

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125472Orig1s000

OTHER REVIEW(S)

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

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: October 21, 2013

Applicant Name: Genentech, Inc.
U.S. License #: 1048
STN(s): 125472/0
Product(s): Tocilizumab (Actemra[®])

Short summary of application: BLA for the use of tocilizumab PFS for the treatment of Rheumatoid Arthritis.

FACILITY INFORMATION (DRUG SUBSTANCE)

Manufacturing Location:

Firm Name: Genentech, Inc.
Address: 1 Antibody Way
Oceanside, CA, 92056
FEI: 3006129086

Short summary of manufacturing activities performed: Drug substance (DS) manufacture, batch release testing (b) (4), stability testing, raw materials testing

This site was inspected by LOS-DO from 5/14/2013 – 5/23/2013 and classified NAI. This was a routine GMP surveillance inspection covering biotech drug substance manufacturing operations. The CBI profile was updated and is acceptable.

¹ The 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.”

Manufacturing Location:

Firm Name: Genentech, Inc.
Address: 1 DNA Way
South San Francisco, CA 94080
FEI: 2917293

Short summary of manufacturing activities performed: (b) (4) testing

This site was inspected by SAN-DO from 7/9/2013 – 7/17/2013 and classified NAI. This was a routine GMP surveillance inspection covering biotech drug substance manufacturing operations. The (b) (4) profiles were updated and are acceptable.

Manufacturing Location:

Firm Name: Roche Singapore Technical Operations Pte. Ltd.
Address: 10 Science Park Road
Singapore 117684
FEI: 3007164129

Short summary of manufacturing activities performed: (b) (4) testing for batch release.

This site was inspected by IOG from 4/26/2012 – 5/3/2012 and classified VAI. This was a routine GMP surveillance inspection covering biotech drug testing operations. The (b) (4) profiles were updated and are acceptable.

Manufacturing Location:

Firm Name: Genentech, Inc.
Address: (b) (4)
FEI: (b) (4)

Short summary of manufacturing activities performed: DS Raw materials testing

An evaluation of this site is not necessary for the responsibility listed.

FACILITY INFORMATION (DRUG PRODUCT)

Manufacturing Location:

Firm Name:

(b) (4)

Address:

FEI:

Short summary of manufacturing activities performed: Drug Product manufacturing, sterility and endotoxin testing

This site was inspected by IOG on (b) (4) and classified VAI. This was a routine GMP surveillance inspection covering biotech drug product manufacturing operations. The (b) (4) profiles were updated and are acceptable.

Manufacturing Location:

Firm Name: F. Hoffmann-La Roche Ltd.

Address: Wurmisweg
4303 Kaiseraugst
Switzerland

FEI: 3003973536

Short summary of manufacturing activities performed: Labeling, assembly with needle safety device, secondary packaging, (b) (4); release testing with exception of sterility and endotoxin

This site was inspected by CDER-OMPQ from 3/1/2012 – 3/9/2012 and classified NAI. This was a routine GMP surveillance inspection covering biotech drug product manufacturing operations. The (b) (4) profile was updated and is acceptable.

CDRH was consulted by OBP to determine if this site had an acceptable device inspectional history in support of this manufacturing change. CDRH (John Diehl) indicated via phone conversation that a review of this facility found that it was acceptable (b) (4).

Manufacturing Location:

Firm Name: Roche Pharma AG

Address: Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

FEI: 3002807206

Short summary of manufacturing activities performed: release testing with exception of sterility and endotoxin.

This site was inspected by IOG from September 19-21, 2011 and classified VAI. This was a PLI and routine GMP surveillance inspection covering Actemra drug product testing operations. The CTL profile was updated and is acceptable.

Manufacturing Location:

Firm Name:

(b) (4)

Address:

FEI:

Short summary of manufacturing activities performed: Sterility and endotoxin testing

This site was inspected by IOG from (b) (4) and classified NAI. This was a routine GMP surveillance inspection covering biotech drug product testing operations. The (b) (4) profile was updated and is acceptable.

Manufacturing Location:

Firm Name:

(b) (4)

Address:

FEI:

Short summary of manufacturing activities performed: Sterility and endotoxin testing

Inspected by IOG (b) (4) and classified NAI. This was a routine GMP surveillance inspection covering biotech drug product testing operations. The (b) (4) profile was updated and is acceptable.

OVERALL RECOMMENDATION

There are no pending or ongoing compliance actions that prevent approval of this application.

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

/s/

CHRISTINA A CAPACCI-DANIEL
10/18/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title ¹	ACTEMRA (tocilizumab) Solution for intravenous infusion Solution for subcutaneous injection
Applicant	Genentech, Incorporated
Application/Supplement Number	BLA 125472
Type of Application	Original application
Indication(s)	Treatment of rheumatoid arthritis (b) (4)
Established Pharmacologic Class ¹	Interleukin-6 receptor antagonist
Office/Division	ODEII/DPARP
Division Project Manager	Philantha Bowen
Date FDA Received Application	December 21, 2012
Goal Date	October 21, 2013
Date PI Received by SEALD	October 11, 2013
SEALD Review Date	October 16, 2013
SEALD Labeling Reviewer	Debra Beitzell
SEALD Division Director	Laurie Burke

¹ The product title or established pharmacologic class that appears in draft agreed-upon prescribing information (PI).

