

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125276/S049

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

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

BLA#: 125276 Supplement Number: 49 NDA Supplement Type (e.g. SE5): _____

Division Name: DPARP PDUFA Goal Date: 10/12/12 Stamp Date: 12/13/2011

Proprietary Name: Actemra

Established/Generic Name: tocilizumab

Dosage Form: Injection, for intravenous infusion

Applicant/Sponsor: Hoffman-La Roche

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

(1) sJIA

(2) Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

(3) _____

(4) _____

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

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

- **Indication:** *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).*

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

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

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

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

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

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

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

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

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

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

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

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

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

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

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

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

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

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

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	__ yr. <u>0</u> mo.	<u>1</u> yr. <u>11</u> 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).

† Ineffective or unsafe:

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

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

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

Δ Formulation failed:

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

Justification attached.

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

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

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

Justification for waiver:

A waiver has been historically granted for polyarticular JIA patients under 2 years of age due to the rarity of this diagnosis in this age group.

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>16</u> yr. 11 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>03/31/14</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 type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

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/s/

PHILANTHA M BOWEN
10/10/2012



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 for the investigation of product Actemra (tocilizumab, MRA, RO4877533) in connection with this Biologic License Application Efficacy Supplement at Genentech, Inc.

Signed by:  10/20/11
Michelle H. Rohrer, Ph.D. Date
Vice President, Regulatory Affairs

Bowen, Philantha

Subject: FW: sBLA 125276/49 (Actemra) - FDA Label Recommendations and Agreement

From: Adamczyk, Scott [mailto:scott.adamczyk@roche.com]
Sent: Thursday, October 11, 2012 1:21 PM
To: Bowen, Philantha
Subject: RE: sBLA 125276/49 (Actemra) - FDA Label Recommendations and Agreement

Dear Philantha

We are in agreement to the changes requested below.

Kind regards
Scott

Scott Adamczyk, Pharm.D.
Pharma Development Regulatory
Hoffmann-La Roche, Inc.
340 Kingsland Street | Nutley, NJ 07110-1199
☎ 973.235.3338 | 📠 973.562.3700
✉ e-mail : Scott.Adamczyk@roche.com

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From: Bowen, Philantha [mailto:Philantha.Bowen@fda.hhs.gov]
Sent: Thursday, October 11, 2012 10:35 AM
To: Adamczyk, Scott {MDRI~Nutley}
Cc: Zimmerman, Sabina {MDRI~South San Francisco}
Subject: FW: sBLA 125276/49 (Actemra) - FDA Label Recommendations and Agreement

Hello Scott,

See our request below regarding labeling recommendations for Actemra supplement 49.

Sincerely,

Philantha

Philantha M. Bowen, MPH, BSN, RN
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Food and Drug Administration
Center for Drug Evaluation and Research/ODEII
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Ave., Bldg 22, Room 3326
Silver Spring, MD 20993
☎ 301-796-2466
📠 301-796-9718
✉ philantha.bowen@fda.hhs.gov

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From: Bowen, Philantha
Sent: Thursday, October 11, 2012 7:32 AM
To: 'Ogozalek, Kristine'
Subject: sBLA 125276/49 (Actemra) - FDA Label Recommendations and Agreement

Hi Kristine,

Your submission dated September 20, 2012, to sBLA 125276/49 is currently under review. We have the request for labeling revisions and your agreement to our recommendations. Please respond to this email stating your agreement to our request.

Highlights:

1. Recent Major Changes (RMC) - *the date of the change should be reflected as shown: Deletions are in strikethrough*

Indications and Usage (1.1)	10/2012
Dosage and Administration (2.1)	10/2012
Indications and Usage (1)	04/2011
Dosage and Administration (2)	04/2011
Contraindications (4)	04/2011
Warnings and Precautions (5.2, 5.3, 5.5, 5.6, 5.8)	04/2011
Warnings and Precautions (5.5)	10/2012
Adverse Reactions (6.1)	04/2011

2. Update the revision date at the end of this section to the Month/Year of approval

Medication Guide

3. Update the revision date to the Month/Year of approval

Sincerely,

Philantha

Philantha M. Bowen, MPH, BSN, RN
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
 Food and Drug Administration
 Center for Drug Evaluation and Research/ODEII
 Division of Pulmonary, Allergy, and Rheumatology Products
 10903 New Hampshire Ave., Bldg 22, Room 3326
 Silver Spring, MD 20993
 ☎ 301-796-2466
 ☎ 301-796-9718
 ✉ philantha.bowen@fda.hhs.gov

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/s/

PHILANTHA M BOWEN
10/11/2012

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

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

Memorandum

Date: September 25, 2012

To: Philantha Montgomery Bowen, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Matthew Falter, Pharm.D., Regulatory Review Officer, Division of
Consumer Drug Promotion (DCDP), Office of Prescription Drug
Promotion (OPDP)

Roberta Szydlo, R.Ph., Regulatory Review Officer, Division of
Professional Drug Promotion (DPDP), OPDP

CC: Lisa Hubbard, Group Leader, DPDP, OPDP
Twyla Thompson, Acting Group Leader, DCDP, OPDP

Subject: BLA 125276/S-049 and S-056
OPDP labeling comments for ACTEMRA[®] (tocilizumab) Injection,
for intravenous infusion (Actemra)

OPDP has reviewed the proposed Package Insert (PI), Medication Guide (MG), and Carton and Container Labeling for Actemra submitted for consult on January 31, 2012. Reference is made to OPDP's previous labeling reviews for Actemra dated December 10, 2010, and March 29, 2011.

Although OPDP was consulted on S-049 specifically, we note that the version of the draft PI provided from DPARP for OPDP's review incorporated changes for both S-049 and S-056. We offer the following comments on the proposed labeling.

OPDP's comments on the PI and MG are based on the proposed draft labeling titled "BLA 125276(49) – DPARP Draft label (9-18-12).doc" that was sent via email from DPARP to OPDP on September 18, 2012. Please note that OPDP's comments on the draft PI are limited to the proposed changes for S-049 and S-056 (i.e., the Highlights and Sections 1, 2, and 5.5 of the full PI). Likewise, OPDP's comments on the draft MG are limited to the proposed changes for

S-049 and S-056. OPDP has no comments at this time on the proposed PI or MG.

OPDP has also reviewed the proposed carton and container labeling submitted by the sponsor on December 12, 2011, and located in the EDR at:

- \\cbsap58\M\leCTD_Submissions\STN125276\0075\m1\us\114-labeling\1141-draft\spl\actemra-02.jpg
- \\cbsap58\M\leCTD_Submissions\STN125276\0075\m1\us\114-labeling\1141-draft\spl\actemra-03.jpg
- \\cbsap58\M\leCTD_Submissions\STN125276\0075\m1\us\114-labeling\1141-draft\spl\actemra-04.jpg

OPDP has no comments at this time on the proposed carton and container labeling.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions regarding patient labeling please contact Matt Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

If you have any questions regarding professional labeling please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

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/s/

MATTHEW J FALTER
09/25/2012

ROBERTA T SZYDLO
09/25/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: September 17, 2012

To: Kristine L. Ogozalek
Program Director

From: Philantha Bowen, MPH
Sr. Regulatory Management Officer

Company: Hoffman-LaRoche

Division of Pulmonary, Allergy, and
Rheumatology Drug Products

Fax number: kristine.ogozalek@roche.com

Fax number: 301-796-9728

Phone number: 973-235-6227

Phone number: 301-796-2466

Subject: BLA 125276/49

Re: REMS Information Request

Total no. of pages including cover: 19

Comments: Please Acknowledge Receipt

Document to be mailed: YES NO

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BLA 125276/49
Actemra (tocilizumab)
Hoffman-LaRoche

Dear Ms. Ogozalek:

Your submission dated July 3, 2012, to BLA 125276/49 is currently under review and we have the following revisions on the proposed REMS Modification.

update the “Most Recent Modification: MM/DD/2012” in the upper left-hand corner of the first page of the REMS Document (see the **appended** REMS Document with track changes).

