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RESEARCH**

APPLICATION NUMBER:

125276

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

from CR
submission



DEBARMENT CERTIFICATION

Hoffmann-La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

A handwritten signature in cursive script that reads "Judith L. Siegel". The signature is written over a solid horizontal line.

Dr. Judith Siegel, Vice President, Pharma Development Operations

Davies, Kathleen

From: Davies, Kathleen
Sent: Friday, January 08, 2010 11:51 AM
To: 'Lamb, Matthew'
Subject: RE: Actemra BLA 125276 - Agree to TNF Failure Indication

JAN - 8 2010
Kathleen Davies

Hi Matthew,

Thank-you for the label.

I wanted to let you know that we are adding the word "efficacy" to the PREA PMR just for clarity purposes since you are currently conducting an efficacy trial in addition to safety. Please let me know if you have any issues with this.

I hope that is the last question I will have for you; I am currently waiting for final concurrence on the REMS documents and upper management signoff, but I do not know exactly how long I'll be waiting. Sometime this afternoon you should hear back from me.

Kathleen

From: Lamb, Matthew [mailto:matthew.lamb@roche.com]
Sent: Thursday, January 07, 2010 5:44 PM
To: Davies, Kathleen
Subject: RE: Actemra BLA 125276 - Agree to TNF Failure Indication

Hi Kathleen,

We accept the revised USPI. I took the version you sent in the below email and accepted all changes and have attached it for your reference.

Please let me know if you need anything else.

Kind regards,
Matthew

Matthew W. Lamb
Group Director
Drug Regulatory Affairs
Roche
973.562.2833 (office)
973.393.8667 (mobile)
973.562.3700 (fax)
matthew.lamb@roche.com

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From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]

1/11/2010

Davies, Kathleen

From: Davies, Kathleen
Sent: Wednesday, January 06, 2010 1:27 PM
To: 'Lamb, Matthew'
Subject: RE: Actemra BLA 125276 - Agree to TNF Failure Indication

JAN - 8 2010



Hi Matthew,

Your proposed change is acceptable.

I received notification from our REMS review committee that I need a timeframe for element 3a) of the communication plan. Currently the communication plan reads as follows for #3 (below). Items b) and c) have timelines; I'm being instructed to request a timeline for a).

If you have any questions, please let me know.

Kathleen

3. Dissemination of information about the known and potential risks associated with ACTEMRA[®] to healthcare providers through certain professional societies' scientific meetings and journals:
 - a) For display as a panel/poster and distribution as printed material at major convention meetings of rheumatologists and other healthcare professionals specializing in rheumatology where the company has a sponsored booth
 - b) For quarterly presentation as a printed information piece in *Arthritis and Rheumatism, The Rheumatologist, Clinical Infectious Diseases, Clinical Gastroenterology and Hepatology, American Family Physician, Annals of Internal Medicine, Annals of Emergency Medicine* and *Neurology* for 3 years
 - c) For quarterly presentation as a printed information piece in the *Journal of Clinical Oncology* for 5 years

From: Lamb, Matthew [mailto:matthew.lamb@roche.com]
Sent: Wednesday, January 06, 2010 9:05 AM
To: Davies, Kathleen
Subject: Actemra BLA 125276 - Agree to TNF Failure Indication

Hi Kathleen,

Following our discussions with management last night, we agree to the proposed labeling from FDA with an indication for patients with an inadequate response to TNF therapy and the revised dosing recommendations as per the label we received Monday evening and Dr. Siegel's requested revision discussed on yesterday's call to combine the monotherapy and combination therapy bullets in the dosing recommendation table.

We are revising the documents right now and my plan is to email you the final label with FDA comments accepted, the revised Figure 1 with the Y-axis expanded to 100% and Dr. Siegel's revision to combine the monotherapy and combination therapy bullets in the dosing

1/11/2010

recommendation table into one statement. There was one discrepancy I identified last night in the indication statement in Section 1 of the USPI versus the indication in the highlights section and the recommendations provided in the dosage and administration section.

We propose the following change to the indication statement in Section 1 of the USPI.

ACTEMRA® (tocilizumab) is indicated for the treatment of adult patients with moderately-to severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

b(4)

This will ensure consistency between the indications statements and the dosage and administration section and is consistent with our discussions yesterday. Please let me know at your earliest convenience if this is acceptable and we will make this minor change as well.

I will also email you the final revised REMS documents so that you have them as soon as possible. As agreed yesterday, we will also make the formal BLA submission of the final REMS documents today, so that you have them officially submitted to the BLA by tomorrow morning.

Please let me know if there is anything else you will need from us.

Kind regards,
Matthew

Matthew W. Lamb
Group Director
Drug Regulatory Affairs
Roche
973.562.2833 (office)
973.393.8667 (mobile)
973.562.3700 (fax)
matthew.lamb@roche.com

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

Assessment of pharmacokinetic (PK/PD) parameters and dosing, safety, tolerance and immunogenicity in the pediatric population ≥ 2 years to < 17 years with polyarticular JIA.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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



(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: 1. Pregnancy registry to evaluate pregnancy outcomes for women exposed to Actemra (tocilizumab) during pregnancy. Utilize the established Organization of Teratology Information Specialists (OTIS) pregnancy registry to evaluate pregnancy outcomes.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>07/30/2010</u>
	Study/Clinical trial Completion Date:	<u>12/31/2016</u>
	Final Report Submission Date:	<u>12/31/2017</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

Animal data suggest that tocilizumab increased the incidence of abortion and embryofetal death at doses above therapeutic human levels. It is not known whether embryofetal exposure to therapeutic doses in humans could negatively impact pregnancy outcomes. A total of 31 pregnancies have occurred in 30 patients exposed to TCZ. Of these pregnancies, 5 are ongoing, 12 underwent therapeutic terminations, 7 spontaneous miscarriages occurred, 4 normal newborns were born, 1 infant died at 3 days of age from respiratory distress, 1 outcome was unknown and 1 was a false pregnancy (gestational trophoblastic tumor). Contraceptive use was mandated in study protocols.

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

The review issue is that no definitive conclusions can be drawn from the limited information thus far and a clinical trial is unethical. An observational study that follows the outcomes of women who happen to become pregnant while receiving tocilizumab, compared to women with RA receiving other immunosuppressives will provide for an expanded database from which to further assess affects of tocilizumab on pregnancy outcomes.

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

- **Which regulation?**

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

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

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

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

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

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

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

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

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

Women with RA who are receiving tocilizumab and become pregnant will be encouraged to enroll in the Organization of Teratology Information Specialists pregnancy registry for women with autoimmune diseases.

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

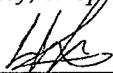
- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different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

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

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

PMR/PMC Development Coordinator:

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



(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: 2. Long-term observational study of patients who continue to be treated with tocilizumab in the open-label part of the treatment trials WA18695 and WA18696 to evaluate long-term serious risks of Actemra and to accrue safety data on at least 1000-1500 patients treated for 5 years.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>12/17/2009</u>
	Study/Clinical trial Completion Date:	<u>06/13/2013</u>
	Final Report Submission Date:	<u>06/30/2014</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

Patients treated in the randomized controlled trials were allowed to enroll in long-term open-label extension studies to continue treatment and observation. This will allow for the most rapid accrual of long-term data possible. Pre-approval safety data are adequate to evaluate for all but the most uncommon of AE with the longest latency--i.e. rare malignancies, therefore approval of this product with a novel mechanism of action need not be delayed while waiting for the long term data to accrue.

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

Patients treated in the randomized controlled trials were allowed to enroll in long-term open-label extension studies to continue treatment and observation. The number of patients (1000-1500) and duration of treatment (5 years) has previously been demonstrated for other approved products to be adequate to capture uncommon AE with longer latency periods, such as malignancies.

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

- **Which regulation?**

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

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

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

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

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

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

Long-term open label extension studies WA18695 and WA18696 are currently ongoing.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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



(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: 3. A randomized controlled trial to rule out a moderate increase in the risk of serious cardiovascular events with tocilizumab, e.g., stroke, non-fatal MI, cardiovascular death, unstable angina with urgent coronary revascularization.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>07/30/2010</u>
	Study/Clinical trial Completion Date:	<u>02/28/2018</u>
	Final Report Submission Date:	<u>02/28/2019</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

Data from the clinical development program for Actemra (tocilizumab) demonstrate that treatment with Actemra is associated with an increase in all lipid parameters, with an average increase of 30 mg/dl in total cholesterol, 20 mg/dl in LDL, 5 mg/dl in HDL, and 30-40 mg/dl in triglycerides. Since elevation in lipids, especially LDL, is considered a risk factor for the development of serious cardiovascular outcomes, these data indicate the potential for an unexpected serious risk of an increase in cardiovascular events in association with Actemra treatment(tocilizumab). However data in the BLA do not demonstrate an increased risk thus far.

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

See #1.

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

- **Which regulation?**

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

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

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

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

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

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

Study details are yet to be determined. The study will likely be a randomized controlled trial of tocilizumab versus an active comparator and will be designed to rule out a pre-specified increase in relative risk for serious cardiovascular adverse events.

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

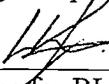
- Quality study without a safety endpoint (e.g., manufacturing, stability)
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 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
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 - Nonclinical study, not safety-related (specify)
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- Other
-

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
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PMR/PMC Development Coordinator:

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



(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: 4. A randomized trial to study the effects of tocilizumab on therapeutic vaccines. B cell-dependent antigens (e.g., pneumococcal polysaccharide vaccine) and T cell-dependent antigens (e.g., tetanus toxoid) will be evaluated.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>04/30/2010</u>
	Study/Clinical trial Completion Date:	<u>10/13/2013</u>
	Final Report Submission Date:	<u>11/30/2012</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

Because Actemra inhibits IL6 activity, it is immunosuppressive, and also may specifically impair the ability of B cells to differentiate into immunoglobulin-secreting cells. Therefore, there are plausible biologic mechanisms as reason to suspect that Actemra treatment may impair immune responses to vaccination. This theoretical risk could be reasonably handled via labeling that with recommendations for actions to be taken for the worst-case scenario of impaired vaccination responses; specifically, to bring patients up to date with vaccinations prior to initiating Actemra. Therefore this study does not need to be done pre-approval.

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

See #1.

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

- **Which regulation?**

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

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

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

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

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

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

A randomized trial to study the effects of tocilizumab on therapeutic vaccines. B cell-dependent antigens (e.g., pneumococcal polysaccharide vaccine) and T cell-dependent antigens (e.g., tetanus toxoid) will be evaluated.

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

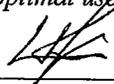
- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different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

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

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

PMR/PMC Development Coordinator:

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



(signature line for BLAs)

Davies, Kathleen

From: Davies, Kathleen
Sent: Thursday, December 31, 2009 9:15 AM
To: 'Lamb, Matthew'
Subject: RE: REMS comments - Actemra

JAN - 8 2010



Hi Matthew,

These are acceptable with the following minor edits (below). You can submit to the BLA.

Kathleen

- 1) Support Document changes OK
- 2) web shot one click away ISI is OK, BUT CHANGE ——— to "journal information pieces" (this is important)
- 3) if possible, consider using bulleted adverse events instead of paragraph format (not crucial)

b(4)

From: Lamb, Matthew [mailto:matthew.lamb@roche.com]
Sent: Wednesday, December 30, 2009 4:06 PM
To: Davies, Kathleen
Subject: RE: REMS comments - Actemra

Hi Kathleen,

Thanks for the REMS feedback.

Attached is the revised REMS supporting document with the requested change by OSE.

Also, attached are two versions of revised screen shots for the ACTEMRA REMS website. One version has a link to the Important Safety Information (ISI) that is one click away (DOA HCP REMS3.pdf) and the second has the ISI on the primary screen (DOA HCP REMS2.pdf). Our preference is for DOA HCP REMS3.pdf with the ISI one click away. This is consistent with our understanding of the Agency's preference based on the journal pieces (which omit the ISI) and consistent with feedback we received from the Agency on other Roche REMS. If, however, our understanding is not correct, the screen shot with the ISI included is also provided for Agency review and is an acceptable alternative.

In response to the questions below:

1. There are no new safety information regarding hypersensitivity/anaphylaxis. Our vendor working on the website picked up incorrect information when preparing the web page and we missed the mistake during our proofing.
2. Revision completed as per OSE request.
3. Revision completed as per OSE request.
4. The ACTEMRA REMS website, which will be accessed via a link from the larger website (www.ACTEMRA.com), is intended only for HCPs and has been revised accordingly as outlined above.

Please let me know if you have any questions.

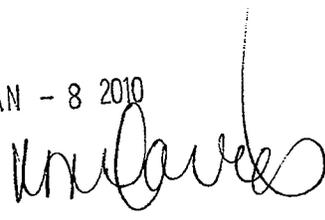
Kind regards,

1/11/2010

Davies, Kathleen

From: Davies, Kathleen
Sent: Wednesday, December 30, 2009 10:55 AM
To: 'Lamb, Matthew'
Subject: RE: REMS comments - Actemra

JAN - 8 2010



Hi Matthew,

OSE has reviewed your documents and has the following comments:

The Supporting Document section shown below should reflect the change made to the REMS such that the generalists will receive the journal information piece content that rheumatologists receive. Thus, it should say

┌
- - - - -
└

INSTEAD of what is now says:

┌
- - - - -
└

Regarding the website screenshot:

1) **WHY DOES THIS WEBSITE target anaphylaxis/hypersensitivity? If there is new safety information, the REMS itself needs to be re-considered.**

2) -
┌
- - - - -
└

Delete this statement; we suggest: ┌

┌
- - - - -
└

The goals of the Actemra REMS are:

- To inform healthcare providers about the risks of serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders, and malignancies associated with ACTEMRA®.
- To inform patients about the serious risks associated with ACTEMRA® treatment.

3) Delete the word 'MUST' regarding AE reporting, since it is voluntary. Instead, we suggest: '

b(4)

4) We find it confusing that the beginning of this website is addressed to HCP, but the end has patient labeling. Please clarify the intended audience for the website...if it is both stakeholders, please redesign to make it clear which part of the message is for whom.

From: Lamb, Matthew [mailto:matthew.lamb@roche.com]

Sent: Tuesday, December 29, 2009 7:51 PM

To: Davies, Kathleen

Subject: RE: REMS comments - Actemra

Hi Kathleen,

Attached are the revised REMS documents as per the Agency requests. We accepted the proposed revisions. I have provided both a red line and clean version of the REMS document and the REMS supporting document. Additionally, the website screen shot is provided as the PDF.

When we do the formal submission to the BLA, we will include all the various attachments for the supporting document (not included here as they haven't changed).

