reach room temperature	70.5% (50/78)	<ul style="list-style-type: none"> <li>• Experimental artifact (=57%)</li> <li>• Forgot to wait/ not use IFU (=35%)</li> <li>• Knew to wait but not how long (=4%)</li> <li>• Assumed product is provided at correct temperature (=4%, 1 subject)</li> </ul>	<p><b>Risk Mitigation:</b> Update the instructions for use to include consequence of not warming up the PFS+NSD to reach room temperature</p> <p><b>Benefit:</b> Providing information to the patient will ensure they understand why warming up the syringe is important</p>

### Q1: Sponsor Response, Cont. (1)

- To instruct physicians on patient counseling the Sponsor intends to include in the proposed USPI (section 17):
  - The first injection should be performed under the supervision of a qualified health care professional. If a patient or caregiver is to administer ACTEMRA, he/she should be instructed in injection techniques and their ability to inject subcutaneously should be assessed to ensure proper administration of ACTEMRA.
  - Prior to use, remove the prefilled syringe from the refrigerator and allow to sit at room temperature outside of the carton for <sup>(b)</sup><sub>(4)</sub> 30 minutes (PFS).
  - Patients should also be advised to consult their healthcare provider if the full dose is not received (e.g., leakage around the injection site).

## Q1: Sponsor Response, Cont. (2)

- Previous experience with minor modifications to the AI IFU and training show improvement in administration and reduction of errors (e.g. adherence to instructions).
- Since these modifications provide additional controls and do not introduce the potential for new use errors, the Sponsor does not intend to validate these changes to the IFU.

*Does the FDA agree with the Sponsor's approach to mitigate use errors and that further design validation would not be required?*

11/19/2011

Richard M. Linn, MD, MPH

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(b) (4)

11/19/2011

Richard M. Linn, MD, MPH

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11/19/2017

Office of Drug Evaluation II

19

**QUESTION 3: SUBMISSION FOR**  
**PFS+NSD**  <sup>(b) (4)</sup>

11/19/2017

19

### Question 3: Sponsor Response

- The sponsor recognizes we are requesting approval of (b) (4)  
(b) (4) PFS+NSD (b) (4)  
(b) (4)

- (b) (4)

11/29/2012

Abdul-Wahab

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**BACK UP**

11/29/2012

Abdul-Wahab

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/s/  
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PHILANTHA M BOWEN  
11/19/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

IND 11972

**MEETING REQUEST -  
Written Responses**

Hoffman-La Roche, Inc.  
340 Kingsland Street  
Nutley, NJ 07110

Attention: Kristine L. Ogozalek, Associate Director  
Regulatory Affairs

Dear Ms. Ogozalek:

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

We also refer to our November 7, 2011, communication notifying you that we would provide a written response to the questions in your October 25, 2011, meeting request following receipt of your background materials. We received your background materials on December 8, 2011.

Our responses to your questions are enclosed. If you have additional questions, you must submit a new meeting request.

If you have any questions, call me, at (301) 796-2466.

Sincerely,

*{See appended electronic signature page}*

Philantha Montgomery Bowen, M.P.H., R.N.  
Sr. Regulatory Project Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

Question 5:

(b) (4)

Question 6:

Following approval of the SC formulation for adult RA based primarily on the two global Phase III studies WA22762 and NA25220, (b) (4)

(b) (4)

FDA Response:

(b) (4)

FDA Response:

The approval of the SC dosage form of TCZ for Rheumatoid Arthritis would trigger a PREA requirement for studies in Polyarticular Juvenile Idiopathic Arthritis, as this is the juvenile equivalent of RA. (b) (4)

(b) (4)

(b) (4) A final determination regarding the pediatric plan will be made during the review cycle of the marketing application for SC TCZ in RA.