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *Waiver of 1/2 page HL limit granted in previous approval letter.*

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *In HL, insert reference at the end of first statement under D&A heading (i.e., "(2)") and insert reference at end of Pregnancy statement under Use in Specific Populations heading (i.e., "(8.1)").*

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required

Selected Requirements of Prescribing Information

• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

NO

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *The initial U.S. approval should be immediately beneath the product title; remove white space in between product title and initial U.S. approval.*

Boxed Warning

YES

12. All text must be **bolded**.

Comment:

YES

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- YES** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- YES** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- YES** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- YES** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

Selected Requirements of Prescribing Information

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *Subsection heading 14.4 does not match heading in FPI; correct heading in TOC or change FPI heading to match TOC. Subsection number and heading for 17.1 is not in TOC; add 17.1 to TOC or remove subsection number from FPI and bullet subheading instead.*

YES

Selected Requirements of Prescribing Information

31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse

Selected Requirements of Prescribing Information

9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: *Attach Medication Guide to the end of the FPI.*

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

Comment: *Subsection 6.4, Anaphylaxis, correct cross reference to subsection 5.5 to read “[see Warnings and Precautions (5.5)]”.*

- NO** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *Insert vertical line in left margin of FPI next to RMCs in subsections 1.1, 1.2, and 5.8.*

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- YES** 42. All text is **bolded**.

Comment:

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

DEBRA C BEITZELL
10/16/2013

LAURIE B BURKE
10/16/2013

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: PK/PD/Safety Study of Actemra SQ in (b) (4) to 17 years of age

PMR/PMC Schedule Milestones:	Final Protocol Submission:	03/20/2013 (submitted)
	Study/Trial Completion:	03/31/2016
	Final Report Submission:	05/31/2018
	Other:	MM/DD/YYYY

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

FDA has deferred submission of pediatric studies for ages 2 through 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

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 primary objective of this study is to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and safety of Actemra in patients with (b) (4) ages (b) (4)-17 years old following SC administration for 14 weeks. The exploratory objective is to evaluate efficacy of TCZ in combination with stable ongoing therapy in patients with (b) (4) following SC administration for 52 weeks.

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.

This is a 52-week, open label, multicenter, PK/PD, and safety study in pediatric patients 2 to 17 years of age with ^{(b) (4)}. Patients who fulfill eligibility criteria will receive Actemtra SC dosed according to body weight. Patients will undergo PK/PD, safety, laboratory, and efficacy assessments.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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)

Continuation of Question 4

- 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)

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/s/

SALLY M SEYMOUR
10/16/2013

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125472
Product Name: Actemra for Subcutaneous Injection

PMC #1 Description: Determine the (b) (4) volume necessary (b) (4) and provide the report to the Agency

PMC Schedule Milestones:

Final Protocol Submission:	<u>MM/DD/YYYY</u>
Study/Trial Completion:	<u>MM/DD/YYYY</u>
Final Report Submission:	<u>10/30/2013</u>
Other: _____	<u>MM/DD/YYYY</u>

PMC #2 Description: _____

PMC Schedule Milestones:

Final Protocol Submission:	<u>MM/DD/YYYY</u>
Study/Trial Completion:	<u>MM/DD/YYYY</u>
Final Report Submission:	<u>MM/DD/YYYY</u>
Other: _____	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDATA OR WILL BE PUBLICALLY REPORTABLE**

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

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Determination of the (b) (4) volume of the (b) (4) will improve the consistency of the (b) (4) integrity test. However, the current method used manufacturer's recommendations and the risk of not detecting (b) (4) is deemed low; therefore the study can be performed post-approval.

2. Describe the particular review issue and the goal of the study.

The (b) (4) will be determined for each volume. The minimum volume (b) (4) will be used (b) (4) integrity testing.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Determination of the volume (b) (4) necessary (b) (4)

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the 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 only)

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/s/

SALLY M SEYMOUR
10/16/2013



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: October 10, 2013

From: Jason To, Biomedical Engineer
CDRH/ODE/DAGRID/General Hospital Devices Branch (GHDB)

To: Philantha Bowen
CDER/OND/ODEII/DPARP

Subject: CDRH Consult Request, ICC1300450
Combination Product Review: BLA 125472, PFS

Firm: Genentech, Inc.
1 DNA Way MS# 241B
South San Francisco, CA 94080-4990

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH) regarding BLA125472. CDRH has been consulted to review the prefilled glass syringe (PFS) and needle safety device (NSD) device performance.