1. Communication Plan materials:

a. Revise the Dear Healthcare Provider (**Attachment A**) letter to include:

1. Modified indication for adult patients with moderately to severely active RA who have had inadequate response to one or more DMARDs
2. Add the header under IMPORTANT SAFETY INFORMATION ON KNOWN AND POTENTIAL RISKS, entitled, **Hypersensitivity Reactions, Including Anaphylaxis** (in bold-font) to follow the header entitled, **Gastrointestinal Perforations** (see appended Dear Healthcare Provider letter with track changes). Added language includes additional data about hypersensitivity reactions, including anaphylaxis and the number of events reported in the 6-month controlled trials, the all-exposure rheumatoid arthritis population, and in a single systemic juvenile idiopathic arthritis controlled-trial.

b. Revise the Prescriber Education Slide Deck as follows:

- Slide 2: Order the list of serious adverse events with Actemra to align with the order of safety risks in the WARNINGS and PRECAUTIONS Section of labeling.
- Slide 3: Revise “Black Box Warning” to read, “Boxed Warning”
- Following Slide 5, insert a new slide entitled, “Hypersensitivity Reactions, Including Anaphylaxis” with new safety data about these events (reported in sBLA 125-276/Supplement 049). See below comment about Slide 12.
- Slide 12: Revised this slide to include new safety data about hypersensitivity reactions, including anaphylaxis and move Slide 12 up to follow Slide 5 (See above comment, 2. c.). Insert the same text used in the Agency’s revisions to the Dear Healthcare Provider letter (**Attachment A**) under the header, **Hypersensitivity Reactions, Including Anaphylaxis**, in Slide 12.

c. Revise journal information pieces (**Attachments C and F**) to include a new header entitled, **Hypersensitivity Reactions, Including Anaphylaxis** (in bold font) in the journal information pieces to follow the header, **Gastrointestinal Perforations**. See track changes in **Attachments C**, Journal Information Piece for Emergency Medicine Physicians and Emergency Medical Services, and

BLA 125276/49
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Hoffman-LaRoche

Attachments F, Journal Information Piece for Internists and Internal Medicine Subspecialists).

- d. On the REMS website for Actemra, www.ACTEMRAREMS.com, update the applicable revised materials to the appropriate links in the REMS website landing-page.

Ensure that all new language in the Attachments describing **Hypersensitivity Reactions, Including Anaphylaxis**, is consistent with the Agency's proposed labeling and that the font-size is consistent throughout each revised appended material.

2. The timetable for submission of assessments is acceptable.
3. The REMS assessment plan is acceptable.
4. Revise the REMS Supporting Document to be consistent with revisions to the REMS Document.
5. General Comments
 - a. 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.
 - b. 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 response to this request by Thursday, September 20, 2012, to the sBLA.

BLA 125276/49
Actemra (tocilizumab)
Hoffman-LaRoche

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

Sincerely,

{See appended electronic signature page}

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

Attachments:

REMS Document
Attachment A: DHCP letter
Attachment C: Journal Information Piece for Emergency Medicine Physicians and
Emergency Medicine Services Professionals
Attachment F: Journal Information Piece for Internists and Internal Medicine
Subspecialists

15 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

PHILANTHA M BOWEN
09/17/2012



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: September 10, 2012

To: Kristine L. Ogozalek Program Director	From: Philantha Bowen, MPH Sr. Regulatory Management Officer
Company: Hoffman-Roche	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: kristine.ogozalek@roche.com	Fax number: 301-796-9728
Phone number: 973-235-6227	Phone number: 301-796-2466
Subject: BLA 125276/49 Re: Labeling Recommendation Request #1	

Total no. of pages including cover: 34

Comments: Please Acknowledge Receipt

Document to be mailed: YES NO

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BLA 125276/49
Actemra (tocilizumab)
Hoffman-LaRoche

Dear Ms. Ogozalek:

Your submission dated July 3, 2012, to BLA 125276/49 is currently under review and we have a request for labeling revisions. The FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all-inclusive and we may have additional comments and/or requests as we continue our review of the label. Submit revised labeling incorporating changes shown in the attached marked up label for the Package Insert.

Submit a clean copy and a tracked-change version of the Package Insert and Medication Guide by Thursday, September 13, 2012 to the BLA. In addition, please forward a courtesy copy to Ms. Colette Jackson (colette.jackson@fda.hhs.gov) via email.

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

Sincerely,

{See appended electronic signature page}

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

Attachment: Package Insert and Medication Guide

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



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/s/

PHILANTHA M BOWEN
09/10/2012



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: August 28, 2012

To: Kristine L. Ogozalek Regulatory Affairs	From: Philantha Bowen, MPH Sr. Regulatory Management Officer
Company: Hoffman- La Roche	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax number: kristine.ogozalek@roche.com	Fax number: 301-796-9728
Phone number: 973-235-6227	Phone number: 301-796-2466

Subject: sBLA 125276/49 - Clinical Information Request

Total no. of pages including cover: 3

Comments: Please Acknowledge Receipt

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sBLA 125276/49
ACTEMRA® (tocilizumab)
Hoffman-La Roche

Dear Ms. Ogozalek:

Your submission dated July 3, 2012, to sBLA 125276/49 is under review. We have the following request for information pertaining to monitoring for anaphylaxis/serious hypersensitivity events:

Based on the cases of anaphylaxis and serious hypersensitivity events you have identified, provide a minimum duration of time for monitoring for these events that could be potentially incorporated in the labeling. This duration should capture the time period from the end of infusion through the potential first occurrence of signs or symptoms of hypersensitivity/anaphylaxis. Include justification for the timeframe selected for monitoring these events. This justification should describe the likelihood of identifying anaphylaxis/hypersensitivity during the proposed timeframe, and what proportion of currently reported cases would have been diagnosed during the proposed monitoring period. Your justification should also address the known facts of the post-marketing cases of anaphylaxis with fatal outcomes and whether additional monitoring might have been relevant to these cases.

Submit your response to the sBLA by Friday, August 31, 2012. In addition, forward a courtesy copy to me via email (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

Drafted	Bowen/8-28-12
Clearance	Jafari/8-28-12 Seymour/8-28-12
Finalized	Bowen/8-28-12

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/s/

PHILANTHA M BOWEN
08/28/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BL 125276/49

FILING COMMUNICATION

February 8, 2012

Genentech, A Member of the Roche Group
c/o Hoffman-La Roche, Inc.
340 Kingsland Street
Nutley, NJ 07110

Attention: Kristine L. Ogozalek, Associate Director
Regulatory Affairs

Dear Ms. Ogozalek:

This letter is in regard to your supplement to your biologics license application (BLA) dated December 12, 2011, received December 13, 2011, submitted under section 351 of the Public Health Service Act, for Actemra® (tocilizumab).

We have completed an initial review of your supplement to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your supplement today. The review classification for this supplement is Standard. Therefore, the user fee goal date is October 12, 2012. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

At this time, we have not identified any potential review issues. Our filing review is only a preliminary review, and deficiencies may be identified during substantive review of your supplement. Following a review of the supplement, we will advise you in writing of any action we have taken and request additional information if needed.

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

Highlights

1. Recent Major Changes

Removal of a section for subsection should be noted, for example, in this format:

Contraindications (4)-----removal 12/2011. Update this section for other removals.

Full Prescribing Information:

2. In Section 17: Patient Counseling Information, *add the wording as follows:*

See FDA-approved patient labeling (Medication Guide)

We request that you resubmit labeling that addresses these issues by February 23, 2012. The resubmitted labeling will be used for further labeling discussions.

REQUIRED PEDIATRIC ASSESSMENTS

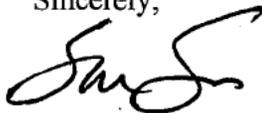
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s)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

We note that you have not addressed how you plan to fulfill this requirement. Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indication(s) proposed in this supplemental application.

If you request a full waiver, we will notify you if the full waiver is denied and a pediatric drug development plan is required.

If you have any questions, call Philantha Bowen, Regulatory Project Manager, at (301) 796-2466.

Sincerely,



/ Sally Seymour /

Sally Seymour, M.D.