**Question 7:**

Following approval of the pre-filled syringe with needle safety device (PFS+NSD) for SC Actemra (tocilizumab) for adult RA, [REDACTED]

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

**FDA Response:**

This is a review issue [REDACTED]

(b) (4)

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PHILANTHA M BOWEN  
02/06/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug  
Administration  
Silver Spring, MD 20993

IND 11972

Hoffmann-La Roche, Inc.  
340 Kingsland Street  
Nutley, NJ 07110

Attention: Alan Mart  
Director, Regulatory Affairs

Dear Mr. Mart:

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

We also refer to the meeting between representatives of your firm and the FDA on September 2, 2010. The purpose of the meeting was to discuss the comments in the no-agreement special protocol assessments (SPA) letters dated March 29 and June 11, 2010

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

If you have any questions, please call me at 301-796-2254.

Sincerely,

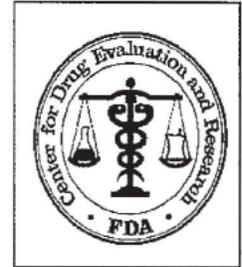
*{See appended electronic signature page}*

Sharon Turner-Rinehardt  
Senior Regulatory Health Project Manager  
Division of Pulmonary, Allergy  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

## MEETING MINUTES

**Meeting Date:** September 2, 2010  
**Meeting Location:** White Oak 22, Room 1311  
**IND/Name:** 11972/Tocilizumab  
**Indication:** Rheumatoid Arthritis  
**Sponsor:** Hoffmann-La Roche  
**Type of Meeting:** Type A- SPA Meeting  
**Meeting Chair:** Sarah Okada, M.D., Division of Pulmonary, Allergy and Rheumatology Products, HFD-570  
**Minutes Recorder:** Sharon Turner-Rinehardt, RPM



**BACKGROUND:** The Sponsor submitted a meeting request dated July 19, 2010 to discuss the responses in the two SPA no agreement letters.

FDA Attendees	
Name	Title
Badrul Chowdhury, MD	Director, Division of Pulmonary, Allergy and Rheumatology Products
Sarah Okada, MD	Clinical Team Leader
Nikolay Nikolov, MD	Clinical Reviewer
Liang Zhao, PhD	Clinical Pharmacology Reviewer
Partha Roy, PhD	Clinical Pharmacology Reviewer
Joan Buenconsejo, PhD	Acting Statistical Team Leader
Thomas Permutt, PhD	Director, Division of Biometrics II
Sharon Turner-Rinehardt	Senior Regulatory Health Project Manager
Hoffmann-La Roche Attendees	
Name	Title
Alan Mart	Director, Regulatory Affairs
Steven Slater, MD	Global Regulatory Leader
Ravi Rao, MD	Clinical Science, Rheumatology Cluster Head
Micki Klearman, MD	Global Clinical Science Leader
Angelika Jahreis, MD	Global Clinical Science Leader
Carol Lau, MD	Drug Safety Specialist
Lucy Rowell	Project Statistician
Amy Zhang, PhD	Clinical Pharmacology
Farah Anwar	Operations Program Leader
Cornelia Kruettli	Technical Development Leader
Deborah Savuto	Pharma Technical Regulatory
Scott Adamczyk	Regulatory

**GENERAL DISCUSSION:**

Following introductions, the meeting focused on the response to questions 3 and 8 included in the August 10, 2010, meeting package for IND 11972. The questions are presented below in *italicized* text. The Division's responses, prepared prior to the meeting and sent to the Sponsor via email on August 30, 2010, are **bolded**. Discussion is presented in normal text. The meeting was conducted via teleconference.