2. Documents

- BLA125472, device sections 3.2.P and 3.2.R.2
- Syringe Supplier Conformity Certificates [REDACTED] (b) (4)
[REDACTED] regarding syringe from BLA125472
- 510(k) submission [REDACTED] (b) (4)
- 510(k) submission [REDACTED]
- 510(k) submission [REDACTED]

- MAUDE adverse reporting

3. Device Description

The NSD is a commercially available device, manufactured by (b) (4) and cleared under 510(k)s (b) (4) was cleared by FDA (b) (4) to expand the intended user population from healthcare professionals (HCPs) to include physician-prescribed-medication self-injecting patients and individuals who assist self-injecting patients. The NSD is intended for use as a safety mechanism designed to reduce the occurrence of accidental needlestick injury to HCPs, physician-prescribed medication self-injecting patients, and individuals who assist self-injecting patients during disposal of a used syringe. The NSD is designed to fit with a standard prefilled glass syringe. The Sponsor's 1 mL PFS is assembled into the NSD to form an integrated combination product that is used to administer tocilizumab while also reducing the occurrence of potential needlestick injuries.

Technical features of the NSD include:

- Passive activation without additional handling by the user
- Automatic coverage of the needle upon completion of the injection and plunger release To use the PFS following: NSD, the user is i
- Remove the rigid needle shield (RNS).
- Insert the needle in the injection site.
- Push down the thumb pad to release the plunger rod and dispense the solution; when the plunger rod is fully depressed, the NSD is activated.
- Remove the needle from the injection site.
- Release the thumb pad to allow the needle guard to extend and cover the needle to a locked position.
- Dispose of the PFS NSD into a sharps container.

Needle Safety Device

Components	Supplier	510(k)	Description	Material
Needle Safety Device	(b) (4)			
Plunger				

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Food and Drug Administration
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Radiological Health
Office of Device Evaluation
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10903 New Hampshire Avenue
Silver Spring, MD 20993

4. CDRH Review and Comments

CDRH's review consisted assessing the sponsor's response to initial deficiencies. Also, CDER has requested that CDRH ODE review the sponsor's response to a 483 observation.

Review of Sponsor's Response

- 1) FDA Question: In BLA 125472 you have provided Certificates of Conformity for the (b) (4) syringe 1ml Long 27G 1/2", colorless (b) (4) glass barrel with 27G 1/2" stainless steel needle. In these certificates you state that your device has conformed to certain standards and testing and meets the criteria. You have not provided any performance test protocols, reports or results for the (b) (4) syringe. Please provide complete performance test reports for our review in accordance to:

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

Reviewer Assessment: The sponsor provided the requested information. The sponsor's response is adequate.

Medical Officer Review of 483 Response

BACKGROUND

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 DMARDs. It is marketed in a prefilled syringe with staked needle and needle shield device. (PFS+NSD).

Additional information is being provided by the firm in response to FDA Form 482, Observation 2 submitted by F. Hoffman-La Roche Ltd. (Roche) to (b) (4) August 15, 2013, regarding the Roche, Kaiseraugst manufacturing facility inspection between July 22 and July 25, 2013.

As part of the response to Observation 2, information regarding a development design verification failure attributed to a clog at the tip of the needle was provided. According to the firm, this is a very low frequency phenomenon that does not impact safety.

DEVICE DESCRIPTION

The syringe is the (b) (4) 1mL long glass syringe with staked 27 gauge 1/2 inch needle and rigid needle shield. The rigid needle shield is supplied by (b) (4) and is cleared under (b) (4).

FIRM'S DESCRIPTION OF EVENTS AND ASSESSMENT

At the 9-month time point for batch (b) (4) one PFS +NSD out of 60 units exceeded the limit of peak force prior to drug being expelled from the syringe. This event was investigated and believed to be random by the firm. They assert that is not associated with any parameters or functional component of the combination product or a function of storage time.

The firm reports that testing of the 0, 3, 6, and 12 months time points was successfully completed thus confirming the proposed shelf life. Additionally, long-term functionality of the PFS+NSD for 2 lots was demonstrated at the recommended storage conditions of 2-8°C for up to (b) (4) months as noted in the BLA.

FIRM'S HAZARD ASSESSMENT

The firm conducted a hazard assessment to assessment the risk to patient safety as a result of solidified drug product following exposure to air.

The firm states: "Potential theoretical risk that could arise from a clog at the tip of the needle include: no dose, delayed dose, injection of very low amounts of solidified drug product solution. Since the presence of a potential clog is of very low frequency the impact to patient harm with a repeated no dose would be considered extremely low.



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Additionally, theoretical harms associated with the injection of very low amounts of solidified drug product solution included irritation at the site of injection of the potential to elicit an immune response. Although these theoretical harms are appropriate to consider for this evaluation, their occurrence is considered extremely unlikely based on knowledge of product quality impact observed during long term stability studies as well as during technical investigation of the needle clogging phenomenon.”