Deputy Director for Safety

Division of Pulmonary, Allergy, and Rheumatology
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE

Memorandum

Food and Drug Administration
Center for Drug Evaluation and Research
CDER/ODE 2/DPARP

Date: January 31, 2012

From: Keith Hull, MD, PhD *KMH*
Medical Officer *1/31/12*

Subject: Filing Meeting

Through: Sarah Yim, MD *SY*
Team Leader *1-31-12*

Product: Tocilizumab (Actemra®)

To: STN 125276/49



U.S. Food and Drug Administration

Center for Drug Evaluation and Research

sBLA 125276

Tocilizumab for the treatment of subjects
with RA who are DMARD-IR

Filing Meeting
Clinical Team
January 25, 2012



Regulatory History

- Nov 2007: Tocilizumab (TCZ) BLA Submission
- Sept 2008: Complete Response
- July 2009: Complete Response Submission
- Jan 2010: Approval of TCZ for use in pts with RA who were TNF-IR
- March 2010: sBLA submission for inhibition of x-ray damage
- Jan 2011: Approval of sBLA for inhibition of x-ray damage
- Oct 2010: sBLA submission for treatment of SJIA
- April 2011: Approval of sBLA for treatment of SJIA
- Nov 2011: pre-sBLA meeting for current submission

Regulatory History

Current Submission

- Original BLA consisted of (5) Phase 3 studies
 - (3) studies included subjects with a DMARD-IR
 - (1) study included subjects with a TNF-IR
 - (1) study included MTX-naïve subjects
- TCZ treatment limited to TNF-IR in the original approval due to potential safety concerns
 - Increased LFTs, Increased LDL, & GI perforation
- Division advised the safety signals would need to be evaluated in Postmarketing (PM) studies before indication could be expanded to DMARD-IR



Regulatory History

Current Submission

- Nov 2011-Division and Sponsor agreed:
 - Safety data and analyses proposed in the current submission were sufficient to assess the TCZ safety concerns
 - Data package was sufficient to evaluate AE's of interest in the DMARD-IR population
 - Inclusion of subjects that escaped therapy within the death analysis of the PC studies & sensitivity analysis
 - Outlined descriptive safety analyses plan and relevant laboratory information for the following events:
 - ILD, pancreatitis, convulsions, pancytopenia

Data Sources

- Postmarketing data from sponsor's global safety database
 - Data up to July 2011 (~65k PY of exposure)
 - In general, this provides ability to rule out an increased risk of AE greater than 1.5x the background rate
 - GI perforation: 1.4x background rate
 - CV event: 1.1x background rate
 - MI event: 1.2x the background rate
 - Stroke: 1.2x the background rate
- Randomized placebo-controlled studies
 - Data from TCZ pivotal RA trials, pooled by population (DMARD-IR, TNF-IR, & MTX-naïve)

Data Sources

- Long-term extension clinical studies
 - Includes 4,000 patients
 - Data up to April 2011 from sponsor's ongoing LTE of clinical trials
 - Previously submitted data was up to Feb 2010
- Epidemiology data
 - Background rates of AEs of interest in RA patients treated with anti-TNF drugs from US-based MarketScan healthcare database. Also from published literature
 - Database is based on > (b) (4) PY of exposure from > (b) (4) RA pts treated with TNF inhibitors

Handling of Comparability of Data from Different Sources

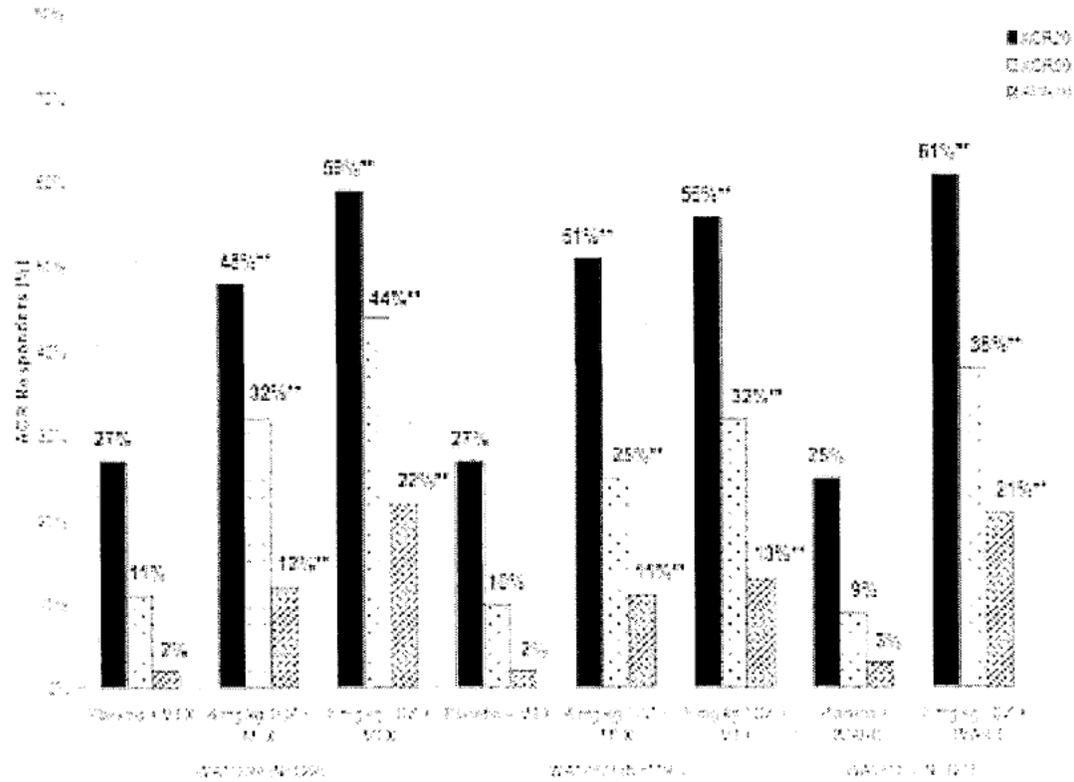
- Statistical
 - Event rates and 95% CI compared in a general manner to compare similar magnitude but interpretation still needs to be cautious
- Data Collection
 - Differences in AE reporting between controlled studies and PM reports
 - PM reports are expected to have under reporting of AE
- Methods of Analysis
 - Differences in definitions

Efficacy



Efficacy

Proportion of ACR 20/50/70 Responders @ Week 24 in DMARD-IR Subjects



* reproduced from sponsor's submission

Safety



Extent of Exposure

Table 5 Overview of Patient Years of Exposure by Data Source

Population	Placebo-controlled studies		LTE studies (to April 1, 2011)	Postmarketing data (to July 29, 2011)
	Placebo	All TCZ		
Overall				
No. patients	1454	2644	4009	68447 ^a
Total PY duration	743 PY	1560 PY	14994 PY	65099 PY
DMARD-IR				
No. patients	1010	2018	2904	
Total PY duration	543 PY	1269 PY	11126 PY	
MTX-naive				
No. patients	190	193	417	
Total PY duration	92 PY	95 PY	1547 PY	
MTX-NR				
No. patients	94	95	224 ^b	
Total PY duration	46 PY	46 PY	913 PY ^b	
TNF-IR				
No. patients	160	338	454	
Total PY duration	62 PY	150 PY	1509 PY	

^a Average number of patients required to achieve 65 099 patient years exposure based on simulations performed for 1000 iterations. 62 713 patients from global sales and 5 374 patients from sponsor-supplied postmarketing clinical trials.

^b Includes MTX-NR patients from study WA17924 and 23 patients from PK study WF18663.

* reproduced from sponsor's submission



Patient Population

- Different sources of information make precise determination of patient demographics and baseline characteristics difficult
- Given the uniformity of RA as a disease and it's response to treatment across the world, subjects included in this submission are representative of the US population



Deaths

	TCZ				
	Placebo-controlled Data in DMARD-IR Patients			Postmarketing Data	Epidemiology Data for TNF Antagonists
	Placebo	All TCZ	LTE Studies		
PY exposure	543	1436	14 954	65 039	3800 [†]
Rate of Deaths	0.74	0.47	0.57	0.39	0.51
(95% CI)	(0.20, 1.89)	(0.19, 0.96)	(0.45, 0.70)	(0.34, 0.44)	(0.38, 0.91) ^{††}
Number of events	4	7	85	253	-
SMR	NA	NA	0.86	NA	NA
(95% CI)			(0.69, 1.06) ^{††}		

* reproduced from sponsor's submission

- Mortality rates of TCZ-treated subjects was similar to than that expected in the general US population
- Rates and causes of deaths were similar across clinical trial populations and were not higher in the PM global safety database
- Rates of death in TCZ-treated subjects was similar to PBO-treated subjects in the controlled trials



SAE's

	TCZ				
	Placebo-controlled Data in DMARD-IR Patients			Postmarketing Data	Epidemiology Data for TNF Antagonists
	Placebo	All TCZ	LTE Studies		
PY exposure	543	1258	14984	65089	3032
Rate of Deaths	11.24	13.85	14.63	8.30	16.46 ^a
(95% CI)	(0.60, 14.44)	(11.30, 16.09)	(14.03, 15.26)	(0.08, 0.52)	(15.05, 17.97)
No of events	61	176	2194	5403	-

* reproduced from sponsor's submission

- TCZ-treated patients had similar rate of SAEs as PBO-treated patients
- TCZ-treated patients were similar/less than TNF inhibitors
- Lower rate of SAEs in the PM data likely due to underreporting
- Rate of SAEs did not increase with increased duration of exposure to TCZ
- Most commonly reported SAEs in all settings were infections
- Rates of pancreatitis, pancytopenia, convulsions, and ILD were consistent with rates expected in patients with RA