I will have a submissions publisher on stand by tomorrow and if we get the go ahead/final comments from you by 1:00 pm or so, we can probably get the REMS incorporated into the BLA amendment that will be submitted tomorrow which currently will include the carton/container labeling, PMRs and MedGuide. Otherwise we will submit the REMS in a separate submission following your feedback.

Kind regards,
Matthew

Matthew W. Lamb
Group Director
Drug Regulatory Affairs
Roche
973.562.2833 (office)
973.393.8667 (mobile)
973.562.3700 (fax)
matthew.lamb@roche.com

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From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]

Sent: Tuesday, December 29, 2009 12:56 PM

To: Lamb, Matthew {PDR~Nutley}

Subject: RE: REMS comments - Actemra

If you prefer us to review it a final time prior to formal submission, you can email it to me first. We can turn it around quickly as our OSE review team is back from leave.

1/11/2010

Kathleen

From: Lamb, Matthew [mailto:matthew.lamb@roche.com]
Sent: Tuesday, December 29, 2009 11:36 AM
To: Davies, Kathleen
Subject: RE: REMS comments - Actemra

Hi Kathleen,

Should we resubmit via email or assuming we agree with the changes go ahead and submit to the BLA as well?

Thanks,
Matthew

Matthew W. Lamb
Group Director
Drug Regulatory Affairs
Roche
973.562.2833 (office)
973.393.8667 (mobile)
973.562.3700 (fax)
matthew.lamb@roche.com

Confidentiality Note: This message is intended for the use of the named recipient(s) only and may contain confidential and/or proprietary information. If you are not the intended recipient, please contact the sender and delete this message. Any unauthorized use of the information contained in this message is prohibited.

From: Davies, Kathleen [mailto:Kathleen.Davies@fda.hhs.gov]
Sent: Tuesday, December 29, 2009 11:27 AM
To: Lamb, Matthew {PDR~Nutley}
Subject: REMS comments - Actemra

Hi Matthew,

OSE has reviewed your REMS submission and has the following comments:

1) Resubmit the REMS with the following changes:

Attachment G: Substitute the content of the general internist journal information piece with the journal information piece content for rheumatologists. The rationale is that generalists may be consulted about any of the targeted adverse events for Actemra, not just the 3 listed currently in the generalist journal piece.

Accordingly, make the following changes to the REMS Communication Plan in the REMS document:

Family practitioners, general practitioners, osteopaths, internists, and internal medicine specialists who may be consulted about serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders, and malignancies associated with Actemra®.

1/11/2010

Emergency medicine specialists who may treat serious infections, gastrointestinal perforations, and changes in liver function.

2) Resubmit the supporting document with the website screenshot Attachment A, which we could not locate.

Davies, Kathleen

From: Davies, Kathleen
Sent: Thursday, December 24, 2009 10:05 AM
To: Lamb, Matthew
Subject: RE: Actemra BLA 125276 - comments on carton/containers

Matthew Lamb
JAN - 8 2010

Hi Matthew,

Thank-you for all the labels, we are currently reviewing them.

I do have comments on the carton/containers:

Please revise the presentation of strength from "X mg in 1 mL" to "(X mg/ mL)" on all labeling to comply with the United States Pharmacopeia, 12/1/09-5/1/10, USP 32/NF27, General Chapter, Injection <1>, "STRENGTH AND TOTAL VOLUME FOR SINGLE-AND MULTIPLE-DOSE INJECTABLE DRUG PRODUCTS". It appears you changed it to X mg/1 mL; the "1" needs to be deleted so that it reads X mg/mL, not X mg/1 mL.

You submitted two distinct panels each for the 80 mg/4 mL and 400 mg/20 mL container labels and carton labeling strength presented in white font versus black font in accordance with a previous request. OSE prefers the white font because of improved contrast and readability compared to the black font on the green and red color bars. The 200 mg/10 mL strength was only presented with a yellow color bar and black font, which is acceptable.

Increase the prominence of the secondary statement of strength (i.e. 20 mg/mL) by increasing the font size. In its current format, the information is difficult to read.

If all of these changes are agreeable to you, please revise and submit officially to the BLA.

The remaining labeling comments will come next week due to reviewers being out of the office.

Happy Holidays,
Kathleen

-----Original Message-----

From: Lamb, Matthew [mailto:matthew.lamb@roche.com]
Sent: Tue 12/22/2009 5:49 PM
To: Davies, Kathleen
Subject: Actemra BLA 125276 - Revised USPI & MedGuide

Dear Kathleen,

I am going to send you 3 emails.

This is the first and includes the revised USPI and MedGuide (with both a version in track changes mode and a clean version). We also have provided a rationale document with explanations for proposed changes. The second email will include the revised REMS documents and the third document will include the revised carton/container labeling.

Please let me know if you have any questions.

Kind regards,
Matthew

Matthew W. Lamb
Group Director
Drug Regulatory Affairs

Roche
973.562.2833 (office)
973.393.8667 (mobile)
973.562.3700 (fax)
matthew.lamb@roche.com

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Davies, Kathleen

From: Davies, Kathleen
Sent: Thursday, December 17, 2009 11:30 AM
To: 'Lamb, Matthew'
Subject: PMRs for Actemra
Attachments: PMRs_Actemra.doc

DEC 17 2009



Hi Matthew,

Please refer to BL 125276 for Actemra. I attached some drafted PMRs from the Division for your consideration. Please review these and edit if needed. In addition, you must provide 3 dates (month/year) for each: Protocol Submission, Study Start Date, Final Report Submission.

If you make edits, please send them back to me via email for our consideration. Once we finalize the PMRs, they must be submitted officially to the BLA.

Kathleen

Davies, Kathleen

From: Davies, Kathleen
Sent: Thursday, October 29, 2009 11:03 AM
To: 'Savuto, Deborah'; 'matthew.lamb@roche.com'
Subject: Nonclinical IR for Actemra

DEC 17 2009



Hi Deb and Matthew,

Please refer to your BLA 125276 for Actemra. We are currently reviewing the nonclinical portion of your BLA and have the following request for information:

Provide historical control data regarding the incidence of full and short supernumerary ribs in F1 mice at weaning. The data should be expressed in terms of both % of pups and # of litters that showed this variation. If available, provide journal references to support your assertion that the incidence of this finding reported in your submitted pre and postnatal development study submitted in your CR to the BLA is part of background.

If you have any questions, let me know.

Kathleen

Dillon, Laura

From: Inyard, April
Sent: Wednesday, December 09, 2009 11:03 AM
To: Dillon, Laura
Cc: CDER-TB-EER
Subject: RE: TB-EER for 125276/0/64
Follow Up Flag: Follow up
Flag Status: Red
Attachments: TB-EER request form_125276-0-64.doc

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER for Genentech, Inc.'s STN 125276/0 and 64. Please see the attached TB-EER response form for the individual compliance status of each site. There are no pending or ongoing compliance actions to prevent approval of STN 125276/0 and 64.

Kind Regards,

April

APRIL INYARD, PHD.
Staff Fellow
CDER/OC/DMPQ/MAPCB
april.inyard@fda.hhs.gov

From: Dillon, Laura
Sent: Thursday, December 03, 2009 9:06 AM
To: CDER-TB-EER
Cc: Hughes, Patricia; Dillon, Laura
Subject: TB-EER for 125276/0/64

Please complete a review and evaluation of the attached TB-EER for 125276/0/64. This is a BLA that was CRed. Approval of the license was pending from a GMP perspective. As of the original review date of 9/16/08, the 483 responses from the inspection were still under review. This TB-EER is to request an update regarding the site. The PDUFA date is 1/8/10 (GRMP date is 12/8/09).

Thanks,
Laura

Laura A. L. Dillon, M.S.
Consumer Safety Officer
Food and Drug Administration
Center for Drug Evaluation and Research
OC/DMPQ/BMT
10903 New Hampshire Avenue
Bldg. 51, Rm. 4359

12/9/2009

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:

The review team should email this form to the email account "CDER-TB-EER" to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing¹ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: 1/8/10

Applicant Name: Genentech, Inc.

U.S. License #: 1048

STN(s): 125276/0/64

Product(s): Tocilizumab (ACTEMRA)

Short summary of application: Submission in Response to a Complete Response letter (BLA - treatment for reducing signs and symptoms in adult patients with moderately to severely active RA)

FACILITY INFORMATION

Firm Name: Chugai Pharma Manufacturing Co Ltd

Address: 16 3 Kiyohara Kogyodanchi, Utsunomiya City, Totigi, 321-3231, Japan

FEI: 3006942691

Short summary of manufacturing activities performed: DS and DP manufacturing (production and testing)

This site was inspected 05/21/2008-06/05/2008 and is classified VAI. This PAI inspection covered the present therapeutic drug (Tocilizumab).

¹The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

MEMORANDUM

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

DATE: December 9, 2009

TO: Division File

THROUGH : DAARP

FROM: Kathleen Davies

SUBJECT: Preapproval Safety Conference

APPLICATION/DRUG: BLA 125276/Actemra

Pre-approval Safety Conference was held December 9, 2009. The team noted that there should be lab monitoring included in the label and that there should be tuberculosis (TB) language similar to the TNF-blocker class of biologics. DAARP concurred with OSE's recommendations.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

STN: BL 125276

LICENSE REVOCATION FOR TRANSFER

NOV 23 2009

Hoffman-La Roche Ltd.
340 Kingsland Street
Nutley, NJ 07110-199

Attention: Matthew Lamb, PharmD
Group Director, Drug Regulatory Affairs

Dear Dr. Lamb:

We acknowledge receipt on October 15, 2009, of your October 14, 2009, correspondence notifying the Food and Drug Administration that Hoffman-La Roche, U.S. License No. 1036, has transferred ownership of Actemra (tocilizumab) to Genentech. In a correspondence dated October 14, 2009, received October 15, 2009, Genentech notified the Agency that they have accepted the transfer of all the rights and responsibilities for the manufacture of Actemra (tocilizumab) from Hoffman-La Roche.

Therefore, under the provisions of Title 21, Code of Federal Regulations, section 601.5(a), we are revoking your biologics license (number 1036) to manufacture Actemra (tocilizumab) effective this date. Your pending application submitted under U.S. License Number 1036 for Actemra (tocilizumab) has been transferred to Genentech under U.S. License No. 1048.

Please note that this letter supersedes any previously issued license certificates. You may place these certificates in your historical files. However, we recommend that you keep a copy of this letter available for review at the time of FDA inspections.

Please cite the BLA 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 Anesthesia, Analgesia
and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact me at (301) 796-2205.

Sincerely,

A handwritten signature in black ink, appearing to read 'Kathleen Davies', written in a cursive style.

Kathleen Davies, M.S.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

STN: BL 125276

LICENSE REISSUANCE FOR TRANSFER

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

NOV 23 2009

Attention: Mary B. Sliwkowski, Ph.D.
VP, Regulatory CMC and Information Systems

Dear Dr. Sliwkowski:

We acknowledge receipt on October 15, 2009, of the October 14, 2009, correspondence notifying the Food and Drug Administration that Hoffman-La Roche, U.S. License No. 1036, has transferred ownership of Actemra (tocilizumab) to Genentech. We have also been advised by your letter dated October 14, 2009, received October 15, 2009, that Genentech has accepted the transfer of all the rights and responsibilities for the manufacture of Actemra (tocilizumab) and will continue to manufacture Actemra (tocilizumab) in the same manner as Hoffman-La Roche, using the same equipment, facilities, manufacturing procedures, controls, and methods, and responsible personnel.

It is also our understanding that you will be the authorized official for Genentech. Draft labeling submitted on July 8, 2009, received July 9, 2009, must be resubmitted with the new license-holder's name and information. Labeling revisions reflecting the name of your establishment and the new license number should be completed within 14 days of receipt of this letter.

Your pending application for Actemra (tocilizumab) under U.S. License Number 1036 has been transferred to U.S. License Number 1048. All future correspondence should be submitted under the originally assigned Submission Tracking Number 125276.

Please submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format.

Please note that this letter supersedes any previously issued license certificates. You may place these certificates in your historical files. However, we recommend that you keep a copy of this letter available for review at the time of FDA inspections.

Please cite the STN 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 Anesthesia, Analgesia
and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact me at (301) 796-2205.

Sincerely,

A handwritten signature in cursive script, appearing to read "K. Davies", written over a horizontal line.

Kathleen Davies, M.S.
Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ODE II/DAARP**

NDA/BLA #s: BLA 125276
PRODUCT: Actemra (tocilizumab) infusion
APPLICANT: Hoffmann La-Roche, Inc.
FROM: Division of Anesthesia, Analgesia and Rheumatology Products
(DAARP)
THROUGH: Bob A. Rappaport, M.D., Director, DAARP
DATE: November 16, 2009


NOV 16 2009

The purpose of this memorandum is to document the rationale for changing the elements of the proposed REMS for Actemra (tocilizumab) from the elements that were required of Hoffmann-La Roche in our September 17, 2008 complete response letter and in our November 14, 2008 letter.

In the August 5, 2008, REMS memorandum, FDA determined that Actemra (tocilizumab) was required to have a REMS to ensure that the benefits of the drug outweighed the risks of serious infections, gastro-intestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, peripheral demyelinating disorders, and malignancies. The REMS was to include the following elements: a Medication Guide, a communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

In a Complete Response submission dated July 8, 2009, Hoffmann-La Roche proposed a REMS including all of the components stipulated in the November 14, 2008 letter. After further internal evaluation and discussion, the Office of Surveillance and Epidemiology (OSE) and DAARP are in agreement that a REMS is necessary to ensure the safe use of Actemra (tocilizumab), but that the ETASU (prescriber certification and attestation, infusion center certification, and mandatory patient monitoring with informed consent) and the implementation system are not warranted at this time.

As indicated in our REMS memorandum from August 5, 2008, we believe that educating healthcare practitioners to understand and adhere to the labeled recommendations for close monitoring of the laboratory parameters and prompt recognition of the critical values indicating toxicities of Actemra (tocilizumab) will be necessary to help ensure safe use of Actemra (tocilizumab) and to prevent occurrence of serious adverse events. Upon further consideration of the proposed REMS program, we have determined that the ETASU and implementation system may not provide additional assurance for adherence to monitoring of the laboratory abnormalities and prevention of the adverse events of interest over and above the impact of recommendations provided in Actemra's (tocilizumab) labeling and Medication Guide supported by an appropriate communication

plan. In addition, the ETASU cannot deliver patient level data needed to address the implementation system analyses. Furthermore, we have determined that at this time, the adverse events and observed laboratory abnormalities are similar to those observed with other products used to treat rheumatoid arthritis. Hoffman La Roche's proposed recommendations for monitoring and possible dose adjustments needed to address the laboratory abnormalities are similar to practices established for other products used to treat rheumatoid arthritis, and we believe that these recommendations will align with the existing practices and be readily adopted. Although changes in hematologic, hepatobiliary, and lipid parameters may potentially lead to serious adverse clinical outcomes, the vast majority of the laboratory abnormalities observed in Actemra's (tocilizumab) clinical development program did not result in adverse clinical outcomes. In the majority of cases the laboratory changes were reversible upon timely dose reduction, or interruption, or discontinuation of Actemra (tocilizumab). FDA, to date, has not required ETASU for laboratory abnormalities without evidence suggesting that such abnormalities result in serious adverse events.