MEDICAL OFFICER DISCUSSION

CDRH defers to the CDER MO regarding clinical risks related to no dose, delayed dose or injection of solidified drug product. The overall frequency of needle clogging appeared low in during development studies and design verification testing (0.1%) and the overall complaint rate was low in the clinical studies (<0.01%). However, it is not clear that the root cause of the clogged needles found upon inspection has been adequately determined (particularly issues with needle or syringe manufacturing.) CDRH would await further input from CDRH OC DRMO regarding further investigation and possible corrective actions.

Sincerely,

Jason To -S

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Date: 2013.10.10 10:03:18 -04'00'

Jason To
Biomedical Engineer

Concurred By:



Richard C. Chapman
2013.10.10 10:33:56
-04'00'

Richard Chapman
Chief, General Hospital Devices Branch

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/s/

PHILANTHA M BOWEN

10/10/2013

Entered in DARRTS on Behalf of CDRH/ODE/DAGID/GHDB

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement A
General Hospital Devices Branch

DATE: October 9, 2012

TO: Philantha Bowen, CDER/OND/ODEII/DPARP, WO-22, Room 3316

THROUGH: LCDR Cesar Perez, CDRH/OC/DOEA/, WO-66, Room 3519

FROM: LT John Diehl, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO-66, Room 3528

SUBJECT: ICC13004955 – Review of Genentech’s additional 483 response

CONSULT INSTRUCTIONS: We are requesting your review of this additional 483 response submitted under BLA 125472 in order to provide the Division with your final/overall recommendation regarding this matter

Digitally signed by Cesar A. Perez
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Cesar A. Perez,
0.9.2342.19200300.100.1.1=2000613874
Date: 2013.10.10 07:56:51 -04'00'

Cesar A. Perez

Objective

The Office of Compliance at CDRH received a consult request from CDER/OND/ODEII/DPARP. The consult requested that CDRH/OC review the firm’s additional response to a FDA 483 it received on July 25, 2013. Specifically, CDRH/OC was requested to review the firm’s additional response to FDA 483 Observation # 2.

Product Description

Actemra (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of adult patients with moderately to severely active Rheumatoid Arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs. It is also indicated for the treatment of Polyarticular Juvenile Idiopathic Arthritis and Systemic Juvenile Idiopathic Arthritis.

Actemra is supplied in a 1 mL ready-to-use, single-use prefilled syringe (PFS) (b) (4) for subcutaneous injection. Each device delivers 0.9 mL of tocilizumab. The syringe is the (b) (4) 1 mL

long glass syringe with staked 27 gauge ½ inch needle and rigid needle shield. The recommended dose of tocilizumab for adult patients is 162 mg, given once every week as a SC injection.

F. Hoffmann-La Roche Ltd., Wurmisweg, 4303 Kasieraugst, Switzerland, FEI. No 3003973536, is the site where final labeling, final assembly with needle safety device, secondary packaging, (b) (4), and release testing (except sterility/endotoxin testing) activities occur. F. Hoffmann-La Roche is a supplier to Genentech (the finished combination product manufacturer).

Review

Following the July 23 – July 25, 2013, inspection of the F. Hoffmann – La Roche Ltd., Switzerland, facility, a 4 Item Form FDA 483 was issued. In a memorandum dated September 11, 2013, CDRH/OC classified the inspection as VAI.

On behalf of the inspected facility (i.e., F. Hoffman-La Roche), the finished combination product manufacturer, Genentech (or “the firm”), submitted the first response to the FDA 483 on August 15, 2013. A follow up response to the FDA 483 was submitted on October 3, 2013. On October 3, 2013, CDER/OND/ODEII/DPARP requested that CDRH/OC review the firm’s additional FDA 483 response and provide a final/overall recommendation.

In the FDA 483 that was issued on July 25, 2013, under item #2, the following was stated by the FDA Investigator:

Procedures for design verification have not been adequately established.

Specifically, the firm does not have adequate procedures to address failures found during design verification. The firm is currently using design control procedures title (b) (4), to manage the design of the Actemra self-injector with needle safety device.

There was a documented failure during the verification testing of the Actemra self-injector with needle safety device product for design input (b) (4), which verifies the correct amount of liquid is dispensed while depressing the plunger (DDE_TOC_BVRR_001, V1). The report documents that the device did not deliver proper dosage due to the possible presence of a clog at the tip of the needle. Retesting was conducted as documented in Design Verification Report (b) (4) using the same amount of devices (300), which showed no failures, but the root cause of the failure was not identified and the testing was considered passing.

Following a review of the firm’s initial response to FDA 483 Observation #2, dated August 15, 2012, a review of the firm’s additional response, dated October 3, 2013, will be provided.