AE's of Special Interest



Serious Hepatic Events

Transaminase & Bilirubin Increases

	TCZ ^a		Epidemiology Data for TNF Antagonists ^b
	LTE Studies	Postmarketing Data	
PY Exposure	14 694	65 095	56 027
No. events	6	36	42 ^c
Rate per 100 PY	0.04	0.06	0.07
95% CI	(0.01, 0.09)	(0.04, 0.09)	(0.05, 0.10)

* reproduced from sponsor's submission

- TCZ-induced elevations in LFTs remained stable
- TCZ-induced LFT elevations did not result in an increased frequency of serious hepatic events in the PM setting
- The rate of reporting of serious hepatic events in the PM setting was similar to the rates observed in the LTE studies and in the TNF inhibitor studies
- No increase in serious hepatic events with continued exposure to TCZ
- No reported events meeting Hy's law
- TCZ associated with increases in LFT's but not serious hepatic events



GI Perforations

- Sponsor performed an unblinded review that first identified the AE via MedDRA term then defined a GI perforation only if specifically defined imaged, of procedural evidence
 - Abscesses and fistulas not considered gross perforations
- PM database demonstrated 96 events in 94 subjects
 - 78/94 subjects had ≥ 1 risk factor
 - 6/94 subjects died due to event
- PC studies, 4 confirmed GI perforations in TCZ arm and zero PBO
- LTE safety population, 30 GI perforations with 2 deaths (previously reported)
- Given the 65k PY exposure in the PM database, a difference in the rate of GI perforations of 1.4x the background rate could have been detected
- Overall, the rate of GI perforations in the PM period was consistent with that seen in the LTE safety population and with TNF inhibitors



Cardiovascular AE

	TCZ				Epidemiology Data for TNF Antagonists
	Placebo-controlled Data in DMARD-IR Patients		LTE Studies	Postmarketing Data	
	Placebo	All TCZ			
PY exposure	543	1258	14,394	65,099	56,027 ^a
Serious MI					
No. events	2	3	38	59	345
Rate	0.37	0.24	0.25	0.09	0.63
95% CI	(0.04, 1.33)	(0.05, 0.69)	(0.18, 0.35)	(0.07, 0.12)	(0.57, 0.73) ^b
Serious stroke^b					
No. events	1	6	37	96	360
Rate	0.19	0.47	0.25	0.15	0.65
95% CI	(0.00, 1.33)	(0.17, 1.03)	(0.17, 0.34)	(0.12, 0.19)	(0.59, 0.73) ^b
Cardiac death					
No. events	1	1	20	46	7
Rate	0.19	0.08	0.13	0.07	0.24
95% CI	(0.00, 1.33)	(0.00, 0.44)	(0.08, 0.21)	(0.05, 0.09)	(0.10, 0.50) ^b
Pooled MI and stroke					
No. events	3	9	75	156	
Rate	0.55	0.71	0.50	0.24	NR
95% CI	(0.11, 1.92)	(0.32, 1.35)	(0.39, 0.63)	(0.20, 0.29)	

- Original clinical trials demonstrated elevated LDL levels that remained elevated and responded to lipid-lowering therapy
- LTE and PM studies confirm this finding but do not demonstrate an increased rate of serious CV AEs
- Given the 65k PY of exposure from the PM database, an increased risk of MI of 1.2x the background rate of 0.66 events/100 PY could have been detected



Serious Infections

	TCZ			Postmarketing Data	Epidemiology of Infections in Patients with RA
	Placebo-controlled Data in DMARD-IR Patients		LTE Studies		
	Placebo	All TCZ			
PY Exposure	543	1260	14 994	65 099	NA
Serious infections					
No. events	17	58	669	1507	NA
Rate	3.13	4.57	4.46	2.31	4.2
95% CI	(1.83, 5.02)	(3.47, 5.91)	(4.12, 4.81)	(2.20, 2.43)	(3.97, 4.35) ^a
Serious opportunistic infections					
No. events	0	2	10	58	NA
Rate	NC	NC	0.07	0.09	0.07 ^b
95% CI			(0.03, 0.12)	(0.07, 0.12)	NA
Tuberculosis					
No. events	0	0	16	24	NA
Rate			0.11	0.04	0.12
95% CI			(0.05, 0.17)	(0.02, 0.05)	(0.06, 0.16) ^c
Serious pneumonia					
No. events	4	14	142	351	NA
Rate	0.74	1.10	0.95	0.55	0.84 ^d
95% CI	(0.20, 1.89)	(0.60, 1.55)	(0.80, 1.12)	(0.50, 0.61)	NA
Fatal infections					
No. patients	1	4	25	89	NA
Rate	NC	NC	0.17	0.14	0.24
95% CI			(0.11, 0.25)	(0.11, 0.17)	(0.13, 0.50) ^e

- Rates of infections were comparable between TCZ trials and background rates reported for patients treated with TNF-antagonists but higher than in the DMARD-IR and PBO groups from the clinical trials
- Overall rate of serious infections remained stable over time and consistent with what was observed in the clinical trials

Malignancies

- During PC trials the malignancy rate was increased for TCZ compared to PBO in the DMARD-IR population but were normal when pooled across all populations
- In the LTE populations, the SIR did not show an increased rate of malignancy in TCZ-treated subjects compared to the US populations except for lung/bronchus malignancies, which was within the range expected for RA subjects in general

Deliverables

- Review of the safety data from all data sources
- Consults as needed



BL 125276/49

**PRIOR APPROVAL SUPPLEMENT
ACKNOWLEDGEMENT**
DATE: December 23, 2011

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 Supplemental Biologics License Application (sBLA) dated December 12, 2011, received December 13, 2011, submitted under section 351 of the Public Health Service Act for the following:

BL NUMBER: 125276
SUPPLEMENT NUMBER: 49
PRODUCT NAME: Actemra®
DATE OF SUBMISSION: December 12, 2011
DATE OF RECEIPT: December 13, 2011
US LICENSE NUMBER: 1048

This supplemental application proposes the following indication: Adult patients with (b) (4)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 11, 2012, in accordance with 21 CFR 601.2(a).

If the application is filed, the user fee goal date will be October 12, 2012

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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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 content and format requirements of revised 21 CFR 201.56-57.

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

Cite the application number listed above 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. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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

Sincerely,



/Philantha M. Bowen

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

Pre-NDA/BLA



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 11972

MEETING MINUTES

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 Actemra® (tocilizumab).

We also refer to the telecon between representatives of your firm and the FDA on November 14, 2011. The purpose of the meeting was to discuss data driven issues regarding the analyses and presentation of the data for the filing of a sBLA to support expansion of the indication to include Adult Onset Rheumatoid Arthritis who have had an inadequate response to a DMARD.

A copy of the official minutes of the telecon 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, Regulatory Project Manager at (301) 796-2466.

Sincerely,

{See appended electronic signature page}

Philantha Montgomery Bowen, M.P.H., RN
Sr. Regulatory Project 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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-sBLA

Meeting Date and Time: November 14, 2011; 9:00-10:00 AM EST
Meeting Location: Teleconference

Application Number: IND 11972
Product Name: Actemra® (tocilizumab)
Indication: Rheumatoid Arthritis
Sponsor/Applicant Name: Hoffman-La Roche

Meeting Chair: Sarah Yim, M.D., Clinical Team Leader
Meeting Recorder: Philantha Bowen, M.P.H., RN, Sr. Regulatory Project Manager

FDA ATTENDEES

Office of Drug Evaluation II

Sarah Yim, M.D., Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

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

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

Sally Seymour, M.D., Deputy Director for Safety, Division of Pulmonary, Allergy, and Rheumatology Products

Office of Surveillance and Epidemiology

Adrienne Rothstein, PharmD, Safety Evaluator Team Leader, Division of Pharmacovigilance I

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

SPONSOR ATTENDEES

Scott Adamczyk, PharmD	Regulatory Affairs
Stephanie Sassman	Regulatory Affairs
Kristine Ogozalek	Regulatory Affairs
Steven Slater, PhD	Global Regulatory Leader, Actemra
Matt Meldorf, MD	Global Development Team Leader
Ariella Kelman, MD	Clinical Science Leader
Ravi Rao, MD, PhD	Clinical Science Cluster Head Immunology
Benjamin Porter-Brown, MD	Clinical Science
Pavel Napalkov, MD	Epidemiology, Director
Liz Thompson	Biostatistics, Deputy Global Head Immunology
Sarah Williams	Biostatistics
Pam Farmer, MD	Safety Science Leader
Natasha Singh, PharmD	Safety Science

1.0 BACKGROUND

Hoffman-La Roche submitted a pre-sBLA meeting request dated August 24, 2011, to discuss data driven-issues regarding the analyses and presentation of the data for the filing of a sBLA to support expansion of the indication to include Adult Onset Rheumatoid Arthritis who have had an inadequate response to a DMARD. The expected outcome of this meeting is to resolve any data-driven issues regarding the analyses and presentation of the data to be submitted in the sBLA. The Division reviewed the briefing package dated October 6, 2011. In a letter dated November 7, 2011, the Division responded to the questions contained in Roche's meeting package.