Therefore, although we continue to believe that a REMS is necessary for Actemra (tocilizumab), we have concluded that it is not necessary to include ETASU or an implementation system as part of the REMS at this time. The elements of the REMS for Actemra (tocilizumab) will be a Medication Guide, a communication plan, and a timetable for submission of assessments.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

BLA 125276

NOV 16 2009

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Attention: Matthew Lamb, Pharm. D.
Director, Global Regulatory Affairs

Dear Dr. Lamb:

Please refer to your November 19, 2007, Biologics Licensing Application (BLA), submitted under section 351(a) of the Public Health Service Act for Actemra (tocilizumab), for the treatment of adult onset rheumatoid arthritis.

We also refer to your submissions dated September 23 and 29, October 27, and November 21, 2008, and March 3 and July 8, 2009.

Your submission dated July 8, 2009 constituted a complete response to our complete response letter dated September 17, 2008.

In our letters dated September 17, 2008 and November 14, 2008, we notified you that a Risk Evaluation and Mitigation Strategy (REMS) was required for Actemra (tocilizumab) to ensure that the benefits of the drug outweighed the risk of serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, peripheral demyelinating disorders, and malignancies. We indicated that your REMS must include a Medication Guide, a communication plan targeted to healthcare providers to support implementation of the elements of your REMS, elements to assure safe use (ETASU) to mitigate specific serious risks listed in the labeling, an implementation system, and a timetable for assessment of the REMS.

We are in the process of reviewing your proposed REMS as described in your submission of July 8, 2009. Although we continue to believe that a REMS is necessary to ensure the safe use of Actemra (tocilizumab), upon further consideration, we do not believe that a restricted program with ETASU and an implementation system are necessary to ensure the benefits of the drug outweigh the risks described above. Specifically, upon our review of the clinical data submitted in your July 8, 2009 submission, we have determined that at this time, the adverse events and observed laboratory abnormalities are similar to those observed with other products used to treat rheumatoid arthritis and do not warrant ETASU to ensure the benefits outweigh the risks. Recommendations for monitoring, possible dose adjustments, and drug discontinuation needed to

address the laboratory abnormalities are similar to those established for other products used to treat rheumatoid arthritis, and we believe that these recommendations can be communicated through labeling, a Medication Guide, and a communication plan. Moreover, serious infection, demyelinating disorders, and malignancy are known risks of biological products with effects on the immune system. The rheumatology community is aware of these risks and, at this time, we do not have data to suggest additional risks are associated with Actemra (tocilizumab) to require additional REMS elements.

Based on our current understanding of the risk of serious infections, gastrointestinal perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, peripheral demyelinating disorders, and malignancies with Actemra (tocilizumab), we have determined that the REMS must include a Medication Guide, communication plan, and timetable for the submission of assessments.

The communication plan must include, at a minimum, the following:

- Dear Healthcare Provider Letters to be distributed at the time of first marketing. Your communication plan should state specifically the types and specialties of healthcare providers to which the letters will be directed.
- Dissemination of information about the need for laboratory monitoring and dose adjustment to health care providers through professional societies.
- A schedule for when and how these letters/materials are to be distributed to healthcare providers at the time Actemra (tocilizumab) is approved, and at specified intervals thereafter. Append the draft letters and other communication materials to the proposed REMS.
- A description of the audience for the communication plan, stating specifically the types and specialties of healthcare providers to whom the communication materials will be directed. These should include non-prescribers in specialties likely to be consulted for complications of Actemra (tocilizumab) therapy.

You should submit a revision to the proposed REMS and REMS supporting document included in your July 8, 2009 submission that includes the Medication Guide, communication plan, and the timetable for submission of assessments described in our November 14, 2008 letter. You should remove the ETASU and implementation system from your proposed REMS, as they are no longer required.

Updates to the REMS supporting document may be included in a new document that references the previous REMS supporting document submission for unchanged portions of the REMS, or updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify subsequent submissions related to the Proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 125276/0
PROPOSED REMS - AMENDMENT**

BLA 125276
Page 3

If you have any questions, call Kathleen Davies, Regulatory Health Project Manager, at (301) 796-2205.

Sincerely,

A handwritten signature in black ink, appearing to read 'Bob A. Rappaport', written in a cursive style.

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Rheumatology Products
Office of Drug Evaluation II
Center of Drug Evaluation and Research



Our STN: BLA 125276/0

ACKNOWLEDGE COMPLETE RESPONSE

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

JUL 29 2009

Attention: Matthew Lamb, Pharm. D.
Group Director, Global Regulatory Affairs

Dear Dr. Lamb:

We have received your July 8, 2009, resubmission to your biologics license application for Actemra (tocilizumab) on July 9, 2009.

The resubmission contains additional nonclinical information as well as updated safety information and labeling and REMS that you submitted in response to our September 17, 2008, complete response letter.

We consider this a complete, class 2 response to our action letter. Therefore, the user fee goal date is January 8, 2010.

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

If you have any questions, please contact Sharon Turner-Rinehardt, Regulatory Health Project Manager at (301) 796-2254.

Sincerely,

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

BLA 125276

December 29, 2008

Hoffman-La Roche Pharmaceuticals
340 Kingsland Street,
Nutley, NJ 07110

Attention: Mathew Lamb
Regulatory Affairs, Global Regulatory Leader

Dear Dr. Lamb:

Please refer to your pending Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act and in accordance with 21 CFR Part 601 for Actemra (tocilizumab).

We also refer to the meeting between representatives of your firm and the FDA on December 1, 2008. The purpose of the meeting was to discuss deficiencies cited in the September 17, 2008, Complete Response letter and the November 14, 2008, request for Risk Evaluation and Mitigation Strategy (REMS) letter.

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

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

Sincerely,

Sharon Turner-Rinehardt

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

Enclosure - Meeting Minutes

MEETING MINUTES

Meeting Date: December 1, 2008
Location: White Oak, Building 22, Conference Room 1315
BLA/ Name: 125276/Acetmra
Indication: Rheumatoid Arthritis
Sponsor: Hoffmann-La Roche
Type of Meeting: Type A – Post Action
Meeting Chair: Sarah Okada, MD
Minutes Recorder: Sharon Turner-Rinehardt, RPM



BACKGROUND: Actemra (tocilizumab) a monoclonal antibody that binds to the interleukin-6 (IL-6) receptor used to treat rheumatoid arthritis. A Complete Response letter and a request letter for REMS were issued on September 17 and November 14, 2008, respectively.

Hoffmann-La Roche Attendees	
Name	Title
Ken Bahrt, MD	Global Head of Auto-Immunity Medical Affairs
Robin Conrad	Senior Director, Regulatory Affairs
Yamo Deniz, MD	Clinical Science Leader
Cynthia Dinella, PhD	Vice President, Regulatory Affairs
Mike Doherty	Global Head, Regulatory Affairs
Richard Erwin	Global Project Leader
Jean-Jacques Garaud, MD	Chief Medical Officer, Global Head of Pharma Development
Joel Krasnow, MD	Clinical Science Leader
Matthew Lamb, PharmD	Regulatory Affairs, Global Regulatory Leader
Jonathan Leff, MD	Global Head Inflammation Clinical Development
Don MacLean, PhD	Lifecycle Leader
Thomas Singer, PhD	Global Head, Nonclinical Safety
Lutz Mueller, PhD	Toxicology Project Leader
Philippe Van der Auwera, MD	Global Head of Drug Safety
David Brewster, PhD	Nonclinical Safety
Lori Martin	Commercial Operations
FDA Attendees	
Curtis Rosebraugh, MD, MPH	Director, Office of Drug Evaluation II
Bob A. Rappaport, MD	Director, Division of Anesthesia, Analgesia and Rheumatology Products
Rigoberto Roca, MD	Deputy Director
Sarah Okada, MD	Medical Officer
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor
Patrick Swann, PhD	Deputy Director, Division of Monoclonal Antibodies (DMA)
Paul, Brown, PhD	Associate Director, Pharmacology/Toxicology, OND
David Jacobson-Kram, PhD	Associate Director, Pharmacology/Toxicology, OND
Gerald Feldman, PhD	Product Review, (DMA)
Lei Zhang, PhD	Clinical Pharmacology Reviewer
Venkatesh Atul Bhattaram, PhD	Pharmacometrics Reviewer
Peter Diak, PharmD, MPH	Safety Evaluator, Office of Surveillance and Epidemiology (OSE)
Claudia Karwoski, PharmD	Acting Director, Division of Risk Management (DRISK), OSE
Parinda Jani	Chief, Project Management Staff
Ramani Sista, PhD, RAC	Regulatory Project Manager
Sharon Turner-Rinehardt	Regulatory Health Project Manager
Jessica Benjamin	Regulatory Project Manager
Diana Walker	Regulatory Project Manager

GENERAL DISCUSSION: Following introductions, the meeting focused on the responses to the questions included in the November 04, 2008, meeting package for BLA 125276. The responses to the questions were provided to the Sponsor on November 26, 2008. The questions are presented below in *italicized* text, the Division's responses, prepared prior to the meeting and presented as handout, are **bolded**. Discussion is presented in normal text.

REMS

Question 1. Roche's interpretation is that the Elements to Ensure Safe Use are specifically related to the "specific risks" associated with potential serious complications related to laboratory changes (liver function, neutrophils, platelets, and increases in lipids). Does the Agency agree with this interpretation? If not, could the Agency please clarify?

FDA Response

Yes. The Elements to Assure Safe Use (ETASU) are specifically related to the risk of potentially serious complications due to laboratory abnormalities (liver function, neutrophils, platelets, and increases in lipids).

Discussion: Refer to Question 4.

Question 2. Reference is made to a "Specified Adverse Event Form" and "Reported Adverse Events of Interest" multiple times in the REMS letter (Elements to Ensure Safe Use 1(b)(iv), 2(a)(iv); Implementation System 1, 5; and Assessments 1). Roche proposes to develop a specific adverse event form capturing requested information for the following events; serious infections, opportunistic infections, GI perforation and related events, MI/Acute coronary syndrome, stroke, malignant neoplasms, anaphylaxis, demyelination related events and serious/medically significant hepatic events. Does the Agency agree with the proposed list? If not please clarify.

FDA Response

At a minimum, the specified adverse event form pertaining to the ETASU should elicit description and reporting on adverse events of interest related to the laboratory changes of concern (liver function, neutrophils, platelets, and increases in lipids). However, we encourage you to include other serious adverse events of interest, as you have proposed. The specific adverse events you have listed would likely capture adverse events related to treatment-related laboratory changes, with the exception of bleeding events related to thrombocytopenia.; therefore, spontaneous or serious bleeding events should also be added to this list.

Discussion: Refer to Question 4.

Question 3. Prescriber training 1(a)(iii) states "Adverse reactions associated with Actemra documented in the product's label." Roche interprets this statement to include the adverse events of interest included in Question 2. Does the Agency have any comment?

FDA Response

Although the adverse reactions could include any that are documented in the product's label, we agree that prescriber training should focus on adverse events of interest related to laboratory changes and the adverse events listed in your Question 2.

Discussion: Refer to Question 4.

Question 4. It is Roche's experience that multiple discussions will be needed with the Review Division and Office of Surveillance and Epidemiology to clarify specific aspects of REMS to ensure mutual understanding between Roche and the Agency on the REMS content. Roche believes additional discussions with the Agency may be needed prior to resubmission of our Complete Response and after resubmission to ensure mutual agreement on the REMS elements. Does the Agency agree this would be appropriate? Can the Agency please comment on the process they would like the Sponsor to follow to obtain such discussions?

FDA Response

The Division will involve appropriate Agency personnel as necessary in future discussions regarding the REMS. We will make every effort to meet your needs regarding clarifications but the number and timing of interactions may be limited by workload and staffing resources. This may necessitate batching of your questions and prioritization of issues on your part. You should contact Sharon Turner-Rinehardt, Regulatory Health Project Manager, to request these discussion and/or clarification interactions and obtain feedback on timing.

Discussion: The Sponsor provided a handout (see attachment) that contained discussion points for the meeting. These included several slides detailing their understanding of the REMS goals and their proposals for how to handle the implementation of the REMS. Dr. Karwoski, from the Office of Surveillance and Epidemiology, stated that, in general, the Sponsor's description of the goals and implementation of the REMS appears to be appropriate, but additional details would have to be provided in order to better assess and comment on their proposals.

The Sponsor sought further clarification as to whether the REMS could be based on the last version of the label received from the Division during the review of the BLA. The Division stated that the label would probably be further revised; however, the recommendations in the label pertaining to the REMS (i.e., laboratory monitoring and dose interruption/modification recommendations) would likely not be changed. Therefore, it is reasonable for the Sponsor to use these sections as a basis for their proposed REMS. The Sponsor inquired as to whether the REMS proposal could be submitted in advance of the BLA resubmission. The Division responded that the Sponsor was welcome to submit a detailed REMS proposal early and every effort would be made to review the proposal and comment. However, the REMS should be formally submitted with the BLA resubmission.

Question 5. Roche wants to take the opportunity to ensure alignment on FDA feedback received regarding the nonclinical study designs submitted to IND 11,972 on October 23 and October 28, 2008. In the event, FDA isn't able to provide feedback prior to this meeting; Roche wants to get Agency feedback on the study designs at this time.

General Comment: Your submissions regarding the use of the MR16-1 protein suggest considerable reservations regarding the utility of this surrogate to appropriately address the lack of adequate information regarding fertility and peri- and post-natal development and the viability of what options are available to assess these endpoints. The Division notes that the decision to employ either the nonhuman primate (NHP) or an alternative model should be based on sound science. Given your reservations noted regarding the applicability of the surrogate protein, provide your justification for not conducting the segment III assessment in the NHP. In addition, submit a detailed description of the MR16-1 protein and include a rationale for why this protein is or is not a useful tool to characterize the potential impact of tocilizumab on fertility and peri- postnatal development.

The following are responses to the questions contained in your submission dated October 23, 2008, submitted to IND 11, 972.