In the firm's initial response to this observation, dated August 15, 2013, the firm indicated that it would be taking the following corrective actions:

-  (b) (4)
- 
- The failure identified during the preliminary design verification (report DDE_TOC_B_VRR_001) was investigated. The firm indicated that the failure was due to the possible presence of a clog at the tip of the needle and the device did not function. Needle studies that investigated the impact of various conditions (e.g., exposure to ambient temperature) were conducted. From these studies, it was concluded that for a viscous protein formulation, such as Actemra, it is possible for drying to occur, resulting in needle clogging.
 - In cases where uncapped pre-filled syringes were exposed to ambient conditions for more than five minutes after cap removal, an increase of injection force was observed, which can be indicative of needle clogging. To mitigate this risk, the firm updated its Instructions For Use (IFU). The firm also indicated that it conducted a design validation study for the update to the IFU.
 - Needle clogging before needle cap removal was observed at a very low frequency in syringes stored at the intended storage conditions (2-8° C).  (b) (4)
- The firm believed that the data collected from development studies and design verification testing demonstrates that there is a low probability of occurrence for a clog at the tip of the needle. The firm also indicated that the overall complaint rate for the clinical studies was very low (<0.01%). The firm also stated that the residual risks related to needle clogging were deemed acceptable. Additionally, the firm indicated that as part of the risk management plan and ongoing stability evaluation, the potential residual risk will be monitored for any chances in occurrence.

In its review of the Establishment Inspection Report associated with the inspection of F. Hoffman-La Roche, CDRH/OC did not review the firm's response to this observation. If CDRH/OC were to have reviewed the firm's response to this observation, it would have been concluded that the adequacy of the firm's response could not be determined at the time of review because the firm was still in the midst of conducting corrections and corrective actions.

In an updated response to the FDA 483, dated October 3, 2013, the firm provided additional information related to the firm's initial response, dated August

15, 2013, to FDA 483 Observation #2. In this response, the firm states that the inspected facility, F. Hoffman-La Roche, has confirmed a second occurrence of clogging at the tip of the Actemra needle. After the clogging occurred, the firm indicated that it followed its updated procedures and conducted a follow-up investigation and hazard assessment.

In this response, the firm stated that clogging in 1 Actemra PFS out of sixty was observed at the 9-month stability testing time point for batch K105AB12. Clogging was believed to be the mode of failure because the failed PFS exceeded the limit of peak force prior to drug being expelled. The firm investigated the incident and believed it to be a random event that is not associated with any parameters or functional component of the combination product. The firm also stated that at the 12 month timepoint all 60 Actemra PFS' passed device stability verification testing.

The firm believes that these results of stability testing with this batch are consistent with results from previous stability batches. The firm also believes that the occurrence of clogging in the Actemra unit does not implicate the proposed shelf life for the PFS. Additionally, the firm stated that long term functionality testing of the PFS at 2-8° C for up to (b) (4) months was demonstrated successfully.

As a part of the follow-up investigation, the firm performed a hazard assessment. The firm stated that the potential theoretical risks that could arise from a clog at the tip of the needle include no dose, delayed dose, and injection of very low amounts of solidified drug product solution. Since the potential of a potential clog is of very low frequency, the firm indicated that the impact to patient health with a repeated no dose would be considered extremely low. The firm indicated that the risk to the patient caused by a clogged syringe remains acceptable and that there is a favorable benefit to risk profile for Actemra.

The firm concluded that the failure at the 9 month time point during the long term functionality design verification testing is not a consequence of component long term aging, or correlated with design of the needle-safety device. Rather, the firm believes that the failure was a random event, which was deemed to be an acceptable risk that does not impact patient safety.

Rather than being a typical response to a FDA 483 observation, where a firm would provide a correction and corrective action to the deficiency, it appears that the firm was only providing FDA with this information in an effort to be transparent. It is noted that the firm did recognize a failure during verification testing and appropriately investigated the issue and tried to determine a cause of failure.

Recommendation

CDRH/OC continues to recommend that the July 22-25, 2013, inspection of the F. Hoffmann-La Roche facility be classified as VAI. Even with the additional

information that was provided by the firm, the violations identified during the inspection appear to have minimal probability of producing nonconforming combination products. With regards to a final BLA recommendation, CDRH/OC defers to CDER, the lead center for the combination product.

As a part of activities that should be conducted prior to or after approval of the BLA, CDRH/OC recommends that CDER request the following from the firm:

1. A copy of documentation pertaining to the investigation of the clogged needle that was conducted after the failure occurred at the 9 month stability testing point. Also, within this documentation, it would be appreciated if the firm could provide its sampling plan for stability testing.
2. A copy of documentation pertaining to the results of the 12 month stability testing and any stability testing conducted thereafter. A copy of the stability testing protocol.
3. If the firm uses the PFS that was subject to the stability testing failure with any other marketed products, the firm should provide information about any corrective actions it has taken to address the potential that clogging could occur in those combination products. If cases of clogging have been reported by users, the firm should provide FDA with the rate of occurrence and any mitigation activities it has conducted for each combination product.