**AGENDA QUESTIONS from SPONSOR and FDA COMMENTS**

*Question 1: The Sponsor proposes that study WA22762 with a non-inferiority margin of 10% is adequately designed (if successful and contingent on review of safety and efficacy data: to allow incorporation of the 162 mg qw SC dosing regimen as an alternative to the current 8 mg/kg iv dosing regimen for the (b) (4) RA indication. Should the study fail to meet the 10% NIM but does meet the 12% NIM then the study (b) (4) (b) (4) In addition the Sponsor acknowledges that the treatment effect as analyzed by both the ITT and PP populations will be considered in the Agency's review of the data.*

- a. *Does this continue to reflect the Agency's understanding of the adequacy of the study design and the RA (b) (4) If not, could the Agency elaborate?*
- b. *Can the Agency comment on the adequacy of this study (b) (4) (b) (4)*
- c. *Can the Agency clarify whether there are any remaining issues that would prevent SPA agreement for study WA22762?*

**FDA Response**

- a. **The Division acknowledges that your summary of the NIM for Study WA22762 and (b) (4) as described in Question 1, is consistent with previous communications between you and the Agency on this topic, including the SPA No-Agreement letter dated March 29, 2010. (b) (4) (b) (4)**

- b. See response to Question 1a.
- c. The primary issue remaining that precludes a SPA agreement would be that we cannot commit to utilizing this study as you are proposing, specifically (b) (4)

Discussion: There was no discussion for this question.

*Question 2: Based on the Agency's feedback in the June 11, 2010 non-agreement letter, the Sponsor proposes that the inclusion of radiographic assessments at 6 months in the placebo controlled study (NA25220) (if successful and contingent on review of safety and efficacy data) would allow incorporation of the 162 mg q2w SC dosing regimen as an alternative to the current 4 mg/kg iv dosing regimen (b) (4) for the RA indication?*

- a. *Does the Agency agree with the adequacy of the study design and the RA labeling this study alone will support? If not, could the Agency elaborate?*
- b. *Can the Agency comment on the adequacy of this study design alone to be supportive of the (b) (4)*
- c. *Can the Agency clarify whether there are any remaining issues that would prevent SPA agreement for study NA25220?*

#### **FDA Response**

- a. **The primary issue with respect to NA25220 study design was the use of a historical control for a comparison with the tocilizumab 4 mg/kg IV dosing regimen. With the new proposal, you have removed this feature and have added a radiographic assessment at Week 24, as the Division suggested in the SPA No-Agreement letter dated June 11, 2010. The Division is in agreement with both these proposed changes. With the proposed revisions, the study would appear to be adequately designed to demonstrate the efficacy of the 162 mg SC q 2 wk dosing regimen for signs and symptoms and effect on structural damage outcomes.**
- b. See response to Question 1a. (b) (4)  
(b) (4) **Conservatively, you should assume that the study would support what it is designed to demonstrate; specifically, an effect on ACR responses and effect on radiographic progression for the 162 mg SC q 2 week dose regimen.**
- c. **We are unable to commit to utilizing the study (b) (4)**  
(b) (4) **Otherwise, Study NA25220 may be acceptable for a SPA agreement with the proposed revisions.**

Discussion: There was no discussion for this question.

*Question 3: The Sponsor proposes that data generated from the two studies WA22762 and NA25220 (contingent upon Agency review of the safety and efficacy data) including a 10% NIM in WA22762 and provisions of the radiographic evidence from study NA25220 could support (b) (4) the RA indication.*

- a. Is this the Agency's understanding as well? If not, could the Agency elaborate?*
- b. Does the Agency foresee any restrictions on the SC label claims?*
- c. Would this data package be considered supportive (b) (4) (b) (4) (b) (4) If not, can the Agency elaborate on potential scenarios for which additional data might be required?*

**FDA Response**

**See responses to Questions 1 and 2 above.**

Discussion: The Sponsor wanted confirmation that the two studies together would provide sufficient data to support (b) (4)

(b) (4) The Division stated that it would depend on the strength of the results of WA22762 and NA25220. Although the Agency had previously considered (b) (4)

(b) (4) responses and radiographic outcomes. However, if the radiographic data demonstrates benefit in study NA25220 and if the ACR responses in the two SC studies appear to be as good or better than for the IV formulation, then it may be possible to extrapolate IV clinical data to support the SC program.

The Sponsor asked whether x-ray data from study NA25220 could be extrapolated to support study WA22762. The Division stated that two studies have not historically been required to support radiographic claims.