Question 1. One deviation from the ICH recommendations is the use of two dose groups instead of three. MR16-1 is a rat monoclonal antibody with significant immunogenicity in the mouse. The immune response to MR16-1 is expected to be lower over the time period of the planned studies if the doses are high enough to induce immune tolerance. A low dose group will be excluded as low doses have been shown to be immunogenic with depletion of exposure, blocking of receptor mediated transfer of MR16-1 across epithelial barriers (placental and testicular transfer, excretion into milk) and risk of induced hypersensitivity reactions. Does the Agency agree?

FDA Response

Your proposal to employ only two dose groups, rather than the traditional three, based on the likelihood that the low dose groups will likely generate the most robust antibody response may be acceptable if the doses proposed demonstrate a clear NOAEL.

Discussion: No discussion required for this question.

Question 2. Regarding dose selection, the MR16-1 antibody blocks chronic inflammation at a dose of 4 mg/kg, representing a full pharmacodynamic effect in an IL-6tg mouse. The proposed doses in the studies will be 50 mg/kg and 10 mg/kg every 3 days resulting in an approximate 20-fold and 4-fold exposure multiple compared to the average human exposure (C-average). Does the Agency agree with the proposed doses?

FDA Response

Your proposed doses appear acceptable based on the approximate exposure multiple compared to the dose that produces a full pharmacodynamic effect in an IL-6 transgenic mouse.

Discussion: No discussion required for this question.

Question 3. Specifically for the pre-natal/post-natal development study, the current study design includes ongoing assessments through mating of offspring once they are sexually mature. Roche also considered an alternative study design terminating the study with weaning of pups similar to the design usually applied in cynomolgus monkey studies, given the available supportive data from the IL-6 knock-out model. Would the Agency agree the alternative study design is acceptable?

FDA Response

The scientific rationale behind the modification of a nonhuman primate segment III study is based on the duration of time required to reach sexual maturity in this species. Such constraints are not present in the mouse model; therefore, there is not sound rationale for the proposed design modification. Your study design can and should conform to standard Segment III study protocols.

Comments regarding the design of the segment III studies with MR16-1

One of the primary objectives of the required segment III study is to characterize the potential effects of IL-6R blockade on the developing immune system. Therefore, your study design should include an assessment of immune system development in neonates by examining T-, B-, NK cell and neutrophil functions. If developmental immunotoxicity is detected, complete recovery should be demonstrated.

Comments regarding the design of the segment I studies with MR16-1

Since the Division is not aware of information regarding the potential effects of MR16-1 on male reproductive organs and there are reports in the literature to suggest a role of IL-6 in testicular development (Potashnik et al., 2005), to ensure adequate effect of the drug on male reproductive systems and spermatogenesis, the Division recommends that the male mice be treated for at least 60 days before mating unless otherwise justified.

Comments regarding the use of the IL-6 knockout model for Segment I and III studies

Your proposal to conduct dedicated GLP toxicology studies using an IL-6 knockout mouse to augment the proposed fertility and peri- and postnatal development studies using the MR16-1 protein is acceptable and would likely provide useful information to contribute to the understanding of the impact of tocilizumab on fertility and development. However, the utility of the studies to provide useful information for product labeling will be dependent

upon the characterization of the knockout mouse employed. Specifically, the model should be characterized to determine if there is any compensatory expression of other proteins which could complicate the interpretation of the study results and lead to an erroneous conclusion of safety that may not be representative of the clinical blockade of IL-6 at different stages of maturation. The Agency notes that if the MR16-1 studies provide adequate assessments of the potential impact of tocilizumab on fertility and peri- and post-natal development, then studies in the IL-6 knockout mouse would not be required by the Agency.

Discussion: For Segment I reproductive studies, the Sponsor requested clarification regarding the Division's suggestion of 60-day exposure data in male mice in comparison to the ICH guideline recommendation of 28 days and whether the increase in the number of days was a new policy change or specific to this product. The Division stated that, in the absence of data from the repeat dose toxicology study with the murine analog, extrapolations from primate data were not acceptable and recommended prolonging exposure to collect more data that could be effectively interpreted.

For Segment III, the Sponsor asked if the T-cell dependent antibody response and lymphocyte subtyping in the spleen using flow cytometry would be sufficient. The Division asked if any NK cell activity and/or neutrophil function in neonates have been detected. The Sponsor stated that they were exploring the issue with a Contract Research Organization and would perform a complete subtyping in the spleen using the flow cell cytometry. The Division encouraged the Sponsor to submit an overview or summary that would be reviewed for comment. The submission of the data from these nonclinical studies would constitute an adequate response to the CR letter; however, the acceptability of the data would be determined upon review of the resubmission.

The Division asked if there were any other concerns with the antibody other than immunogenicity. The Sponsor stated that there were no other concerns except for the increase in clearance with prolonged exposure of tocilizumab.

Question 6. Roche recognizes that limited animal data currently exist for regulatory decision making and understands that until the requested nonclinical studies are completed, information on certain aspects of the effects of ACTEMRA on reproductive function and postnatal development in animals is incomplete i.e. they can be based only on surrogate data with limited documentation on IL-6 knock-out animals covering the full reproductive cycle and studies of ACTEMRA in monkeys that do not cover the full reproductive cycle.

Roche wants to discuss with the Agency, a proposal and justification for bringing ACTEMRA to market while confirmatory nonclinical studies are completed as postmarketing commitments.

- Roche would like to understand the Agency's concern regarding reproductive function and postnatal development given available nonclinical data and clinical data on pregnancy and outcomes.*

- *Does the Agency agree with Roche's proposal? If the Agency does not agree, what additional elements would the Agency find acceptable to allow ACTEMRA to come to market while the nonclinical studies are completed as post-marketing commitments?*

FDA Response

The available nonclinical data and clinical data on pregnancy, reproductive function, and postnatal effects are not sufficient to support your proposed indication, since the majority of RA patients are women and many are of childbearing potential. Given the severity of the consequences should the currently available information be misleading, we do not agree with your proposal to handle the concerns via labeling alone. Your proposal will need to include an active method of limiting exposure in the population most at risk and justification as to the medical necessity of this medication compared to currently available therapies.

Discussions: The Sponsor requested clarification regarding acceptable "active methods" of limiting exposure, given that no teratogenic effects have been observed with tocilizumab thus far (Sponsor's slide P5). Dr. Rosebraugh reiterated that the nonclinical studies are required for approval, and that the clinical pregnancy outcomes data are limited and insufficient to support approving the product with labeling restrictions alone. The Sponsor would need to provide a strong justification for why the product should be made available prior to the submission and review of the required nonclinical studies (i.e., unmet medical need), and how they would propose to limit its distribution, such as a restricted distribution program similar to Accutane.

Proposed Dosing and Labeling

Question 7. FDA noted in the proposed UPSI provided to Roche on August 28, 2008, that dose was still under discussion within the Agency and in the Complete Response letter dated September 17, 2008, FDA requested additional information on justification for the benefit risk of the 8 mg/kg dose. The Sponsor provided a justification of the 8 mg/kg dose in the Complete Response submission dated September 29, 2008, and proposes the following dose recommendations:

Does the Agency have any comment on the proposed dosing regimen?

FDA Response

While there may be some subpopulations or individuals who would achieve greater benefit from the higher dose, there are also safety concerns that may be dose-related. There appears to be a dose-related increase in the incidence of serious infections when patients were treated with 8 mg/kg as compared with patients treated with 4 mg/kg tocilizumab.

b(4)

Moreover, all GI perforation events occurred in patients taking 8 mg/kg, including 3 patients on tocilizumab 8 mg/kg during the 6-month controlled period of the RA studies compared to 0 patients on either 4 mg/kg tocilizumab or placebo during this same period. Finally, there may be dose-related increase in liver enzyme abnormalities with 8 mg/kg tocilizumab when used in combination with MTX or other DMARDs compared to 4 mg/kg tocilizumab combination therapy. In addition, the increased efficacy associated with the higher dose appears to be primarily driven by the product's effect on the CRP levels. The actual clinical components of the ACR20 demonstrate less of an advantage for the higher dose. Therefore, from a safety standpoint, it may be prudent to recommend a default 4 mg/kg starting dose with increase to 8 mg/kg if needed and as tolerated.

Discussion: The Sponsor sought clarification regarding the Division's recommendation of starting with the 4 mg/kg dose. The Division reiterated that many of the safety concerns (noted in the response above) appear to increase in incidence with the 8 mg/kg dose as compared to 4 mg/kg dose, and since the 4 mg/kg dose was also efficacious, it would be prudent to start at the lower 4 mg/kg dose and increase to 8 mg/kg, if necessary. The Sponsors asked if the dose recommendation would apply to all population groups or primarily the DMARD inadequate population, since they do not have data for 4 mg/kg monotherapy in the methotrexate-naïve RA population. The Division stated that the recommendation was for the DMARD inadequate population, but cautioned that the lack of data for 4 mg/kg monotherapy should not be a reason to recommend a higher starting dose in other RA populations.

Question 8. Does the Agency have any other significant labeling comments not yet communicated to the Sponsor based on the BLA review?

FDA Response

Additional labeling negotiations will occur in the setting of the complete response resubmission cycle for the BLA.

Discussion: No discussion required for this question.

Question 9. Does the Agency have any other clinical efficacy or safety concerns to share with the Sponsor at this time?

FDA Response

No.

Discussion: No discussion required for this question.

Post-Marketing

Question 10. Roche is planning to collect cardiovascular outcomes data in the following planned or ongoing studies included in the proposed list of post-marketing commitments submitted September 29, 2008 in the Complete Response resubmission:

- *Observational cohort studies conducted in the US and EU totaling approximately 5000 patients treated for 5 years*
- *Ongoing long-term extension studies (WA18695, WA18696 & WA17823) totaling approximately 2000-2500 patients treated for 5 years.*
- *T J proposed as a pharmacoepidemiology study to assess short term and potential long term risks including myocardial infarction and stroke.*
- *Surveillance data from the post-marketing experience in Japan.*

b(4)

Can the Agency comment on their expectations for additional cardiovascular outcomes data to be collected as part of post-marketing commitments?

FDA Response

We are concerned that the uncontrolled data proposed will be inadequate to determine whether tocilizumab treatment and the associated lipid abnormalities increase the risk for cardiovascular adverse events; therefore, a cardiovascular outcomes study with an appropriate control group will be necessary. However, we recognize that designing such a study is challenging. One approach you might consider would be to conduct a large simple study comparing the strategy of adding a TNF blocker versus adding tocilizumab onto patients' current regimens. Such a study should be designed with a sample size and duration sufficient to ensure that there are enough events to rule out a moderate increase in risk with tocilizumab.

Discussion: Since there was no apparent increase in cardiovascular adverse events in the Roche clinical trials, and adequate cardiovascular outcomes studies are difficult to conduct due to the very large numbers of patients and lengthy observation period required, and due to confounding as a result of changes in RA therapies as well as concomitant medications such as statins, the Sponsor suggested doing a meta-analysis for the Phase 2 and 3 studies in lieu of performing a cardiovascular outcomes study. They noted recent Agency guidance for one of their diabetes products where a meta-analysis of the Phase 2 and 3 trials was considered to be possibly sufficient, if the analysis demonstrated a relative risk of less than 1.3. Dr. Rosebraugh noted that the trials in diabetes were generally much larger than those for RA. Furthermore, the diabetes trials in question had pre-specified adjudication methods for cardiovascular outcomes, whereas the tocilizumab trials did not. Nonetheless, Dr. Rosebraugh stated that the Sponsor could perform a meta-analysis and present the results to the Agency for further consideration. The Sponsor was advised to submit the meta-analysis of cardiovascular outcomes in the BLA resubmission, keeping in mind that the meta-analysis may be determined to be insufficient, and that a cardiovascular outcomes study would then be required. The Sponsor then asked whether

all-cause mortality would be an adequate endpoint, since few mortality events were noted. Dr. Rosebraugh stated that the Agency would consider a composite endpoint that includes cardiovascular mortality and all-cause mortality, but not all-cause mortality alone.

Question 11. It would be helpful if the Agency commented on any other post-marketing commitment requests?

FDA Response

It is likely that post-marketing requirements will include continuing the ongoing long-term, open-label treatment studies out to 5 years to further assess long-term safety of tocilizumab; a registry with an internal control arm to assess the relative rates of important adverse events including cardiovascular events, malignancies, GI perforation events, clinical hepatotoxic events that may be associated with use of tocilizumab; a controlled trial of the effects of tocilizumab on therapeutic vaccination; and a study in children with polyarticular juvenile idiopathic arthritis (JIA), as per PREA requirements.

Major Points and Action Items for BLA 125276

1. The Sponsor will make changes to the nonclinical protocols and submit for final comment before starting the study.
2. If the Sponsor plans to seek approval of tocilizumab prior to the completion of the required nonclinical studies, they will need to provide strong justification of its medical necessity and a plan for restricted distribution.
3. The Sponsor will discuss with the Division prior to resubmission any outstanding questions regarding the content of the REMS and submit a REMS with all the required components as stated in the November 14, 2008, request letter with the Complete Response resubmission.
4. The Sponsor will consider starting with the 4 mg/kg dose and provide a rationale for not starting at this dose.
5. The Sponsor will perform a meta-analysis as a justification for not performing the cardiovascular outcome study and submit the analysis with the Complete Response resubmission.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Manufacturing and Product Quality
International Compliance Team, HFD-325
10903 New Hampshire Avenue – WO51
Silver Spring, MD 20993

TELEPHONE: (301) 796-3191
FAX: (301) 827-8908

September 16, 2008

To: Sharon Turner-Reinhardt, Regulatory Health Project Manager,
Division of Anesthesia, Analgesia and Rheumatology Products

From: Colleen Hoyt, Compliance Officer, CDER Office of Compliance, Division of
Manufacturing and Product Quality

Thru: Anthony Charity, Acting Team Leader, International Compliance Team (ICT),
Division of Manufacturing and Product Quality

Subj: ACTEMRA® (tocilizumab, MRA, RO4877533) STN 125276/0
Review of Inspectional Observations from 5/21-6/6/08 Prior Approval
Inspection of Chugai Pharmaceutical Manufacturing Corporation (CPMC)

The Office of Compliance has completed the review of firm responses and information provided to the Agency during the September 12, 2008 teleconference and September 15, 2008 regulatory meeting. The Office of Compliance recommendation is to withhold approval of STN 125276/0 pending an adequate response to the following:

- _____ used for the production of ACTEMRA drug substance, specifically, _____

b(4)

We recommend equipment to be appropriately designed and suitable for the operation intended. _____

b(4)

Please submit further information to determine what controls are in place to ensure the dependability of your _____ system used to manufacture ACTEMRA® drug substance.

b(4)

We remain concerned regarding your overall global quality controls. Your ability to maintain an aseptic environment should be continuously evaluated to ensure your ongoing compliance with current good manufacturing practices.