Also, if the firm's Actemra IFU does not describe the actions users should take in the event that clogging of the needle occurs, CDRH/OC is requesting that CDER consider whether the firm should provide this information in its IFU.

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LT John Diehl

Prepared/typed: JDiehl: October 9, 2013

Reviewed:

Revised:

Finalized:

cc:

WO66-3523	(DOEA Chron File)
WO66-3528	(J. Diehl, Lead Reviewer)
WO66-2567	(K. Marin, ODE)

CTS No: ICC1300495

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/s/

PHILANTHA M BOWEN

10/10/2013

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling, and Packaging Review Memo

Date: October 8, 2013

Reviewer(s): Teresa McMillan, PharmD
Division of Medication Error Prevention & Analysis

Team Leader: Lubna Merchant, PharmD
Division of Medication Error Prevention & Analysis

Drug Name and Strength: Actemra (Tocilizumab)
Injection
162 mg/0.9 mL

Application Type/Number: BLA125472

Applicant/sponsor: Genentech

OSE RCM #: 2012-311-1

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the revised 162 mg/0.9 mL Actemra (Tocilizumab) container labels, carton labeling, Instructions for Use, (b) (4) submitted by Genentech in response to the Division of Medication Error Prevention and Analysis's (DMEPA's) previous comments in OSE Review #2013-311, dated September 19, 2013.

2 METHODS AND MATERIALS REVIEWED

The revised container labels, carton labeling, Instructions for Use, (b) (4) submitted to the FDA on September 27, 2013 (See Appendix A for images of the container labels, carton labeling, Instructions for Use, (b) (4) and OSE Review #2013-311, dated September 19, 2013, were evaluated to assess whether the revisions adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised labels and labeling addressed all of DMEPA's concerns with the exception of the comment to adequately differentiate the container and carton labeling of the proposed strength from the currently marketed 80 mg/4 mL vial. The applicant states that there are several measures currently in place to help avoid selection errors and the following factors support clear and easy differentiation of the products:

- Vial and PFS cartons are noticeably different sizes and different configurations making each easily distinguishable at first glance
- Package labeling includes prominent text indicating that SC should not be used for IV administration, and vice versa
- Selection error by RA outpatients will not be possible given they will have access to the PFS only (IV administrations are performed by a healthcare provider in a clinical setting only)
- SC product labeling includes Instructions for Use, with descriptive text and figures for home administration with the PFS

DMEPA acknowledges the applicant's rationale; however, if the applicant decides not to implement this recommendation to the carton labeling and container labels and we identify selection errors post marketing, we may recommend additional regulatory action at that time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Nichelle Rashid, at 301-796-3904.

REFERENCES

1. OSE Review #2013-311, Label, Labeling, and Packaging Review for Actemra, September 19,, 2013, McMillan,T.

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/s/

TERESA S MCMILLAN
10/08/2013

LUBNA A MERCHANT
10/09/2013

Medical Consultation

Date: October 7, 2013
From: Jacqueline Ryan, Medical Officer, ODE/ DAGID/ GHDB
Through: Richard Chapman, Branch Chief, ODE/ DAGID/ GHDB
To: Jason To, Lead Reviewer, ODE/ DAGID/ GHDB
Subject: BLA 125472 ACTEMRA Firm Response to FDA 482 Observations

RECOMMENDATION

BACKGROUND

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 DMARDs. It is marketed in a prefilled syringe with staked needle and needle shield device. (PFS+NSD).

Additional information is being provided by the firm in response to FDA Form 482, Observation 2 submitted by F. Hoffman-La Roche Ltd. (Roche) to (b) (4) August 15, 2013, regarding the Roche, Kaiseraugst manufacturing facility inspection between July 22 and July 25, 2013.

As part of the response to Observation 2, information regarding a development design verification failure attributed to a clog at the tip of the needle was provided. According to the firm, this is a very low frequency phenomenon that does not impact safety.

DEVICE DESCRIPTION

The syringe is the (b) (4) 1mL long glass syringe with staked 27 gauge ½ inch needle and rigid needle shield. The rigid needle shield is supplied by (b) (4) and is cleared under (b) (4)

FIRM'S DESCRIPTION OF EVENTS AND ASSESSMENT

At the 9-month time point for batch (b) (4) one PFS +NSD out of 60 units exceeded the limit of peak force prior to drug being expelled from the syringe. This event was investigated and believed to be random by the firm. They assert that is not associated with any parameters or functional component of the combination product or a function of storage time.

The firm reports that testing of the 0, 3, 6, and 12 months time points was successfully completed thus confirming the proposed shelf life. Additionally, long-term functionality of the PFS+NSD for 2 lots was demonstrated at the recommended storage conditions of 2-8°C for up to (b) (4) months as noted in the BLA.

FIRM'S HAZARD ASSESSMENT

The firm conducted a hazard assessment to assessment the risk to patient safety as a result of solidified drug product following exposure to air.