In an email correspondence, dated November 8, 2011, Roche communicated that clarification and discussion was sought for questions 5 and 6 of the preliminary meeting responses. Any discussion that took place at the telecon is captured directly under each question in section 2.0 including any changes in our original position. Roche's questions are in *bold italics*; FDA's response is in *italics*; and the discussion is in normal font.

2. QUESTIONS AND DISCUSSION

Question 1:

Safety analyses from the above mentioned data sources is provided herein to support expansion of the tocilizumab indication to include adult RA patients who had an inadequate response to a DMARD.

a. In a teleconference on January 5, 2010 prior to the issuance of the action letter, the Agency communicated that the potential associated risks with increases in hepatic aminotransferases and increases in LDL-C, and GI perforations should be studied further in the postmarketing setting for this first in class therapy prior to consideration of expansion of the indication to a broader population. The Sponsor believes the safety data and analyses (outlined in Sections 2 and 3) of this briefing package are sufficient to assess these potential risk associated with TCZ use. Does the Agency agree?

FDA Response:

Yes, we agree.

Discussion:

There was no discussion on question 1a.

b. The Sponsor believes the briefing package outlines a sufficient amount of supportive data to enable the review of the sBLA to assess the overall safety profile

and risk benefit of TCZ in the DMARD IR population. Does the Agency agree that the data package to be provided is sufficient to enable the review of this sBLA?

FDA Response:

Yes, we agree.

Discussion:

There was no discussion on question 1b.

Question 2:

To assess the potential risks associated with TCZ related increases in hepatic aminotransferases in the DMARD IR population, the Sponsor plans to provide safety analyses of serious hepatic events from the above mentioned data sources. Does the agency agree that the data analyses concerning serious hepatic events, in addition to relevant laboratory analyses from the Sponsor clinical trial data set as outlined in the briefing package, are sufficient to enable the review of this sBLA?

FDA Response:

Yes, we agree.

Discussion:

There was no discussion on question 2.

Question 3:

To assess the potential risk associated with TCZ of serious gastrointestinal (GI) perforations in the DMARD IR population, the Sponsor plan to provide safety analyses of GI perforations from the above mentioned data sources. Does the Agency agree that the data from the analyses concerning GI perforation as outlined in the briefing package are sufficient to enable the review of this sBLA?

FDA Response:

Yes, we agree.

Discussion:

There was no discussion on question 3.

Question 4:

To assess the potential risk associated with TCZ related increases in LDL in the DMARD IR population, the Sponsor plans to provide safety analyses of cardiovascular (CV) events from the above mentioned data sources. Does the Agency agree that the data analyses concerning CV events in addition to relevant laboratory analyses from the Sponsor clinical trial data set as outlined in the briefing package, are sufficient to enable the review of this sBLA?

FDA Response:

Yes, we agree.

Discussion:

There was no discussion on question 4.

Question 5:

In the planned sBLA, the Sponsor intends to provide a comprehensive analysis of additional adverse events of special interest. A summary of these additional analyses are provided within the briefing package. Does the agency agree that the analyses concerning these additional adverse events of interest are sufficient to enable the review of this sBLA?

FDA Response:

The proposed analyses of additional adverse events of interest appear generally acceptable.

The briefing package states:

“PY exposure of the placebo controlled analyses of the pivotal studies includes exposures while patients are receiving escape therapy for death analysis. This approach differs from other analyses on placebo controlled analyses of pivotal studies where escape data are excluded.”

Provide your rationale for selecting a different approach for death analyses from the placebo-controlled registration studies.

As specified in our written response to question 2 (c) dated September 29, 2011, we request that in addition to MedWatch forms you also provide narratives of malignancies and serious infections from the global safety database.

Discussion:

Roche began the discussion by providing a rationale for selecting a different approach for death analyses from the placebo-controlled registration studies. Roche stated that the approach to deaths occurring in patients who entered escape treatment is intended to be consistent with the data provided through week 52 of WA17823. Roche noted that in actuality this only includes a difference of 2 deaths, but will include the alternate analysis, excluding escape treatment mortality events as a sensitivity analysis and sought confirmation of the acceptability of this approach. The FDA agreed that Roche's rationale and proposal were acceptable.

In terms of the narratives from the global safety database for malignancy and serious infections, Roche proposed to provide this data for review within the 4-Month Safety Update, which would represent all data/information outlined in the Medwatch forms that will also be submitted for review with the initial submission. The FDA agreed that the submission of the narratives for malignancy and serious infections in the 4-Month Safety Update would be acceptable.

In providing the narratives of adverse event malignancy cases, Roche requested a clarification from the Agency on whether the recommendation for the narratives pertained to only serious and *not* non-serious adverse events malignancy cases (i.e. non-melanoma skin cancer) from the long term extension studies. The FDA responded that only the narratives for the *serious* adverse event malignancy cases need to be submitted.

Question 6:

Following the Agency's review of the data to be presented within the briefing package, are there additional analyses from the above mentioned data sources the Agency recommends the Sponsor to provide during the review of the application?

FDA Response:

Yes. Recent review and analysis of the Adverse Event Report System (AERS) database has identified safety issues, some fatal, potentially associated with the use of tocilizumab for RA. Specifically:

- *Interstitial lung disease, including new-onset and exacerbation of underlying disease*
- *Pancreatitis, including necrotizing pancreatitis*
- *Convulsions*
- *Pancytopenia, bone marrow failure*

Therefore, we request that you include descriptive safety analyses of these events and any related laboratory parameters in the sBLA submission.

Additional analyses may be required if deemed necessary during the review process.

Discussion:

Roche commented that they were aware of the new potential safety issues identified for tocilizumab. Roche proposes to submit an integrated assessment, to include rates and listings, from the long term extension (LTE) studies, post-marketing data, and from the placebo-controlled study, divided by treatment and population groups. For the pancytopenia safety concern, Roche proposes to address the matter by providing analyses of laboratory data regardless if an adverse event was noted. In addition, Roche intends to include narratives for serious adverse event cases and treatment withdrawals for this analysis. The FDA, noting that Roche will use three sources of information, LTE studies, post-marketing, and the randomized study, asked whether Roche plans to include other accessible databases. Roche responded that three areas mentioned would be the only sources of data accessible to them. The FDA agreed that the three data sources mentioned would be acceptable. For interstitial lung disease (ILD), the FDA reiterated that new onset and exacerbations of disease should also be included in the descriptive safety analyses.

Roche requested that the Agency provide more details on the AERS data analyses and the reasoning for the request. The FDA responded that in 2007 FDAAA Section 915 mandated a safety summary of new products on the market. As apart of this requirement, the Agency conducted research through AERS, data mining, literature, and sponsor's safety summaries and identified these potential safety signals for further assessment and/or continued monitoring. Recognizing that some data may be missing from the post-marketed reports, the FDA requested that Roche explore these issues further.

For the sBLA, the FDA asked Roche about their timeline for submission of the application. Roche commented that their approximate date for submitting the sBLA is December 12, 2011.

Meeting Summary:

- FDA agreed to Roche's proposal regarding the death analysis from the placebo-controlled studies.
- FDA agreed to submission of the narratives for malignancy and serious infections in the safety update.
- FDA clarified that Roche does not need to submit *non-serious* adverse event malignancy cases (i.e. non-melanoma skin cancer cases) from the long term extension studies.
- Roche intends to provide descriptive analysis of the identified safety issues for review and acknowledged that new onset and exacerbations of disease need to be included for ILD.

- The FDA recommends that Roche further explore the potential safety issues in their clinical trials and through available data sources to address the Agency's potential safety issues identified from the AERS database.

Question 7:

Are there any other aspects the Agency feels are important to convey to the Sponsor with regard to the planned sBLA to resolve any potential review issues?

FDA Response:

No, we have no additional comments at this time.

Discussion:

There was no discussion on question 7.

Question 8:

What are the Agency's views regarding the likelihood of an Advisory Committee being convened to discuss the data to be provided to support this sBLA?

FDA Response:

Based on the Pre-sBLA meeting package information, it is unlikely that an Advisory Committee will be convened to discuss the data to be provided to support this sBLA. However, a final decision will be determined upon submission of the sBLA.

Discussion:

There was no discussion on question 8.

GENERAL INFORMATION

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

If your supplement involves a change in manufacturing facility, in order 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.				