Ripper, Leah W

From: Hoyt, Colleen
Sent: Wednesday, September 17, 2008 12:33 PM
To: Rosebraugh, Curtis
Cc: Friedman, Rick L; Rivera Martinez, Edwin; Randazzo, Giuseppe; Ripper, Leah W; Charity, Anthony; Rappaport, Bob A; Hughes, Patricia; Famulare, Joseph; Turner-Rinehardt, Sharon
Subject: RE: Actemra action
Attachments: OC Recommendation - Chugai ACTEMRA.doc

Attached is the Office of Compliance overall recommendation for BLA 125276/0.

Colleen F. Hoyt
Consumer Safety Officer/DMPQ Biotech Liaison
U.S. Food and Drug Administration
CDER/OC/DMPQ
o - (301) 796-3251
f - (301) 842-8742
colleen.hoyt@fda.hhs.gov

10903 New Hampshire Avenue
WO51-Room 4308
Silver Spring, MD 20993

From: Rosebraugh, Curtis
Sent: Wednesday, September 17, 2008 12:08 PM
To: Friedman, Rick L; Randazzo, Giuseppe; Hoyt, Colleen
Cc: Ripper, Leah W; Rappaport, Bob A; Roca, Rigoberto A; Charity, Anthony; Hughes, Patricia; Rivera Martinez, Edwin; Famulare, Joseph; Turner-Rinehardt, Sharon
Subject: RE: Actemra action

Rick,
Checking on the progress. We need to finalize, where are you guys with your recommendations?

From: Friedman, Rick L
Sent: Tuesday, September 16, 2008 3:43 PM
To: Rosebraugh, Curtis; Randazzo, Giuseppe; Hoyt, Colleen
Cc: Ripper, Leah W; Rappaport, Bob A; Roca, Rigoberto A; Charity, Anthony; Hughes, Patricia; Rivera Martinez, Edwin; Famulare, Joseph
Subject: RE: Actemra action

Curt, Thanks for the update. Can we have until tomorrow at noon?

Giuseppe, please work with Colleen to provide the needed content.

Rick

From: Rosebraugh, Curtis
Sent: Tuesday, September 16, 2008 3:40 PM
To: Roca, Rigoberto A; Friedman, Rick L; Hoyt, Colleen
Cc: Ripper, Leah W; Rappaport, Bob A
Subject: RE: Actemra action

rick and Colleen,
if you have unresolved issues, we need those asap to put into the letter.

Curt

From: Roca, Rigoberto A
Sent: Tuesday, September 16, 2008 3:35 PM
To: Friedman, Rick L; Hoyt, Colleen
Cc: Rosebraugh, Curtis; Ripper, Leah W; Rappaport, Bob A
Subject: Actemra action

Hi Rick and Colleen ,
An update to my update from ~30 minutes ago: we are going to do our best to take our action tomorrow, and it is going to be a CR.

Thanks,
Rigo

From: Roca, Rigoberto A
Sent: Tuesday, September 16, 2008 3:09 PM
To: Hoyt, Colleen
Subject: Re: Actemra's dosing schedule

Hi Colleen,
Nothing new that I am aware of.

Thanks,
Rigo

From: Hoyt, Colleen
To: Roca, Rigoberto A
Sent: Tue Sep 16 13:35:20 2008
Subject: RE: Actemra's dosing schedule

Hi Rigo -

Can you give me an update on your side? I am in the process of completing the review of the box of material submitted yesterday afternoon.

Thanks,

Colleen

From: Roca, Rigoberto A
Sent: Friday, September 12, 2008 4:24 PM
To: Hoyt, Colleen
Subject: Actemra's dosing schedule

Hi Colleen,
The company is proposing a schedule of one dose every month (8 mg/kg).

Thanks,
Rigo

ADRA Rev #1 of Action Package for BLA 125276/0, Actemra (tocilizumab)

Reviewer: Lee Ripper, ADRA, ODE II *JRipper 9/17/08*
Date received: 8/28/08
Date of review: 9/17/08
Date original BLA received: 11/19/07
UF goal date: 9/18/08

Proposed Indication: Reducing signs and symptoms in adults with moderately to severely active RA who had an inadequate response to one or more DMARDs or TNF antagonists or in whom DMARDs are not considered appropriate.

Action type: CR
RPM: Sharon Turner-Rinehardt
Drug Classification: 1S

Debarment Certification: Wording acceptable but certification is not signed; deficiency added to CR letter.

Financial Disclosure: In addition to the FD information included in the original submission, additional FD information was submitted July 23, 2008, as a result of an FDA inspection. Deficiencies added to letter.

Safety Update: Submitted 3/31/08; addressed in MOR

REMS: To be requested in action letter

Clinical Inspection Summary: 8/27/08: Two U.S. and 3 Mexican clinical sites and the applicant were inspected. EIRs for the 3 Mexican sites have not been rec'd; conclusions are based on the 483 and communication with the investigator. Although one Mexican site deemed OAI, data from all sites is considerable acceptable at this time.

DMEDP Review of Proprietary Name: Actemra acceptable 7/29/08

DMEDP Review of Carton and Container Labels: 7/29/08

DRISK Review of PPI: N/A, converted to MedGuide

DDMAC Review: 2/5/08 review of PI and carton and container labeling; *DR letter of labeling comments needs to be added to action package*

DRISK Review of Risk Mgmt Plan: 8/13/08

SEALD Review of PLR: None

CSS: N/A

EA: Categorical exclusion

EER: TB-EER not in package, according to Quality review, Chugai, Utsunomiya, was unacceptable GMP status.

PSC Mtg: N/A

CDTL Review: 8/1/08

P/T section to Paul Brown, review completed 9/16/08

1. The Product Quality review has the correct STN number on the cover sheet and on page 1 of the review but the wrong number in the footer throughout the review. The Quality TL review has the wrong BLA number throughout the review – cover sheet, header, cc block.
3. TB-EER was not received. Action package includes an email dated 9/17/08 and attached memo from Colleen Hoyt in DMPQ.

4. Additional financial disclosure information was submitted midway through the review clock based on comments from an FDA investigator. See comments I added to the CR letter.
5. The DMEPA review says to consult Rik Lostritto about the correct dosage form nomenclature. Rik and I discussed and agreed that the CDER Data Standards Manual terminology should be used. He also recommended adding wording to the effect that the product must be diluted before use. Comments added to action letter.



Our STN: BLA 125276

August 29, 2008

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Attention: Matthew Lamb, Pharm. D.
Director, Global Regulatory Affairs

Dear Dr. Lamb:

Please refer to your pending biologics license application (BLA) dated and received November 19, 2007, for Actemra (tocilizumab).

The Division of Medication Errors Prevention and Analysis (DMEPA), of the Office of Surveillance and Epidemiology, and the Chemistry, Manufacturing and Controls (CMC) reviewer have completed their review of your proposed carton and container labeling. DMEPA has also completed their review of the tradename. We have the following comments and have identified the following deficiencies.

1. PROPRIETARY NAME

DMEPA does not object to the use of the proprietary name Actemra for this product at this time. However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be submitted for review. This name will be re-evaluated 90 days prior to approval.

2. GENERAL LABELING COMMENT

Clarify whether the drug comes in contact with natural rubber or latex. If so, a natural rubber and/or latex caution should be added to the vial, carton and package insert.

3. CARTON LABELING

- a. Add a statement of strength in terms of mg/mL immediately beneath the total drug content for follows:
80 mg/4 mL
(20 mg/mL)

- b. The proprietary name should not be more prominent than the proper name on the vial or carton label. The proper name should be at least half the size or the same size as the trade name or remove the bold from the trade name.
- c. Increase the prominence of the route of administration.
- d. Increase the prominence of the storage requirements in order to ensure this product is refrigerated.
- e. Remove the duplicate statements of strength from the side panel of the container label.
- f. Clarify which is the required barcode on both the carton and vial labels.
- g. Change the background color of the 80 mg/4mL and the 400 mg/20 mL carton and vial labels, as the color makes the strength difficult to read.
- h. The statement “No U.S. Standard of Potency” should be moved to an area with other pertinent information. We recommend moving the expiration date and lot number to the back panel on all single dosage cartons.
- i. Clarify whether “Batch” is the same as the lot number. If so, change “Batch” to Lot.

4. CONTAINER LABELING: Vials

- a. Relocate the route of administration to the principal display panel so that it is apparent when reading the trade and established name and strength. This location will also help minimize the risk of wrong route of administration errors.
- b. Remove the duplicate statements of strength (for example, vial contains 400 mg in 20 mL) from side pane of container label and the principal display panel of the carton labeling.
- c. Increase the prominence of the storage requirement in order to ensure this product is refrigerated.
- d. Add the National Drug Code (NDC) number to the vial label.
- e. See comment 2a, b, c, e, g, f and i.

5. PACKAGE INSERT: DOSAGE AND ADMINISTRATION

- a. Clarify the preparation instructions in terms of amount of sodium chloride to withdraw from the bag or bottle prior to adding the Actemra dose so that a secondary calculation is not required.
- b. Add information regarding whether or not it is necessary to flush the intravenous line before and after the Actemra dose, since it should not be infused concomitantly in the same intravenous line with other drugs.
- c. Clarify whether there are particular infusion bags or bottles in which Actemra should not be diluted. The exceptions should be listed in lieu of the list in its entirety.

We are providing these comments before completing our review of your entire application to give you advance notice of labeling issues that we have identified. These comments are subject to change as we complete the review of your application. If you respond, we may or may not consider your response before taking a complete action on your application. If we determine that your response constitutes a major amendment, we will notify you of this decision in writing. We are continuing to review the remaining sections of your application.

If you have any questions, call Sharon Turner-Rinehardt, Regulatory Health Project Manager, at (301) 796-2254.

Sincerely,



Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Turner-Rinehardt, Sharon

From: Turner-Rinehardt, Sharon
Sent: Thursday, August 07, 2008 2:27 PM
To: 'Krumholz, Stephanie'
Cc: 'Lamb, Matthew'
Subject: BLA 125276 Tocilizumab: Information Request- Hepatobiliary data for the Hy's Law Case Discussed at the Advisory Committee Meeting

Importance: High

Dear Stephanie,

I am requesting the following data for the Hy's law case discussed at the Advisory Committee meeting:

1. Provide the data for that patient from the lab at which the tests were performed, along with the normal ranges for the women at that laboratory (include data from all available sampling dates).
2. Include all bilirubin values; include direct bilirubin as well as total bilirubin and indirect bilirubin. Also, provide the corresponding values for AST, ALT, and alkaline phosphatase in the same data.

I ask that you provide this information by 2pm, tomorrow (Friday), August 8, 2008. If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Phone: (301) 796-2254
Fax: (301) 796-9722/9723
Email: sharon.turner-rinehardt@fda.hhs.gov

Turner-Rinehardt, Sharon

From: Turner-Rinehardt, Sharon
Sent: Sunday, August 03, 2008 6:03 PM
To: 'Lamb, Matthew'
Subject: BLA 125276 Tocilizumab: CMC Information Request

Importance: High

Dear Matthew,
I have the following CMC information request for tocilizumab.

1. A number of your DS/DP release assays appear to be qualified rather than validated (i.e. pH, appearance). Provide a rationale for not fully validating these assays.
2. Some of your IEC release test criteria is based on several peaks. Those that do have release criteria do not add up to 100%, though the release criteria for _____ . Provide a rationale on your decision to have such vague release specifications. **b(4)**
3. In your comparison of registration batches between DS and DP using IEC, it is noted that the peak areas for ' _____
↑ Provide some indication as to why these
changes are occurring between DS and DP, and how the shift in one affects the other. **b(4)**

I ask that you provide me a response by August 8, 2008. If you have any questions, please contact me.

Regards,
Sharon

Turner-Rinehardt, Sharon

From: Turner-Rinehardt, Sharon
Sent: Sunday, August 03, 2008 6:26 PM
To: 'Lamb, Matthew'
Subject: BLA 125276 Tocilizumab: Clinical Information Request

Importance: High

Dear Matthew,
I have the following clinical information request for tocilizumab.

1. For patients treated with tocilizumab who experienced grade 3 and 4 abnormalities in absolute neutrophil count, platelets, and ALT, identify at what time points these events occurred during treatment. Were there time points after which grade 3 and grade 4 elevations did not occur if they were not observed previously?
2. For the individual patients on tocilizumab treatment who experienced changes in LDL categories (your advisory committee slide P106), at what time point were these changes noted? Were there time points after which these changes did not occur, if they were not observed previously?
3. For the 180 patients you noted who have been prescribed concomitant –statin therapy, identify which statins were used and how many patients were using each particular statin.

I ask that you provide me a response by 5 pm, Tuesday, August 6, 2008. If you have any questions, please contact me.

Regards,
Sharon

Turner-Rinehardt, Sharon

From: Turner-Rinehardt, Sharon
Sent: Monday, July 14, 2008 12:49 PM
To: 'Krumholz, Stephanie'
Cc: Lamb, Matthew {PDR~Nuttley}
Subject: BLA 125276 Tocilizumab Information Request
Importance: High

Dear Stephanie,

Submit information on patient ID numbers used in NONMEM analysis who had Positive anti-tocilizumab HAHAAs and negative anti-tocilizumab HAHAAs. Also, submit information in SAS dataset format including patient numbers, related PK, anti-tocilizumab antibody status and neutralizing anti-tocilizumab antibody status during the course of the studies. I ask that you provide a response by 5 pm (EST) Tuesday, July 15, 2008.

If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager

Division of Anesthesia, Analgesia and Rheumatology Products

Phone: (301) 796-2254

Fax: (301) 796-9722/9723

Email: sharon.turner-rinehardt@fda.hhs.gov

8/7/2008

Turner-Rinehardt, Sharon

From: Turner-Rinehardt, Sharon
Sent: Monday, July 07, 2008 3:50 PM
To: 'Lamb, Matthew'
Subject: BLA 125276 Tocilizumab Information Request

Importance: High

Attachments: BLA 125276 Tocilizumab_Half-life Question.pdf

Dear Matthew,

We have an follow-up question regarding your response to the reported effective half-life of tocilizumab. Please see the attached WORD document with our comment and question. I ask that you provide a response by 5 pm (EST) Tuesday, July 8, 2008.



BLA 125276
Tocilizumab_Half-li..

If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22 Room 3191
Silver Spring, MD 20993-0002
Phone: (301) 796-2254
Fax: (301) 796-9722/9723
Email: sharon.turner-rinehardt@fda.hhs.gov

1 Page(s) Withheld

 ✓ Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Turner-Rinehardt, Sharon

From: Turner-Rinehardt, Sharon
Sent: Thursday, June 26, 2008 3:41 PM
To: 'Lamb, Matthew'
Subject: BLA 125276 Tocilizumab Information Request #2

Importance: High

Dear Matthew,
I have an additional information request.