The firm states: "Potential theoretical risk that could arise from a clog at the tip of the needle include: no dose, delayed dose, injection of very low amounts of solidified drug product solution. Since the presence of a potential clog is of very low frequency the impact to patient harm with a repeated no dose would be considered extremely low. Additionally, theoretical harms associated with the injection of very low amounts of solidified drug product solution included irritation at the site of injection of the potential to elicit an immune response. Although these theoretical harms are appropriate to consider for this evaluation, their occurrence is considered extremely unlikely based on knowledge of product quality impact observed during long term stability studies as well as during technical investigation of the needle clogging phenomenon."

DISCUSSION

I defer to the CDER MO regarding clinical risks related to no dose, delayed dose or injection of solidified drug product. The overall frequency of needle clogging appeared low in during development studies and design verification testing (0.1%) and the overall complaint rate was low in the clinical studies (<0.01%). However, it is not clear that the root cause of the clogged needles found upon inspection has been adequately determined (particularly issues with needle or syringe manufacturing.) I would await further input from CDRH OC DRMO regarding further investigation and possible corrective actions.

Jacqueline S.
Ryan -S

Jacqueline Ryan, MD
CDRH/ ODE/ DAGID/ GHDB

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PHILANTHA M BOWEN

10/08/2013

Entered in DARRTS on Behalf of ODE/DAGID/GHDB

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

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

Memorandum

Date: October 1, 2013

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

From: Adewale Adeleye, Pharm. D., MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm. D., Acting Team Leader, OPDP

Subject: BLA# 125472 - ACTEMRA (tocilizumab)
Solution for intravenous infusion
Solution for subcutaneous injection (Actemra)

Reference is made to DPARP's consult request dated January 29, 2013, requesting review of the proposed Package Insert (PI), Carton and Container Labeling, and Medication Guide (MG) for ACTEMRA (tocilizumab) Solution for intravenous infusion, Solution for subcutaneous injection (Actemra).

OPDP has reviewed the proposed PI entitled, "BLA 125472 - DPARP Label - Consults (tracked).doc" that was sent via e-mail from DPARP to OPDP on September 18, 2013. OPDP comments are provided directly on the attached copy of the labeling (see below).

OPDP has reviewed the proposed Carton and Container labeling titled "draft-cart-cont-labels.pdf" submitted by the sponsor on September 27, 2013. OPDP does not have comments on the proposed Carton and Container labeling at this time.

Please note that comments on the proposed MG were provided on September 30, 2013, under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

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/s/

ADEWALE A ADELEYE
10/01/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: September 30, 2013

To: Badrul Chowdhury, M.D.
Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Adewale Adeleye, Pharm. D., MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established
name): ACTEMRA (tocilizumab)

Dosage Form and Route: pre-filled syringe, for subcutaneous injection

Application
Type/Number: BLA 125472

Applicant: Genentech, Inc

1 INTRODUCTION

On December 21, 2012, Genentech, Inc submitted for the Agency's review an Original Biologic License Application (BLA) supporting the use of ACTEMRA (tocilizumab) for subcutaneous (SC) treatment of adult patients with moderately to severely active Rheumatoid Arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). The application seeks marketing approval for ACTEMRA (tocilizumab) administered subcutaneously via a pre-filled syringe (PFS).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on December 21, 2012 and January 29, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG), and Instructions for Use (IFU) for ACTEMRA (tocilizumab) pre-filled syringe for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on September 19, 2013.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DNP under separate cover.

2 MATERIAL REVIEWED

- Draft ACTEMRA (tocilizumab) MG and IFU received on December 21, 2012, and received by DMPP on January 29, 2013.
- Draft ACTEMRA (tocilizumab) MG and IFU received on December 21, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on September 24, 2013.
- Draft ACTEMRA (tocilizumab) Prescribing Information (PI) received on December 21, 2012 revised by the Review Division throughout the review cycle, and received by DMPP on September 13, 2013.
- Draft ACTEMRA (tocilizuma) Prescribing Information (PI) received on December 21, 2013 revised by the Review Division throughout the review cycle, and received by OPDP on September 18, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Verdana font, size 11.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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page

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/s/

SHARON W WILLIAMS
09/30/2013

ADEWALE A ADELEYE
09/30/2013

MELISSA I HULETT
09/30/2013

QUALITY SYSTEM EIR REVIEW

DATE: September 11, 2013

FROM: General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH

THROUGH: Chief, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH
 9/13/13

TO: Philantha Bowen, Division of Pulmonary, Allergy, and Rheumatology Products, Office of Drug Evaluation II, Office of New Drugs, CDER

CC: Miya Paterniti, Division of Pulmonary, Allergy, and Rheumatology Products, Office of Drug Evaluation II, Office of New Drugs, CDER

Zhihao Peter Qiu, Biotech Manufacturing Assessment Branch, Division of Good Manufacturing Practice Assessment, Office of Manufacturing and Product Quality, Office of Compliance, CDER