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

There were no action items for this meeting.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

PHILANTHA M BOWEN
11/16/2011



IND 11972

**MEETING REQUEST -
Written Responses**

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

Attention: Kristine L. Ogozalek
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 July 13, 2011, communication notifying you that we would provide a written response to the questions in your July 6, 2011, meeting request following receipt of your background materials. We received your background materials on August 15, 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

FDA Summary Comments

The approach to content and format of the planned supplemental BLA submission described in the briefing package appears reasonable. However, some of the questions in this package are more appropriate for discussion as part of a Pre-sBLA meeting package, since the extent and the detail of the information required for a sBLA review will depend on the proposed labeling changes. Therefore, we will defer definitive responses to these questions to a Pre-sBLA meeting.

Clinical Summary of Efficacy

Question 1: The planned content of Module 2 is provided in Appendix 2. The current USPI describes evidence of efficacy in DMARD-IR patients. The Sponsor does not intend to submit additional efficacy data that has not been previously submitted.

a) Does the Agency agree with the Sponsor's proposal to not submit a new Clinical Summary of Efficacy, but to cross-reference previously submitted efficacy data where applicable?

FDA Response:

Your proposal to not submit a new Clinical Summary of Efficacy, but cross reference to previously submitted Summary of Clinical Efficacy (BLA 125276/0, 7, 10, 11) is acceptable.

b) Does the Agency have any further comments on the contents of Module 2?

FDA Response:

Appendix 2, outlined Section 2.7.4, Summary of Clinical Safety, states:

“the integrated analyses traditionally found in the Integrated Summary of Safety (ISS) will be provided in a Summary of Clinical Safety and therefore a separate ISS is not necessary.”

Your proposal would be acceptable, as long as you perform and submit the integrated analyses required in an ISS, as required by 21 CFR 314.50(d)(5)(v)-(vi), and not just provide summaries. Since the CTD Clinical Overview and Summary in Module 2 do not usually contain the level of detail expected for an ISS and have format limitations you may need to submit the required integrated analyses in Section 5.3.5.3.

TCZ Global Safety Database Analysis

Question 2: As agreed during the June 28, 2010 meeting, the Sponsor will provide an analysis of the global safety database which includes all spontaneous reports from RA patients received by the Sponsor, reports from the completed Japanese postmarketing RA surveillance program, external registries, published reports, as well as data from the Sponsor's ongoing unblinded or open label post marketing studies once 64,000 patient years (PY) of TCZ exposure have been reached. As agreed, the analysis will consist of adverse event rate per 100 PY exposure, together with a 95% confidence interval (CI) for the following:

- Serious hepatic events
- Serious GI perforations

- **Serious cardiovascular events**

In addition, the Sponsor plans to provide rates per 100 PY exposure, together with a 95% confidence interval (CI) for other adverse events of interest including but not limited to the following

- **Serious infections**
- **Anaphylaxis and hypersensitivity reactions**
- **Deaths**
- **Malignancies**

a) An example of an output from a preliminary analysis (pre-64,000 patient years of exposure) for serious infection from the global safety database is provided below. Does the Agency agree that this output will adequately present the rate of these adverse events for this analysis?

FDA Response:

We agree with your proposal. The proposed output appears to represent the rate of the respective adverse events.

b) For the global safety database analysis, the Sponsor will provide Raw Datasets which will include all minor derivations that are required for the analyses (dataset and definition files) in electronic SAS transport file format (.xpt). Does the Agency agree with this approach?

FDA Response:

In general, your proposal is reasonable.

c) The Sponsor will provide MedWatch forms for relevant cases of the above listed adverse events contained within the global safety database used to generate the Raw Datasets. Does the Agency agree with this approach for documenting individual case information?

FDA Response:

In addition to MedWatch forms, we request that you also submit narratives of the cases.

d) TCZ exposure data will be estimated from global sales data, unblinded and open label post marketing studies, and the completed Japanese post-marketing surveillance program. The estimate of exposure from global sales data is based on total sales of TCZ and a series of assumptions, including average weight of patients, average frequency of dosing and average dose. Does the agency agree with the Sponsor's assumptions in calculating the TCZ exposure?

FDA Response:

You propose to estimate TCZ exposure in the Global safety dataset based on global sales data and assumptions, including average weight of patients, average frequency of dosing and average. This approach appears reasonable and is acceptable.

Anti-TNF Health Care Claims Database Analysis

Question 3: As agreed during the June 28, 2010 meeting, the analysis of anti-TNF-exposed patients with rheumatoid arthritis from a healthcare claims database will include adverse event rate per 100 PY of exposure, together with a 95% CI for the following adverse events: acute hepatic events, GI perforation events and cardiovascular events. In addition data will be provided for malignancy events. Data for these analyses will come from the Thomson Reuters MarketScan (MarketScan) administrative healthcare claims database.

Deaths in TCZ exposed patients will be compared with expected deaths in the general population using indirect standardization (standardized mortality ratios, SMR). The SMR for TCZ exposed patients will be based on all cause age and gender specific mortality rates within the US general population for 2007 according to U.S. National Center for Health Statistics, Health, United States, 2009 report (US National Vital Statistics Reports).

As data sources for these databases are commercially (MarketScan) or publically available (US National Vital Statistics Reports), the Sponsor does not plan to provide Raw Datasets or Analysis Datasets for the TNF a Healthcare claims database analyses. Does FDA agree with this approach?

FDA Response:

Yes, your approach to not provide Raw Datasets or Analysis Datasets for the TNF a Healthcare claims database analyses is acceptable. Clarify whether the death rates in the TCZ-exposed patients will be compared only with the expected deaths in the general population as stated in the question or also with the death rates in the Anti-TNF Health Care Claims Database.

Randomized Placebo Controlled Periods of TCZ Pivotal Studies Pooled by Population Analysis

Questions 4: As requested by FDA during the June 28, 2010 meeting, the Sponsor will provide safety analyses using data from controlled periods of pivotal RA trials, pooled by population, i.e.:

- DMARD-IR patients (Studies WA17822, WA17823, and WA18063)
- TNF inhibitor-IR patients (Study WA18062)
- MTX-naïve patients (Population Subset of Study W AI7824).

As requested, this analysis will include exposure-adjusted incidence rates per 100 PY exposure, together with a 95% confidence interval (CI), for deaths, SAEs, serious infections, and malignancies. In addition, the Sponsor will provide rates per 100 PY exposure, together with a 95% CI for serious hepatic events, GI perforations, and cardiovascular events as well as other AEs of special interest.

a) The Sponsor will provide Analysis Datasets (datasets and data definition files) in electronic SAS transport file format (.xpt) for these analyses and cross reference the Raw Datasets (dataset and definition files) provided in previous filings supporting these analyses. Does the Agency agree with this approach?

FDA Response:

Your proposal to submit Analysis Datasets (datasets and definition files) is acceptable. Clarify if you plan to submit three sets of analysis datasets based on population or in one single dataset.

b) Since all relevant case report form data will be included in the electronic SAS datasets, as was done in previous TCZ filings, Roche does not plan to resubmit Subject/Patient Profiles in this filing. Does the Agency agree?

FDA Response:

Yes, this is acceptable.

Sensitivity Analyses: TCZ Long Term Extension Studies Analysis

Questions 5: In the background document supporting the June 28, 2010 meeting, in addition to the overall global safety database rates where the events will have come from a number of sources, the Sponsor proposed conducting at least one of the following analyses, depending on data availability, to look for consistency of results among data sources:

- US Healthcare Claims Database (comparing TCZ to anti-TNFs); dependent on the timing of assignment of the reimbursement code for identification of TCZ-exposed patients
- Ex-US registries of RA patients (comparing TCZ to anti-TNFs); dependent on available study reports from registries run independently of the Sponsor in UK, Germany, and Sweden
- The Sponsor's clinical trial database (estimating TCZ rate within clinical trials)

a) Due to the relatively recent assignment of a TCZ specific J-Code (January 1, 2011) and the lag time for the inclusion of market data suitable for epidemiological analysis into administrative claims databases, TCZ administration cannot be studied using claims databases at this time. Additionally there are insufficient TCZ data available in ex-US registries to conduct a comparative safety analysis. Therefore, the Sponsor proposes to use the third option listed above for these analyses, specifically data from the long-term extensions (LTE) of registration clinical trials (WA17823, WA18695, WA18696). The LTE analyses will include the adverse event rate per 100 PY exposure, together with 95% CI for the adverse events listed in Question 2 above. Does the Agency agree with this approach?