Submit the dataset which has the post-hoc estimates of PK parameters from the basic PK model with all covariates evaluated in GAM analysis. The submitted dataset has only the GAM identified covariates and does not have information on covariates not identified by GAM analysis.

I ask that you provide this information along with the request below by Monday, June 30, 2008. If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22 Room 3191
Silver Spring, MD 20993-0002
Phone: (301) 796-2254
Fax: (301) 796-9722/9723
Email: sharon.turner-rinehardt@fda.hhs.gov

From: Turner-Rinehardt, Sharon
Sent: Thursday, June 26, 2008 2:22 PM
To: 'Lamb, Matthew'
Subject: BLA 125276 Tocilizumab Information Request
Importance: High

Dear Matthew,

I have the following information request to BLA 125276 Tocilizumab:

Submit the dataset code used to estimate the reported effective half-life of Tocilizumab.

I ask that you submit this information by Monday, June 30, 2008. If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22 Room 3191

Turner-Rinehardt, Sharon

From: Turner-Rinehardt, Sharon
Sent: Thursday, June 26, 2008 2:22 PM
To: 'Lamb, Matthew'
Subject: BLA 125276 Tocilizumab Information Request

Importance: High

Dear Matthew,

I have the following information request to BLA 125276 Tocilizumab:

Submit the dataset code used to estimate the reported effective half-life of Tocilizumab.

I ask that you submit this information by Monday, June 30, 2008. If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22 Room 3191
Silver Spring, MD 20993-0002
Phone: (301) 796-2254
Fax: (301) 796-9722/9723
Email: sharon.turner-rinehardt@fda.hhs.gov

Turner-Rinehardt, Sharon

From: Turner-Rinehardt, Sharon
Sent: Tuesday, June 03, 2008 3:01 PM
To: Lamb, Matthew {PDR~Nutley}
Subject: BLA 125276: Information Request

Importance: High

Attachments: Picture (Enhanced Metafile)

Dear Matthew,

I am requesting information for the attached table. I ask that you complete the table based on the information your immunogenicity reports. I ask that you submit this completed table to me by June 13, 2008. If you have any questions, please contact me.

Summary of Immunogenicity Testing Results					
	6 month pooled safety population				
	Placebo + DMARD	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD	TCZ 8mg/kg
Safety Population					
Tested in Screening Assay					
Tested after Escape					
Positive Screening/Confirmation Assays*					
Positive neutralizing antibody					
Number of patients with event-driven testing					
Patients with event-driven testing who tested positive					
positive screening/confirmation					
positive neutralizing					
Antibody positive patients with events causing withdrawal					
positive screening/confirmation					
positive neutralizing					
Patients with LoE testing					
Antibody positive patients withdrawing due to LoE					
positive screening/confirmation					
positive neutralizing					
*Repeatedly positive or at last testing on study					

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Phone: (301) 796-2254
Fax: (301) 796-9722/9723
Email: sharon.turner-rinehardt@fda.hhs.gov

Turner-Rinehardt, Sharon

From: Turner-Rinehardt, Sharon
Sent: Friday, April 18, 2008 12:16 PM
To: 'Lamb, Matthew'
Subject: BLA 125276 Tocilizumab Information Request

Importance: High

Dear Matthew,

For Study WA17824, provide the SAS program to calculate the treatment differences (and corresponding 95% confidence intervals) in the ACR20, ACR50, and ACR70 response rates adjusting for stratification applied at randomization. I ask that you provide this information by April 28, 2008. If you have any questions, please contact me.

Regards,
Sharon

Turner-Rinehardt, Sharon

From: Turner-Rinehardt, Sharon
Sent: Wednesday, April 02, 2008 6:27 PM
To: 'Lamb, Matthew'
Subject: FW: BLA 125276 Tocilizumab Information Request
Importance: High

Dear Matthew,

Please provide a response to the following requests for information by April 25 , 2008.

1. Specify whether a CRO (contract research organization) conducted any of the pivotal RA trials, and if so, which trials? Also,
 - a. For each of the 5 pivotal studies, specify how studies were monitored; how quality control was handled.
 - b. For each of the 5 pivotal studies, specify how investigators were trained.
 - c. Specify whether all patient records are available and whether you have verified this in a sample of patients.

2. For malignancy incidence rates in the global tocilizumab RA program compared to the SEER database, provide a breakdown of malignancies by age group, compared to the malignancy rates in that same age group in the SEER database.
 - a. For example:

Organ class	No. reported	observed per 100 pt-yr	Expected male	Expected female	Expected combined
Age 50-54					
all sites	44	0.82	0.58	0.67	0.65
GI	12	0.22	0.13	0.07	0.08
Lung	6	0.11	0.06	0.04	0.05
Female reproductive	7	0.13	-	0.26	0.21
Urogenital	5	0.09	0.17	0.02	0.05
Lymphoma	2	0.04	0.03	0.02	0.02
Age 55-59					
all sites					
GI					
Lung					
Female reproductive			-		
Urogenital					
Lymphoma					
Age 60-64					

If you have any questions, please contact me.

Regards,

8/7/2008

Turner-Rinehardt, Sharon

From: Turner-Rinehardt, Sharon
Sent: Tuesday, March 18, 2008 4:10 PM
To: 'Lamb, Matthew'
Subject: BLA 125276 Tocilizumab Information Request
Importance: High

Dear Matthew,

Please provide a response to the following request for information by 3pm Thursday, April 3, 2008.

1. GI Perforations:

- For all GI perforations in the TCZ global safety database please provide the following information in tabular format (see below):

No. of TCZ infusions prior to event	Latency (Time of diagnosis relative to first TCZ infusion)	GI event (type and location of perf)	Pt. number/ MCN number	Study	Indication (RA, JIA, Castleman, multiple myeloma)	Treatment (TCZ dose) May include relevant concom. meds.	Outcome (death, withdrawal from study, continued treatment)
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If patients experienced an event while on an open-label extension study, count TCZ infusions from first dose in the controlled study and annotate whether the identity of the treatment in the controlled period remains blinded or is confirmed as TCZ.

- Provide a similar table with separate events that may have begun with a GI perforation, e.g., colovesical fistula, intra-abdominal abscess, if the patient has not already been identified in the GI perforation table.

2. Provide a line-listing of all patients in the Roche and Chugai RA trials (including long-term extensions) who experienced transaminase elevations ≥ 3 x ULN **with** bilirubin elevation ≥ 2 x ULN. For these patients also annotate associated alkaline phosphatase level, relevant clinical outcomes (e.g. hospitalization, liver biopsy, liver failure), temporal relationships to TCZ treatment (onset, discontinuation, or re-exposure), and relevant concomitant meds.

3. Provide additional and/or updated information (including study, patient number and MCN number of safety report, temporal relationship to TCZ treatment, etiologies evaluated and ruled out, etc.) in narrative format regarding the following patients with possible demyelinating AE:

- 73 year old female in WA17823 with bilateral optic neuritis following 22 doses of study medication. (section 6.1.2 of Module 2.7.4, page 239)
- 64 year old male in an open-label extension with MRI white matter lesions (section 6.1.2 of Module 2.7.4, page 240)
- 72 year female RA patient, in MRA214JP and MRA216JP who developed MRI white matter lesions and progressive cognitive dysfunction starting in November 2007, after approximately 44 doses of TCZ. (MCN 541656)
- 68 year old female (MCN 462192) with chronic idiopathic demyelinating polyradiculoneuropathy
- Any additional cases reported to the tocilizumab global safety database.

If you have any questions, please contact me.

Regards,
 Sharon

8/7/2008



February 1, 2008

FILING COMMUNICATION

Our STN: BLA 125276/0

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Attention: Matthew Lamb, Pharm. D.
Director, Global Regulatory Affairs

Dear Dr. Lamb:

This letter is in regard to your biologics license application (BLA) submitted and received November 19, 2007, under section 351 of the Public Health Service Act, Actemra (tocilizumab).

We also refer to your submissions dated December 20, 2007 and January 4 and 10, 2008.

We have completed an initial review of your application to determine its acceptability for filing. Under 21 CFR 601.2(a), we filed your application on January 18, 2008. The review classification for this application is Standard. Therefore, the user fee goal date is September 18, 2008. 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.

During our filing review of your application, we have identified the following potential review issues and we request that you submit the following information.

1. Provide the coding dictionary used for mapping investigator verbatim terms to preferred terms. If submitted as a PDF document, submit as verbatim to preferred term and preferred to verbatim term.
2. Rename all the variables in the revised datasets submitted January 10, 2008, for the five pivotal studies, according to their actual test names; for example, rename ENS00001 to ACR20LOCF1. Resubmit the new datasets and provide the data definitions.
3. Clarify which variable was used for the primary analysis in each of the five pivotal studies.
4. Submit the certificates of analysis in English for the batches used in the nonclinical studies.

5. Provide a status update as to when the study reports for the two ongoing clinical pharmacology studies, WP18663 and BP19461 Part 2, will be available.

In addition, we have the following comments regarding the PLR labeling submitted with this BLA. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

1. Delete the modifier “RA” from the Highlights **INDICATION AND USAGE** and **DOSAGE AND ADMINISTRATION** sections.
2. Delete dash lines from the Highlights **INDICATION AND USAGE** and **DOSAGE AND ADMINISTRATION** sections.
3. Delete underline from references throughout entire label; for example, *[see Warnings and Precautions (5.4)]* and not *[see Warnings and Precautions (5.4)]*. See “Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements” at <http://www.fda.gov/cder/guidance/6005dft.htm>].
4. The first statement under Highlights and Full Prescribing Information (FPI): **DOSAGE AND ADMINISTRATION** section, “ACTEMRA is administered by intravenous infusion.” should be deleted due to redundancy.
5. Indent all paragraphs under headings and subheadings throughout the FPI. For overall formatting, refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for examples of labeling in the new format.
6. Under FPI: **ADVERSE REACTIONS**, subsection 6.1, remove the bold font from the subheadings (Infections, Infusion Reactions, Laboratory Tests, and Other Adverse Reactions), and consider using italics or underline to distinguish subheadings.
7. Under FPI: **CLINICAL PHARMACOLOGY**, subsection 12.3, remove the bold font from the subheadings (Distribution, Elimination, Pharmacokinetics in Special Populations, Hepatic Impairment, and Renal Impairment) and consider using italics or underline to distinguish subheadings.

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

application. Following a review of the application, we will advise you in writing of any action we have taken and request additional information if needed.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients less than 2 years of age. We also acknowledge receipt of your request for a deferral of pediatric studies for this application for pediatric patients 2 to 16 years of age.

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

If you have any questions, call Sharon Turner-Rinehardt, Regulatory Health Project Manager, at (301) 796-2254.

Sincerely,

A handwritten signature in black ink, appearing to read "Bob Rappaport", with a long horizontal line extending to the right.

Bob Rappaport, M.D.

Director

Division of Anesthesia, Analgesia and
Rheumatology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

Turner-Rinehardt, Sharon

From: Turner-Rinehardt, Sharon
Sent: Thursday, January 03, 2008 1:12 PM
To: 'Lamb, Matthew'
Subject: BLA 125276 Tocilizumab Request for Change to Lab Datasets

Importance: High

Dear Matthew,

Provide the integrated lab datasets in a format broken down by type of labs; for example, an integrated lab chemistry dataset, an integrated hematology dataset, etc., instead of organized by subject ID as in the original submission. I ask that you include these datasets in your January 11, 2008 submission of the efficacy datasets. If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Phone: (301) 796-2254
Fax: (301) 796-9722/9723
Email: sharon.turner-rinehardt@fda.hhs.gov

Turner-Rinehardt, Sharon

From: Turner-Rinehardt, Sharon
Sent: Tuesday, December 18, 2007 3:35 PM
To: 'Lamb, Matthew'
Subject: RE: BLA 125276 Tocilizumab - TC Follow-up: Statistical Request

Matthew,
Please find below the statistical request discussed in yesterday's teleconference. I will provide a response to the eSub question in a separate email.

In Study WA17822, you have three datasets for efficacy.

1. Efficacy core components
2. Efficacy endpoints (EEN.xpt)
3. Efficacy endpoints (EENPS.xpt)

Included in the EEN dataset is the unique subject ID, the visit number, the actual treatment sequence, the reason for non-ACR20 response, the test code, the baseline result and the actual result by visit. The structure of the datasets for EEN and EENPS are the same. That is, each row consists of patient ID, each of their visits and their derived test and scores for that visit. This data is provided in vertical format. The total number of rows for WA17822 (EEN.xpt) is 124,080.

In the variable 'Test', you included more than 30 test codes. This includes the raw and LOCF-derived ACR20/50/70/90 responders, AUC, ACRN, and DAS scores (including EUL, LDA, REM scores), as well as Time to ACR response. For ease of review, provide these variables in separate columns. This will yield 6,220 (622 subjects * 10 visits) lines/rows instead of the 124,080.

Aside from NRSPREAS and CENSREAS, include four new columns for disposition of subjects and their reason for dropout: (1) whether subject Completed or Withdrew from the Study; (2) reason for withdrawal (i.e. AE, Death, Insufficient Therapeutic Response, etc.); (3) last visit before they discontinued from the study; and (4) whether subject entered escape or not.

In the core datasets (ECO_1.xpt), separate the datasets by core components instead of by subject ID. For example, create a separate dataset for 'swollen joint counts', 'tender joint counts', 'HAQ', and others.

If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Phone: (301) 796-2254
Fax: (301) 796-9722/9723
Email: sharon.turner-rinehardt@fda.hhs.gov

8/7/2008

Turner-Rinehardt, Sharon

From: Turner-Rinehardt, Sharon
Sent: Monday, December 17, 2007 12:53 PM
To: 'Lamb, Matthew'
Subject: BLA 125276 Tocilizumab CMC Items for Teleconference
Importance: High

Dear Matthew,

Here are the CMC items regarding the submission we would like to discuss this afternoon at the teleconference. If you could provide some responses for the teleconference that would be good; however, if timing doesn't permit a response for the teleconference then we will establish an adequate date for the responses.