(b) (4)

*Question 4: Alternatively, given the Agency's most recent feedback received June 11, 2010 for study NA22520 the Sponsor seeks to clarify if data generated from a development program which includes radiographic data from study NA22520 along with study WA22762 with a 12% NIM could support (b) (4)*

- a. Is this the Agency's understanding as well? If not, could the Agency elaborate?*
- b. Does the Agency foresee any restrictions on the SC label claims?*

c. *Would this data package be considered*

(b) (4)

(b) (4)

*If not, can the Agency elaborate on potential scenarios for which additional data might be required?*

**FDA Response**

**See responses to Questions 1 and 2 above. An approved label for a SC tocilizumab product would likely contain data specific to the SC route of administration, including data from the SC clinical studies. Apart from pharmacokinetic bioequivalence, we cannot commit to a pathway which would include both routes in a single label at this time.**

Discussion: No discussion required for this question.

*Question 5: The Sponsor understands that from the March 29, 2010 feedback that in principle tocilizumab SC could be approved for home use if home use is deemed safe. We also understand that (b) (4) we would provide a comprehensive assessment that analyzes cases of anaphylaxis in the SC program using the "Sampson criteria" and compare the incidence and type of anaphylaxis seen with SC use to that seen in the TCZ IV program and what is known about other RA therapies approved for home injection. In addition, the Sponsor will summarize data from the clinical program relating to the safety of home use. Does this continue to reflect the Agency's view? If not could the Agency elaborate?*

**FDA Response**

**The application you submit for marketing approval of your SC formulation should contain all the analyses necessary to evaluate the safety of your product for home use.**

Discussion: No discussion required for this question.

*Question 6: In protocols WA22762 and NA25229, the first four self-injected SC administrations will occur at the investigational site under the supervision of study personnel. All subsequent self-injections will be administered by patients as home use with appropriate instructions. The Sponsor proposes this will provide sufficient experience to market the product as self-administered SC formulation for home use. Does the Agency agree?*

**FDA Response**

**The process by which patients are selected, educated regarding self-injection, and prepared to respond to hypersensitivity reactions, should mimic the scenario you expect to deploy in clinical practice. If the process in the clinical trials is much more extensive than would be expected in clinical practice, then questions may be raised regarding the translatability of those results to clinical practice.**

Discussion: No discussion required for this question.

*Question 7: Previous experience indicates approximately 8% of patients are expected to be >100 kg in body weight and 25% will be <60 kg body weight. Based on the estimated distribution across the weight ranges, does the Agency agree the data could provide adequate evidence that there are no important differences in the efficacy and safety profile of the product across weight (exposure) ranges?*

**FDA Response**

**We cannot comment on the adequacy of the data until it is reviewed. For example, it may be difficult to conclude that patients >100 kg do not experience less efficacy at the same fixed dose if there are few patients and much individual variability in the responses.**

Discussion: No discussion required for this question.

*Question 8: Comment 4, page 2-3 – Adequacy of evidence to support the to-be-marketed presentation*

a.

b.

c.

d. *The PFS to be used in Protocols WA22762 and NA25220 will be identical to the to-be-marketed PFS with the exception that we plan*

*To support the handling features of the to-be-marketed PFS, equivalence of the devices will be demonstrated for deliverable volume, and an ease-of-use/handling study of the to-be-marketed PFS will be performed. Does the Agency agree that this is an acceptable approach to qualifying the to-be-marketed PFS?*

**FDA Response**

a.

(b) (4)

- b. You should conduct the clinical studies with the to-be-marketed presentation, as this would provide the best representation of results. With each change you make to the presentation, the possibility exists that changes in the operating characteristics could have clinical implications. Although, this is a particular concern with a big change, (b) (4) even a small change (b) (4) could alter the angle and depth of administration of the product. Therefore, we recommend you minimize or eliminate, if possible, the number of changes between the clinical trial presentation and the to-be-marketed presentation.
- c. See response to Question 8b.
- d. See response to Question 8b.

Discussion:

(b) (4)

(b) (4)

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/s/

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