FDA Response:

You propose to conduct safety sensitivity analyses using the TCZ clinical trial database (long-term extensions of registration clinical trials). This approach is generally acceptable.

b) The Sponsor will provide Raw Dataset (dataset and definition files) and Analysis Datasets (datasets and data definition files) in electronic SAS transport file format (.xpt), for the LTE extension studies analysis. Since all relevant case report form data will be included in the electronic SAS datasets, as was done in previous TCZ filings, the Sponsor

does not plan to provide Subject/Patient Profiles in the submission. Dose the Agency agree with this approach?

FDA Response:

This approach is reasonable.

c) The Sponsor will provide cross reference to CRFs for all deaths and withdrawals due to an AE from the long term extension studies (WA17823, WA18695, WA18696) previously submitted to the BLA; and provide all new CRFs for deaths and withdrawals due to an AE from the long term extension studies until April 1st, 2011 (clinical cut-off date). Does the Agency agree with this approach?

FDA Response:

Yes, we agree.

d) Within the Clinical Summary of Safety the Sponsor proposes to include narratives from the long-term extension studies for the following:

- all death cases
- all SAEs
- all AEs leading to withdrawal (premature discontinuation),

Does the Agency agree that providing narratives for these relevant categories are appropriate?

FDA Response:

In addition to providing narratives for all deaths, SAEs and AEs leading to withdrawal, we request that you submit narratives for the special events of interest (GI perforations, CV events, hepatic events) from the LTE studies.

Module 1 Components

Question 6: The planned components of Module 1 are provided in Appendix 1. Does the Agency agree with the planned components of Module 1, specifically the proposal not to provide updated financial disclosure information for LTE studies as they do not qualify as covered studies, consistent with FDA Guidance on Financial Disclosure by Clinical Investigators?

FDA Response:

Yes, your proposal to not provide updated financial disclosure information for LTE studies as they do not qualify as covered studies is acceptable.

Module 5 Components

Question 7: As agreed at the June 28, 2010 meeting, this sBLA filing to support expansion of the tocilizumab indication to include adult RA patient who had an inadequate response to a DMARD will only include safety data analyses. The Sponsor does not plan to provide the executable SAS programs in the proposed sBLA for these safety data analyses, consistent with previous tocilizumab filings. The Sponsor does intend to provide a Reviewers Guide for the global safety database and the randomized placebo controlled datasets. Does the Agency agree with this approach?

FDA Response:

Yes, your proposal to not provide the executable SAS programs for safety data analyses in the proposed sBLA is acceptable, however, these may be requested if deemed necessary during the review.

Four Month Safety Update (4MSU)

Question 8: An updated global safety database analysis (comprising of the data sources described in Question 2) used for the purposes of a 4MSU, is expected to result in an increase of approximately 10,000 patient years of exposure to tocilizumab beyond that provided in the supplemental filing. Therefore, the Sponsor proposes to provide a 4MSU that consists of an analysis of the global safety database for adverse events of special interest, deaths and other notable events with accompanying MedWatch forms. Does the Agency agree?

FDA Response:

Yes, the proposed content of the 4 month safety update appears acceptable. The format of the 4 month safety update listings and summary tables should be consistent with the format of the initial submission.

Question 9: Relatively limited increases in exposure to tocilizumab within the LTE studies will occur for the purposes of a 4MSU beyond that provided in the supplemental filing. Therefore, the Sponsor proposes to provide a 4MSU that consists of narratives and assessment of new SAEs, deaths and adverse events of special interest from the LTE studies. Does the Agency agree?

FDA Response:

Yes, your proposal to provide narratives and assessment of new SAEs, deaths and adverse events of special interest from the LTE studies in the 4MSU is acceptable.

REMS Assessment

Question 10: Roche seeks guidance from the Agency on whether a REMS Assessment is required for this sBLA filing to support expansion of the tocilizumab indication to include adult RA patient who had an inadequate response to a DMARD. Given the short time between the 18 month REMS Assessment (submission date of July 7, 2011) and this sBLA filing (planned for submission in Dec 2011), the Sponsor proposes [REDACTED] ^{(b) (4)} Does the Agency agree?

FDA Response:

If you plan to modify the REMS in your supplemental BLA, you will need to provide an assessment of the REMS. If the REMS has had a full assessment in the previous 18 months, you may refer to that assessment. You should also note whether the REMS would be adequate with the proposed modifications to achieve its purpose. Your assessment should also include an update on the status of any post approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any material or significant updates to the status information since the annual report was prepared.

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/s/

PHILANTHA M BOWEN
09/29/2011

Sponsor Meeting Agenda

MEETING DATE: June 28, 2010

TIME: 1:00 pm - 2:00 pm

LOCATION: CDER White Oak, Conference Room 1417, Building 22
10903 New Hampshire Ave., Silver Spring, MD 20993

APPLICATION (DRUG): BLA 125276-Actemra

INDICATION: Rheumatoid Arthritis (RA)

SPONSOR: Hoffmann-La Roche

MEETING RECORDER: Sharon Turner-Rinehardt, RPM

MEETING OBJECTIVE: Post-Action meeting

MEETING REQUEST: dated and received –April 21, 2010/ The meeting was granted on April 30, 2010.

FDA Attendees	
Name	Title
Curtis Rosebraugh, MD, MPH	Director, Office of Drug Evaluation II
Badrul Chowdhury, MD	Director, Division of Pulmonary, Allergy and Rheumatology Products
Sarah Okada, MD	Clinical Team Leader
Nikolay Nikolov, MD	Medical Officer
Asoke Mukherjee, PhD	Pharmacology/Toxicology Reviewer
Molly Topper, PhD	Pharmacology/Toxicology Supervisor
Robert Abugov, PhD	Statistical Reviewer
Joan Buenconsejo, PhD	Acting Statistical Team Leader
Xiao Ding, PhD	Statistical Reviewer
Mat Soukup, PhD	Acting Statistical Team Leader
Sally Seymour, MD	Deputy Director, Safety
Ladan Jafari	Safety Regulatory Project Manager
Sharon Turner-Rinehardt	Senior Regulatory Health Project Manager
Hoffmann-La Roche Attendees	
Name	Title
Robin Conrad	Senior Director, Regulatory Affairs
Cynthia Dinella, PhD	Vice President, Regulatory Affairs
Snehal Shah, PharmD	Associate Director, Regulatory Affairs
Ravi Rao, MD	Clinical Science, Rheumatology Cluster Head
Micki Klearman, MD	Global Clinical Science Leader
Joel Krasnow, MD	Global Clinical Science Leader
Don Maclean, PhD	Lifecycle Leader
David Yocum, MD	Drug Safety Science Leader
Pam Farmer, MD	Drug Safety Science Leader
Philippe Van der Auwera, MD	Global Head of Drug Safety
Winnie Werther, PhD	Senior Epidemiologist
Raymond Malamet, MD	Medical Director
Liz Thompson	Statistical Team Leader

AGENDA QUESTIONS from SPONSOR and FDA COMMENTS

DMARD-IR Indication

~~Question 1: Does the Agency agree that the sponsor's proposed analysis plan and overall approach as described below will provide appropriate data to determine whether the potential safety concerns outlined by the Agency are actual safety signals and if no actual safety signals are detected will the data support a filing for the use of TCZ treatment in the DMARD-IR population?~~

FDA Response

In order to provide a reasonably stable and precise estimate of the rate of the most important adverse events of interest (i.e., cardiovascular, hepatotoxicity, and GI perforation), you have estimated the required exposure would be 2744 patient-years for cardiovascular events, 63913 patient-years for serious hepatotoxic events, and 45653 patient-years for GI perforation events. The required exposure is calculated to be able to determine with 90% probability that the lower bound of the TCZ confidence interval is greater than the background rate, if the observed TCZ rate is 1.5x the background rate (based on a Poisson distribution). You are proposing to analyze the global safety data once the highest estimated required exposure is reached, and to provide comparisons for the safety analyses using TNF inhibitor data obtained from healthcare databases and foreign registries.

Overall, the proposed analysis plan and approach is reasonable. To support the assessment of the relative safety in the DMARD-IR population we recommend you also provide safety analyses using data from the controlled periods of the pivotal RA trials, pooled by population, i.e., DMARD-IR patients (Studies WA17822, WA17823, and WA18063), TNF inhibitor-IR patients (Study WA18062), and MTX-naïve patients (Study WA17824). These analyses should include exposure-adjusted incidence rates for deaths, serious adverse events (SAE), serious infections (SIE), and malignancies, as well as other adverse events of interest, by treatment group.

Question 2. Does the Agency agree that if serious hepatotoxic events are not identified as a safety signal that unfavorably impacts the overall benefit/risk based on a minimum of 64,000 patient years of exposure that the data will provide adequate support for the use of TCZ in DMARD-IR patients?