CMC Items for Discussion:

1. We note that summaries are provided for the methods validation of assays used in the characterization and QC testing of tocilizumab rather than the actual validation reports. If these analytical methods validation reports are currently contained within the BLA, describe the location of the reports. If they have not been submitted with the BLA, provide copies of these reports to the BLA as soon as possible to allow a timely review. If translations are required, provide the translated reports available for review during the inspection.
2. We note that for sterility, and mycoplasma testing you have used standard USP, Ph Eur., or Ph Japan criteria rather than methods specified in 21 CFR 610.12 (sterility) and 21 CFR 610.30 (mycoplasma). 21 CFR 610.9 allows use of alternate tests but requires evidence that the modified method provides assurances of the safety, purity, potency, and effectiveness of the biological product equal to or greater than the methods in 21 CFR. If these studies have been performed, provide them to the BLA. If they have not been performed, initiate these validation studies and submit the results to the BLA for review as soon as possible.
3. We also note that 21 CFR 610.13 (b) requires the rabbit pyrogen test for licensed material. We accept endotoxin testing (LAL gel clot or chromogenic testing) in lieu of rabbit pyrogen testing provided that the endotoxin assay has been validated against the rabbit pyrogen test. Initiate this validation study (if you have not already done so) and submit the results to the BLA for review as soon as possible.

If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt

Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Phone: (301) 796-2254
Fax: (301) 796-9722/9723
Email: sharon.turner-rinehardt@fda.hhs.gov

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CDER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (<http://www.fda.gov/cber/regsopp/8404.htm>). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see <http://www.fda.gov/cber/ich/ichguid.htm>).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications. ~~You cannot have multiple indications under supplement submissions. If the sponsor submits multiple indications under a supplement, you must unbundle the submission.~~

CDER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125276/0 Product: Tocilizumab Applicant: Hoffam La-Roche

Final Review Designation (circle one): XStandard Priority

Submission Format (circle all that apply): Paper Electronic XCombination

Submission organization (circle one): Traditional XCTD

Filing Meeting: Date December 11, 2007

Committee Recommendation (circle one): File RTF

RPM: Sharon Turner-Kinelandt 12-3-07
(signature/date)

Attachments:

- Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
 - Part A – RPM
 - ____ Part B – Product/CMC/Facility Reviewer(s): _____
 - ____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____
 - ____ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers _____
- Memo of Filing Meeting

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	<input checked="" type="radio"/> Y N	
Form 356h completed	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> If foreign applicant, US Agent signature.	Y N	
Comprehensive Table of Contents	<input checked="" type="radio"/> Y N	
Debarment Certification with correct wording (see * below)	<input checked="" type="radio"/> Y N	
User Fee Cover Sheet	<input checked="" type="radio"/> Y N	
User Fee payment received	Y N	
Financial certification &/or disclosure information	<input checked="" type="radio"/> Y N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	<input checked="" type="radio"/> Y N	
Pediatric rule: study, waiver, or deferral	<input checked="" type="radio"/> Y N	
Labeling:	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> PI –non-annotated	Y N	
<input type="checkbox"/> PI –annotated	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> PI (electronic)	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> Medication Guide	Y N	
<input type="checkbox"/> Patient Insert	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> package and container	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> diluent	Y N	
<input type="checkbox"/> other components	Y N	
<input type="checkbox"/> established name (e.g. USAN)	Y N	
<input type="checkbox"/> proprietary name (for review)	<input checked="" type="radio"/> Y N	

* The Debarment Certification must have correct wording, e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,..."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> English (or translated into English)	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> summary reports reference the location of individual data and	<input checked="" type="radio"/> Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
records <input type="checkbox"/> protocols for clinical trials present <input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y N Y N	
companion application received if a shared or divided manufacturing arrangement	Y N	
if CMC supplement: <input type="checkbox"/> description and results of studies performed to evaluate the change <input type="checkbox"/> relevant validation protocols <input type="checkbox"/> list of relevant SOPs	Y N Y N Y N	
if clinical supplement: <input type="checkbox"/> changes in labeling clearly highlighted <input type="checkbox"/> data to support all label changes <input type="checkbox"/> all required electronic components, including electronic datasets (e.g. SAS)	Y N Y N Y N	
if electronic submission: <input type="checkbox"/> required paper documents (e.g. forms and certifications) submitted	Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?
 If yes, review committee informed? _____

Does this submission relate to an outstanding PMC? No

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: _____
- Dates: 7-29-08

Recommendation (circle one): File RTF

RPM Signature: Sharon Lums-Lindhart Branch Chief concurrence: _____



BLA ACKNOWLEDGEMENT

Our STN: BLA 125276/0

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

NOV 29 2007

Attention: Matthew Lamb, Pharm. D.
Director, Global Regulatory Affairs

Dear Dr. Lamb:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following:

Name of Biological Product: Actemra (tocilizumab)

Date of Application: November 19, 2007

Date of Receipt: November 19, 2007

Our Submission Tracking Number (STN): BLA 125276/0

Proposed Use: For the treatment of adult onset rheumatoid arthritis

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

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

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

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

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

Sincerely,



Sharon Turner-Rinehardt
Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 11972

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

10/9/07

Attention: Matthew W. Lamb, Pharm. D.
Director, Global Regulatory Affairs

Dear Dr. Lamb:

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

Attached are the Division's responses to the questions from your meeting package for our upcoming meeting, scheduled for October 12, 2007, to discuss your BLA submission for tocilizumab for the treatment of adult onset rheumatoid arthritis. Your questions are in italics and the Division's responses are in bold.

The previously agreed upon time is still set aside to meet with you, but, if you would like to either cancel the meeting, because you feel all your questions have been answered to your satisfaction, or re-focus the meeting (i.e., only focus on items which you feel require additional clarification), that would be acceptable to the Division as well. Alternatively, you can change the format of the meeting from face-to-face to teleconference. If you decide to change the format of the meeting, please contact us promptly by phone or e-mail.

We will be happy to provide clarification on any of the Division's responses, but **WILL NOT entertain any NEW questions, topics or review additional data** (there is simply not enough time prior to the meeting for the team to review such materials). Please let me know if you would like to change anything about our forthcoming meeting.

If you have any questions, please call me at 301-796-1175.

Sincerely,

{See appended electronic signature page}

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

SPONSOR MEETING AGENDA

MEETING DATE: September 12, 2007
TIME: 11 AM
LOCATION: 10903 New Hampshire Avenue; Silver Spring, MD 20903; Building 22; Conference Room 1313
APPLICATION: IND 11972
APPLICATION STATUS: Active
PRODUCT: tocilizumab
INDICATION: Rheumatoid Arthritis
SPONSOR: Hoffmann-La Roche Inc.
TYPE OF MEETING: pre-BLA
MEETING CHAIR: Jeff Siegel, MD, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
MEETING RECORDER: Lisa Basham, Regulatory Project Manager

FDA Attendees	Title
Bob Rappaport, MD	Division Director
Rigoberto Roca, MD	Deputy Division Director
Jeffrey Siegel, MD	Clinical Team Leader, Rheumatology
Sarah Okada, MD	Clinical Team Leader, Rheumatology
Suresh Doddapaneni, PhD	Team Leader, Clinical Pharmacology
Dan Mellon, PhD	Supervisory Pharmacologist
Dionne Price, PhD	Team Leader, Statistics
Marjorie Shapiro, PhD	Chief, Laboratory of Molecular and Developmental Immunology (LMDI)
Sarah Cochran, MD	Clinical Reviewer
Srikanth Nallani, PhD	Clinical Pharmacology-Reviewer
Mamata De, PhD	Preclinical Pharmacology/Toxicology Reviewer
Katherine Meaker, PhD	Statistics Reviewer
Gerald Feldman, PhD	Senior Investigator, LMDI
Michelle Clark-Stuart, MGA/MIS, MT (ASCP)	Acting Team Leader, OC, DMPQ
Bo Chi, PhD	Microbiologist, OC, DMPQ, TFRB
Lisa Basham, MS	Regulatory Project Manager
Hoffman La-Roche Inc. Attendees	Title
Dr. Matthew Lamb	Regulatory Affairs, Global Regulatory Leader
Ms. Robin Conrad	Regulatory Affairs
Dr. Cindy Dinella	Regulatory Affairs
Mr. Philip Johnson	Regulatory Affairs
Ms. Deborah Savuto	Regulatory Affairs - CMC
Dr. Akiko Koga	Analytical Development - Chugal
Mr. Tetsuya Kawakami	Regulatory Affairs, CMC - Chugai
Dr. Thasia Woodworth	Clinical Science Leader
Dr. Elena Fischeleva	Clinical Science
Dr. Claire Davies	Clinical Science

Ms. Barbara Leishman	Clinical Science
Dr. Penelope Ward	Clinical Science, Therapeutic Area Expert
Dr. John Leff	Clinical Development Head – Inflammation
Dr. Kenneth Bahrt	Global Medical Director – Autoimmunity
Dr. Phil Watson	Drug Safety
Dr. Susan Grange	Clinical Pharmacologist
Dr. Emma Alecock	Statistician
Dr. Michael Winter	Nonclinical Pharmacology/Toxicology
Dr. Donald MacLean	Life Science Leader
Dr. Stephen Smolinski	Marketing Director

Question 1: Roche believes that the clinical data as described herein, are sufficient to support the submission of a BLA for tocilizumab for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis. Given the efficacy and safety data presented in Appendix 2, the sponsor considers that the recommended dose of tocilizumab should be 8 mg/kg IV (either as monotherapy or in combination with methotrexate or other DMARDs) every 4 weeks.

1a. Does the Agency have any comments on the planned submission and the contents of the package to support the proposed indication?

FDA Response:

The planned submission will contain 24 week safety and efficacy data from 5 pivotal trials: WA17822, WA17824, WA18062, WA18063, and WA17823 (6-month interim data). In addition to individual study reports, you propose to pool efficacy data by treatment groups for WA17822, WA17823 and WA18063, but keep displays for WA18062 and WA17824 separate due to differences in study populations. For pooled analyses of safety, 6-month data for all 5 studies will be pooled by treatment groups. These proposals are acceptable.

Your submission should also contain the following:

- a. event per patient-time exposure tables for adverse events of interest, e.g., stroke, MI, GI perforations, serious infections, and malignancy, for placebo vs. tocilizumab treatment groups;
- b. event per patient-time exposure tables for adverse events of interest for placebo vs. tocilizumab groups, broken down by 6-month intervals (0-6 months, 6-12 months, 12-18 months, etc.); and
- c. a comparison of standardized incidence ratios (SIR) of malignancy for the placebo vs. tocilizumab treatment groups with rates in the SEER (Surveillance Epidemiology and End Results) database.

1b. Does the Agency have any comments concerning the sponsor's recommendations for the dose regimen?

FDA Response:

Based on the summary information in the briefing package, the dose and regimen selected (8 mg/kg every 4 weeks) appear reasonable. As you have noted in Appendix 3 (Summary of FDA feedback), the BLA should include an analysis of safety and efficacy by body weight and body mass index (BMI). This analysis should include a rationale for why a lower dose regimen would not be necessary for patients receiving high total doses when dosed by weight (i.e., patients with high body weight/BMI).

1c. Does the Agency have any comments on the safety profile of tocilizumab as described in Appendix 2 and the data provided to date on the gastrointestinal events, stroke and hypertension summaries which have been submitted to date?

FDA Response:

The analyses provided thus far have been the types of analyses sought by the Division in order to assess the risk:benefit of tocilizumab treatment. Based on the data submitted to the IND thus far on GI events, stroke and hypertension, the Division determined that the risk:benefit ratio of tocilizumab favored continued study of tocilizumab under the IND and did not warrant additional action. Conclusions regarding the safety profile and risk:benefit ratio of tocilizumab in RA will be determined upon review of the BLA.

Question 2: Roche will submit a Risk Management Plan in Item 3 of the BLA, which will focus on the identified and potential risks for tocilizumab and a plan for managing those risks via labeling and pharmacovigilance activities. Does the Agency have any comment on the preliminary aspects of the Risk Management Plan?

FDA Response:

As described in the briefing package, your proposed risk management plan will entail professional and patient labeling and other pharmacovigilance measures not yet specified, based on:

- identifying patient subgroups or issues where there may be insufficient information available for an evaluation of risk via the adult RA clinical trial program;
- assessing the clinical trial safety database for potential risks to the RA population in general or in particular subgroups;

- **characterization of increased risks in the adult RA population due to underlying disease, co-morbidities or concomitant medications; and**
- **considerations related to potential risks which may not have been seen in the tocilizumab clinical development program but may have been identified for other biologic DMARDs used in adult RA.**

You have also mentioned that you are in the process of evaluating designs for potential patient registry programs.

Based on the summary of the safety data described in the briefing package, your current plans appear to be acceptable. However, additional risk management activities or a RiskMAP may be required if review of the data reveals safety concerns that would be better addressed by such measures.

Refer also to the additional comments from the Office of Surveillance and Epidemiology (OSE) under the response to Question 12, below.

Question 3: Roche intends to provide a 4-month safety update with safety data from Roche studies as described below, with a clinical cut-off date of October 22, 2007. Is this proposal acceptable to the Agency?

FDA Response:

The 4-month safety update will be comprised of data from the 2 long-term extensions studies, WA18695 and WA18696, along with data from transition phase patients from the 2-year study WA17824 (patients with >50% improvement in tender/swollen joint counts at Week 24 and who choose to remain blinded after Week 24). This proposal is acceptable. However, significantly more patients with ≥ 12 and ≥ 18 months exposure will be included in this update (700 to 800 additional patients in each of these exposure categories). In case the Division determines further analyses of these data are indicated, it would facilitate the process to have updated safety datasets; therefore, we request you provide updated safety datasets with the 4-month safety update. You should also provide updated event per patient-time exposure tables (including those broken down by 6-month intervals, see response to Question 1) for adverse events of interest, e.g., stroke, MI, GI perforations, serious infections, and malignancy.

Question 4: Does the Agency agree with the planned content of the Non-Clinical section of the BLA?

FDA Response:

Your proposed BLA submission does not contain any data regarding the potential pre- and post-natal developmental effects of the drug product (segment III). You should submit studies in either the monkey or a surrogate model to address such effects or provide clear rationale for why such studies are not possible.

Although carcinogenicity assessment may not be feasible for this product, your BLA should include a detailed discussion of why such studies are not possible. In addition, your BLA should discuss the available information you have collected via your own studies as well as those published in the literature regarding the potential impact of IL-6 neutralization on tumor surveillance and tumor development. You should also specifically state how you intend to address the carcinogenicity section of your product labeling.

Question 5: Does the Agency agree with the planned content of the Clinical Pharmacology section of the BLA?