FDA Response

Note that an increase in serious hepatotoxic events of less than 50%, which would not be ruled out by these exposures, could still represent a safety signal that could preclude expansion of the indicated population. Therefore the point estimate and confidence intervals, as well as the clinical context for and types of serious hepatotoxic events observed, will be carefully evaluated when the data are submitted for review, in order to make a determination whether the data are adequate to support the use of TCZ in DMARD-IR patients.

Question 3. Does the Agency agree that if GI perforations are not identified as a safety signal that unfavorably impacts the overall TCZ benefit/risk based on a minimum of 46,000 patient years of exposure that the data will provide adequate support for the use of TCZ in DMARD-IR patients?

FDA Response

See response to Question 2. Presumably a smaller increase in GI perforation events can be reasonably ruled out with the 64,000-patient-years of exposure planned for the serious hepatotoxicity evaluation. If so, we recommend you provide analyses describing what degree of risk increase could be ruled out with what degree of certainty.

Question 4. Does the Agency agree that if CV events are not identified as a safety signal that unfavorably impacts the overall TCZ benefit/risk based on a minimum of 46,000 patient years of exposure that the data will provide adequate support for the use of TCZ in DMARD-IR patients?

FDA Response

Refer to the responses for Questions 2 and 3.

Question 5. If the above proposal is not acceptable as described in questions 1 through 4, can the Agency please specify what aspects of the approach are unacceptable and provide feedback on the overall analysis approach, type, and quantity of data that would be acceptable?

FDA Response

Refer to the responses for Questions 1 through 4.

CV Outcome Study

Introductory Comment: As the briefing package contains only a protocol synopsis, it is difficult to provide sufficiently detailed comments. We recommend you submit a full protocol for review at which time, detailed comments will be provided.

Question 1. In principle does the Agency agree that the key elements (eg, sample size, duration, number of events, non-inferiority margin) of the proposed randomized clinical trial design (see Appendix 2) are adequate to fulfill PMR #4 in the January 8, 2010 approval letter?

FDA Response

We do not agree. The Division does not agree with the composite endpoint you proposed and would prefer Major Cardiovascular Adverse Events (MACE) be used as the primary endpoint for the study. Since revision of the composite endpoint will affect the number of events, sample size, and non-inferiority margin, we cannot agree to any of those key elements at this time. When you submit your revised proposal using MACE as the endpoint, you will need to provide a detailed justification of your sample size and proposed NI margin. The justification should include the number of patients eligible for the study, estimated recruitment rate, and justification for the number of sites.

Question 2. Does the Agency agree with the primary endpoint of the proposed study as time to first occurrence of any component of the composite event listed below as adjudicated by the Clinical Cardiac event Committee (CEC):

- Myocardial infarction
- Hospitalization for unstable angina
- Stroke
- Cardiovascular death
- Coronary revascularization

FDA Response

Because of the potentially confounding factors that can influence the clinical decision-making regarding hospitalization or revascularization procedures, the Agency prefers the primary endpoint for the proposed study be the MACE endpoint. These would include events of cardiovascular mortality, myocardial infarction, and stroke. Your protocol should include detailed information on how the independence and blinding of the CEC will be ensured.

Question 3. The sponsor proposes to conduct the study in patients with an inadequate response to non-biologic and biologic DMARDS who are at high risk for CV events and to use TCZ given intravenously every 4 weeks with or without a non-biologic DMARD. Does the Agency agree with the choice of patient population?

FDA Response

Yes.

Question 4. Consistent with FDA feedback, the sponsor proposes to use a comparator arm consisting of TNF antagonists. The sponsor plans to randomize patients to treatment with one of two TNF antagonists (adalimumab or etanercept) versus tocilizumab 8 mg/kg with or without a non-biologic DMARD. Does the Agency agree with the choice of study medications for this study?

FDA Response

Yes.

Question 5. To provide sufficient long term follow up of patients, the sponsor intends to conduct an ITT analysis with an on treatment analysis for sensitivity. Does the Agency agree with this proposed primary endpoint analysis?

FDA Response

You should conduct the primary analysis on both the ITT analysis population and the on treatment analysis population. Consistent results across these two populations are important to demonstrate non-inferiority. Clear definitions of these analysis populations should be provided in the protocol. Refer to the FDA Draft Guidance for Industry: Non-Inferiority Clinical Trials for details.

Regarding the statistical model, the use of Cox proportional hazards model is acceptable to analyze the data of time to first CEC adjudicated event. However, the protocol should pre-specify the full Cox proportional hazards model that will be used for the primary endpoint. Include all factors on which randomization has been stratified in the analysis (see ICH E9 Guidance).

Question 6. Does the Agency agree with an interim analysis when 50% and 75% of the events have occurred and for the proposed study stopping criteria to include

- *Futility*
- *Non-inferiority*

FDA Response

We do not agree with the proposed interim analysis for the following reasons:

- 1. The timing of the first interim analysis after 50% of the observed CEC adjudicated events is problematic as it may be too early for a non-inferiority claim. With only a limited number of observed CEC adjudicated events, the estimate of the hazard ratio may not be robust enough to demonstrate non-inferiority (i.e. safety of the drug).**
- 2. Stopping the study early for so-called “futility” may result in loss of valuable safety information. Even if the study is determined to be unable to meet its statistical goals, important descriptive information could be obtained regarding cardiovascular outcomes.**

Question 7. The interim analysis of the primary endpoint and the ongoing review of the data will be monitored by the independent Data Safety Monitoring Board, governed by a Charter. Does the Agency agree with this governance model?

FDA Response

Any unplanned interim analyses to stop the trial for non-inferiority claim are not acceptable. Further more, you should submit a copy of the DMC charter and operational procedures to the BLA when available. The submitted details should include describing how the data management and statistical support for the DMC remains insulated from personnel involved with trial operations. Refer to the FDA Guidance for Clinical Trial Sponsors on Establishment and Operation of Clinical Trial Data Monitoring Committees, <http://www.fda.gov/cber/gdlns/clintrialdmc.pdf>.

Question 8. Does the Agency have any additional feedback to assist the sponsor in adequately addressing the Agency's PMR #4 for a post-marketing commitment CV outcomes study?

FDA Response

The Agency has no additional feedback.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
BLA 125276	BLA Supplement #49	If NDA, Efficacy Supplement Type:
Proprietary Name: <i>Actemra</i> Established/Proper Name: <i>tocilizumab</i> Dosage Form: <i>injection (for intravenous infusion)</i>		Applicant: <i>Genentech, A member of the Roche Group</i> Agent for Applicant (if applicable):
RPM: Philantha M. Bowen		Division: DPARP
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> </div> <div style="width: 50%;"> <p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> </div> </div>		
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>October 12, 2012</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

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

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

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics ³</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>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><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>REMS: <input 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 type="checkbox"/> Yes, dates</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 type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<p><input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other</p>

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

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

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

❖ Copy of this Action Package Checklist ⁴		
Officer/Employee List		
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)		<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees		<input checked="" type="checkbox"/> Included
Action Letters		
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)		Action(s) and date(s) AP: October 11, 2012
Labeling		
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)		
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 		9/12/12
<ul style="list-style-type: none"> • Original applicant-proposed labeling 		12/12/11
<ul style="list-style-type: none"> • Example of class labeling, if applicable 		

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

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	9/12/12
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	12/12/11
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	none
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	N/A
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 2/6/12 <input checked="" type="checkbox"/> DMEPA 8/6/12 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 9/24/12 <input checked="" type="checkbox"/> ODPD (DDMAC) 9/25/12 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (e.g., RPM Filing Review⁵/Memo of Filing Meeting) (<i>indicate date of each review</i>) 	2/27/12
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>8/22/12</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ 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 type="checkbox"/> Verified, statement is acceptable

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

❖ Outgoing communications (<i>letters, including response to FD RR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	10/11/12; 9/17/12; 9/10/12; 8/28/12; 2/8/12; 12/23/11
❖ Internal memoranda, telecons, etc.	12/21/11
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg 6/28/10
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg <i>pre-sBLA</i> 11/16/11
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	written responses – 9/26/11
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/10/12
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/22/12
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<i>See concurrence on clinical review</i>
• Clinical review(s) (<i>indicate date for each review</i>)	1/31/12; 9/10/12
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Clinical review pg. 17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	7/3/12; 9/20/12
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	<input type="checkbox"/> None
• 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>)	9/17/12; 10/3/12
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None memo 8/28/12
Statistical Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
Clinical Pharmacology		<input checked="" type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>		<input type="checkbox"/> None
Nonclinical		<input checked="" type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>		<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>		<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>		<input type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	5/11/12
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: 9/19/12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

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

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

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

/s/

PHILANTHA M BOWEN
10/11/2012