FDA Response:

The proposed layout for submission and description of Biopharmaceutics and Clinical Pharmacology study reports appears reasonable. However, to facilitate ease of review of the Clinical Pharmacology data, please note the following;

1. **TQT data:** In order for the QT –Integrated Review Team (IRT) to review a Thorough QT Study Report, and to accelerate the review process, the following items should be submitted:
 - a. Electronic or hard copy of the study report
 - b. Electronic or hard copy of the clinical protocol
 - c. Electronic or hard copy of the Investigator’s Brochure
 - d. Annotated CRF
 - e. Copies of the study reports for any other clinical QT study for this product that has been performed
 - f. A Define file which describes the contents of the electronic data sets
 - g. Electronic data sets as SAS transport files
 - h. SAS code for the primary statistical analysis

- i. **Data set whose QT/QTc values are the average of the replicates**
- j. **Statistical programs with analysis datasets that were used to analyze the study endpoints as well as to perform exposure-response analysis**
- k. **Narrative summaries and case report forms for any of the following that occur in this thorough QT study:**
 - (1). **Deaths**
 - (2). **Serious adverse events**
 - (3). **Episodes of ventricular tachycardia or fibrillation**
 - (4). **Episodes of syncope**
 - (5). **Episodes of seizure**
 - (6). **Adverse events resulting in the subject discontinuing from the study**
- l. **ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)**
- m. **A completed Highlights of Clinical Pharmacology Table (Table 1. shown below) – to be provided by sponsor.**

Please submit all data sets in CDISC SDTM format if possible.

Table 1. Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t½	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

2. Population PK/PD data:

The general approach to PK data analyses appears acceptable. If possible, apply the structural model developed from PK analysis of intensive sampling data from Phase 1/2 PK studies in RA/healthy subjects to the Phase 3 PK data in your analysis.

Submit the following datasets to support the population PK analysis:

- a. All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- b. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- c. A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports, submit individual plots for a representative number of subjects, in addition to the standard model diagnostic plots. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, SC route clearance should be presented as CL/F (L/h) and not as THETA(1). Also, provide in the summary of the report, a description of the clinical application of modeling results.

Question 6: The CMC section of the briefing package provides our proposal for translation of documents that will be available for review during the Pre-Approval Inspection (PAI). Are there any other documents or information that the inspection team will require to be available and/or translated?

FDA Response:

A list of additional documents will be compiled and submitted to you during the planning stages of the PAI, with sufficient time to allow their translation.

Question 7: With respect to Batch Record translation, does the Agency agree with our proposal to provide one executed drug substance batch record and one executed drug product (200 mg strength) batch record in the BLA?

FDA Response:

The Agency agrees with your proposal to submit a single executed batch record for both DS and DP (translated) with the BLA. Translated batch records for the remaining 2 qualification lots (for both DS and DP) should be available for review during the PAI.

Question 8: As discussed in the briefing package, there are two drug substance manufacturing facilities located within the same building at the Utsunomiya site. The 2nd facility will be added in a supplemental BLA (sBLA) to be filed immediately post original BLA approval. Would the Agency be interested in viewing the 2nd Utsunomiya facility during the original BLA PAI? We would be able to provide facility floor plans, material, personnel and equipment flow; however specific process and facility data associated with the 2nd facility would not be available until the filing of the sBLA.

FDA Response:

It may be feasible to inspect the UT2 facility during the PAI of the UT1 site. This would depend upon the status of the UT2 facility at the time of the PAI. Please provide more information regarding the qualification of the UT2 facility and timing for production of qualification and other lots of tocilizumab. Be advised that an extended inspection may be required.

Question 9: Does the Agency believe that Roche is providing sufficient information to allow the evaluation of a new IEC method to replace the current IEC release method?

FDA Response:

Yes. You have provided sufficient data to allow the Agency to perform a comparative evaluation of your new IEC method. Please provide the full validation report in the BLA.

Question 10: The Sponsor will be submitting an electronic version of this Biologics License Application using the e-BLA structure and individual item tables of contents (TOCs) containing documents individually formatted in accordance with Common Technical Document guidelines. Electronic SAS datasets and data definition files will be submitted for the pivotal Phase 3 clinical studies, and pharmacokinetic datasets will be provided for the pivotal pharmacokinetic studies. Patient profiles will not be submitted. This e-BLA will be submitted on DLTs (digital linear tapes). It is not planned to provide paper review copies. Does the Agency anticipate the need for paper review copies?

FDA Response:

Paper review copies will not be necessary.

Question 11: Does the Agency anticipate that an Advisory Committee meeting will be convened for this product?

FDA Response:

The Division notes that tocilizumab is a new molecular entity (NME), and that there is a higher likelihood that an Advisory Committee (AC) meeting will be convened for an NME. However, the determination of whether an AC meeting is necessary will be made once the BLA is submitted and the data are available for assessment.

Question 12: Are there any other aspects the Agency feels are important to convey to the Sponsor with regard to the planned BLA, future interactions, et cetera?

FDA Response:

The BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: <http://www.fda.gov/cder/mapp.htm>.

To facilitate the review, we request you provide analyses that will address the items in the template, including:

1. **Section 2.6 Other Relevant Background Information- important regulatory actions in other countries or important information contained in foreign labeling**
2. **Section 5.3 Exposure-Response Relationships - important exposure-response assessments**
3. **Section 7.1.6 – Less common adverse events (between 0.1% and 1%)**
4. **Section 7.1.7.3.1 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values**
5. **Section 7.1.7.3.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers**
6. **Section 7.1.7.3.3 - Marked outliers and dropouts for laboratory abnormalities**

7. **Section 7.1.8.3.1 - Analysis of vital signs focused on measures of central tendencies**
8. **Section 7.1.8.3.2 -Analysis of vital signs focused on outliers or shifts from normal to abnormal**
9. **Section 7.1.8.3.3 -Marked outliers for vital signs and dropouts for vital sign abnormalities**
10. **Section 7.1.9.1 – Overview of ECG testing in the development program, including a brief review of the nonclinical results**
11. **Section 7.1.9.3. – Standard analyses and explorations of ECG data**
12. **Section 7.1.16 – Overdose experience**
13. **Section 7.4.2.1 - Explorations for dose dependency for adverse findings**
14. **Section 7.4.2.2 - Explorations for time dependency for adverse findings**
15. **Section 7.4.2.3 - Explorations for drug-demographic interactions**
16. **Section 7.4.2.4 - Explorations for drug-disease interactions**
17. **Section 7.4.2.5 - Explorations for drug-drug interactions**
18. **Section 8.2 - Dosing considerations for important drug-drug interactions**
19. **Section 8.3 - Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.**

Also provide subset analyses for the primary endpoint, including subgroups by:

1. **baseline demographics (age, gender, race, weight),**
2. **baseline disease characteristics (CRP, ESR, RF status, total tender joints, total swollen joints, baseline HAQ),**
3. **investigational site.**

Regarding the clinical datasets, issues have been identified in other applications which have made it more difficult for FDA reviewers to utilize certain review tools for further analysis of the data. Please assess the planned datasets for the tocilizumab BLA for the following, and address where applicable/feasible prior to submission:

1. **Unique Subject Identifier (USUBJID):**
 - a. Each patient should have a single unique subject identifier for the entire BLA.
 - b. The unique subject identifier should be in the same format (e.g. character or numeric) across all datasets.
2. **Demographic data set:**
Provide only one line per patient.
3. **Dates:**
Dates should follow one specific standard format throughout the BLA, e.g. ISO8601 or SAS format.
4. **For laboratory data:**
 - a. Please provide a variable for numeric laboratory results in which the data has been standardized to one reference range and provide the reference range and units as additional variables. This assists in situations where a single central laboratory was not used and therefore, individual lab tests (such as ALT) have multiple reference ranges.
 - b. Do not combine central and local laboratory data into one variable.
5. **Terminology issues:**
 - a. For concomitant medications, ensure that individual drugs have one consistent spelling (including case sensitivity). The generic name should be utilized.
 - b. For past medical history, utilize one consistent spelling for each disease (including case sensitivity). This may not be an issue if a standardized adverse event dictionary, such as MedDRA, has been used.
6. For numeric variables such as body weight, body mass index, creatinine clearance, etc., please provide these variables in numeric format, not character format.
7. ISS datasets should include their own demographic dataset and, ideally, should include at least the following domains: demographics, adverse events,

concomitant medications, laboratory results, vital signs, drug treatment (exposure).

8. For coded and decoded variables, the variable label names need to indicate whether the variable is coded or decoded.
9. Do not provide coded variables without decoded variables.
10. Do not duplicate records while creating vertical datasets. For example, each laboratory test result should be represented one time in the dataset.

The following comments relate specifically to the submission of CDISC Data and will be applicable to the BLA if data will be submitted using CDISC standards. This information may be updated prior to your BLA submission date. Refer to <http://www.fda.gov/oc/datacouncil/cdisc.html> for additional information.

1. Safety Analysis Plan

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, please include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org).

At a minimum the Safety Analysis Plan should address the following components:

- a. Study design considerations (See: FDA Guidance to Industry: Pre-Marketing Risk Assessment, <http://www.fda.gov/CDER/guidance/6357ful.pdf>);
- b. Safety endpoints for Adverse Events of Special Interest (AERI);
- c. Definition of Treatment Emergent Adverse Event (TEAE);
- d. Expert adjudication process (Expert Clinical Committee Charter);
- e. Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP);
- f. Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered; and
- g. When unanticipated safety issues are identified the QSAP may be amended.

2. Study Data Tabulation Model (SDTM)

- a. **The current published SDTM and Implementation Guide (SDTMIG) should be followed carefully; refer to the SDTMIG section on Conformance (3.2.3).**
- b. **Domains:**
 - (1) **The additional domains listed below are not included in the current SDTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG. If applicable, use these domains:**
 - (a) **(DV) Protocol deviations;**
 - (b) **(DA) Drug Accountability;**
 - (c) **(PC, PP) Pharmacokinetics;**
 - (d) **(MB, MS) Microbiology; and**
 - (e) **(CF) Clinical Findings.**
 - (2) **The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains:**
 - (a) **Tumor Information;**
 - (b) **Imaging Data; and**
 - (c) **Complex Inclusion/Exclusion Criteria.**
- c. **Variables:**
 - (1) **All required variables are to be included.**
 - (2) **Expected variables should be included in all SDTM datasets.**
 - (3) **Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the division.**
 - (4) **A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the Division, if necessary.**
 - (5) **A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.**
 - (6) **Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.**
- d. **Specific issues of note:**
 - (1) **SDTM formatted datasets will not provide replication of core variables (such as treatment arm) across all datasets.**
 - (2) **Only MedDRA preferred term and system organ class variables are allowed in the AE domain; however, all other levels of the MedDRA**

hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.

- (3) These issues can be addressed through the request for ADaM datasets.

3. Analysis Data Model (ADaM)

- a. Specify which ADaM datasets you intend to submit.
- b. Include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.
- c. Discuss the structure of the datasets with the reviewing Division and specify it in the QSAP.
- d. Within each adverse event analysis dataset, include all levels of the MedDRA hierarchy as well as verbatim term.
- e. Indicate which core variables will be replicated across the different datasets, if any.
- f. SDTM and ADaM datasets should use the same unique subject ID (USUBJID). Each unique subject identifier should be unique across the entire submission.

4. Controlled terminology issues:

- a. Use a single version of MedDRA for a submission. It does not have to be the most recent version.
- b. We recommend that the WHO drug dictionary be used for concomitant medications.
- c. Refer to the CDISC terminology for lab test names.
- d. Issues regarding ranges for laboratory measurements should be addressed.

Additional comments from the Office of Surveillance and Epidemiology (OSE):

- 1. If the you believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then you are encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP). If you plan to submit a RiskMAP with the original submission, please remember to submit all planned materials identified within the RiskMAP that will be necessary to implement your proposal.**

- 2. For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:**
 - a. Premarketing Risk Assessment:**
<http://www.fda.gov/cder/guidance/6357fnl.htm>

 - b. Development and Use of Risk Minimization Action Plans:**
<http://www.fda.gov/cder/guidance/6358fnl.htm>

 - c. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:**
<http://www.fda.gov/cder/guidance/6359OCC.htm>

- 3. If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA/BLA application.**

- 4. You are encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.**

Linked Applications

Sponsor Name

Drug Name

IND 11972

HOFFMANN-LA ROCHE
INC

Humanized Monoclonal Antibody (MRA) to
Interleukin-6 Receptor

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

/s/

LISA E BASHAM

10/09/2007

Regulatory Project Manager

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 125276	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Actemra Established/Proper Name: tocilizumab Dosage Form: IV		Applicant: Genentech Agent for Applicant (if applicable):
RPM: Kathleen Davies/Sharon Turner-Rinehardt		Division: Division of Anesthesia, Analgesia and Rheumatology Products
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>	<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(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"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</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> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is January 8, 2010 		<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 type="checkbox"/> None CR, September 17, 2008

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.

<p>❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), 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 ²</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 BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p>	
<p>❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Yes, date</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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<p>• Office of Executive Programs (OEP) liaison has been notified of action</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Press Office notified of action (by OEP)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Indicate what types (if any) of information dissemination are anticipated</p>	<p><input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other Information Advisory</p>

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

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

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

Answer the following questions for each paragraph IV certification:

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Copy of this Action Package Checklist ³	Included
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) CR, September 18, 2008, AP, January 8, 2010
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. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	November 20, 2007
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 12/4/09

❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <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. 	Medication Guide: July 8, 2009
<ul style="list-style-type: none"> Original applicant-proposed labeling 	PPI: November 20, 2007
<ul style="list-style-type: none"> Example of class labeling, if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	November 17, 2007
❖ 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>) 	N/A July 29, 2008
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 1/15/08 <input checked="" type="checkbox"/> DMEDP 7/29/08, 12/17/09 <input checked="" type="checkbox"/> DRISK 8/18/08, 12/8/09 <input checked="" type="checkbox"/> DDMAC 2/15/08 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM filing review
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant in 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 type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	Included

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

Minutes of Meetings	
• Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)	12/9/09 - Not applicable
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg January 9, 2009
• 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 December 1, 2008
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg March 20, 2009
• Other milestone meetings (e.g., EOP2a, CMC pilot programs) (<i>indicates dates</i>)	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	July 29, 2008
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	X
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 18, 2008
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 10, 2008
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/14/09, 8/1/08
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 45
Clinical Information⁵	
Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	See CDTL review
• Clinical review(s) (<i>indicate date for each review</i>)	12/11/09, 7/31/08
• 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 reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> • REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo (<i>indicate date</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	11/16/09 <input type="checkbox"/> None 8/13/08,
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 8/27/08

11/18/09

⁵ Filing reviews should be filed with the discipline reviews.
Version: 12/4/09

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 7/25/08
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 7/28/08, 8/25/08
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None 1/7/09
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 12/17/09, 9/16/08, 8/20/08
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 12/17/09, 8/15/08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 8/21/08
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 6/26/08
❖ Microbiology Reviews	<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>)	Date completed: 12/9/09 <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

Appendix A 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.