Office of Combination Products at combination@fda.gov

SUBJECT: Review of Establishment Inspection Report (EIR), FDA 483, and Exhibits

EI dates July 22-25, 2013
CDRH Receipt Date of EIR: September 4, 2013

Site Inspected: (Manufacturer)
F. Hoffmann-La Roche Ltd.
Wurmisweg, Kaiseraugst
Switzerland

FEI/CFN: 3003973536

DEVICE: Actemra Pre-filled Syringe with Needle Safety Device

INVESTIGATOR: Benjamin J. Dastoli, CIN-DO

ORA

RECOMMENDATION: VAI

OC

DECISION: VAI for QS reg; Overall Classification Pending

I. Purpose and Type of Inspection

The purpose for this inspection was to conduct a pre-approval inspection for the Actemra Pre-filled Syringe with Needle Safety Device, a combination product, under BLA 125472. It was conducted in accordance with CP 7382.845, Inspection of Medical Device Manufacturers (FACTS No. (b) (4)).

The current inspection was a For Cause Level 3 inspection which focused on the needle safety device, the primary medical device component. This inspection was requested by CDER.

II. Background Information

F. Hoffmann-La Roche Ltd. was founded in 1896 and is headquartered in Basel, Switzerland. Inspection site activities include (b) (4)

(b) (4)

The firm is currently registered and listed as a drug manufacturer. The firm does not have any medical device registrations and listings.

There are no regulatory actions against the firm. The firm has had one recall of US product since the last FDA inspection. It was initiated on (b) (4)

(b) (4) and involved the (b) (4) drug product which was (b) (4)

The recall was submitted to FDA but has not yet been classified.

III. Regulatory History

March 1-9, 2012 A pre-approval inspection which covered the (b) (4) (b) (4) was conducted by CDER-DMPQ. No violations were revealed, and the inspection was classified as NAI.

IV. Current Inspection

The General Hospital Devices Branch of the Division of Enforcement A has completed its good manufacturing practices review and evaluation under the

Quality System regulation of the Establishment Inspection Report (EIR) and exhibits for the inspection which closed on July 25, 2013, and which took place at F. Hoffmann-La Roche Ltd., Kaiseraugst, Switzerland, facility. The inspection of this firm indicates that it meets the criteria of a Situation II, in Compliance Program, CP 7382.845, Part V, dated February 2, 2011, in that the deficiencies do not qualify as major at this time and the inspection is being classified as VAI.

From the quality system deficiencies observed and the particular product and manufacturing processes involved, the inspection documents QS deficiencies of a quantity and/or type which appear to have minimal probability of producing nonconforming devices and/or defective finished devices.

CDRH concurs with the classification recommendation of VAI based on the information present.

V. Quality System Review

The review of the EIR, exhibits, and the FDA 483 follows below. The QS regulation violations appear in a descending order of significance.

▪ 21 CFR 820.30(g)

Failure to establish and maintain procedures for validating the device design, as required by 21 CFR 820.30(g). For example, the firm's risk management process does not adequately mitigate the hazards of users removing the needle cap of the device.

This cite is supported by Observation 3 of the FDA 483, pages 18-20 of the EIR, and Exhibit Nos. 11, 24, 38, and 40.

▪ 21 CFR 820.100(b)

Failure to document corrective and preventive action activities, as required by 21 CFR 820.100(b). For example, the firm did not formally document corrective actions for a batch of needle safety devices, which was rejected due to embedded artifacts, from ^{(b)(4)} a supplier to the firm. The firm did not relay this information to ^{(b)(4)} for investigation or possible corrective action according to the firm's supplier corrective action procedures.

This cite is supported by Observation 4 of the FDA 483, pages 20-21 of the EIR,

and Exhibit Nos. 31 and 41-44.

▪ **21 CFR 820.50(a)(3)**

Failure to establish and maintain records of acceptable suppliers, contractors, and consultants, as required by 21 CFR 820.50(a)(3). For example, the firm did not qualify and list [REDACTED]^{(b)(4)} as an approved supplier of the sterile pre-filled syringes used in the manufacturing of the Actemra self-injector with needle safety device according to its purchasing control procedures. Additionally, the firm did not have data to show that [REDACTED]^{(b)(4)} is monitored for performance metrics.

This cite is supported by Observation 1 of the FDA 483, pages 15-16 of the EIR, and Exhibit Nos. 32-34.

▪ **21 CFR 820.30(f)**

Failure to establish and maintain procedures for verifying the device design, as required by 21 CFR 820.30(f). For example, the firm identified a failure during verification testing of the Actemra self-injector with needle safety device for design input [REDACTED]^{(b)(4)} which verifies the correct amount of liquid is dispensed while depressing the plunger. The firm's design control procedures do not address the root cause of this failure in design verification and what levels of investigation are needed for testing which does not meet specification.

This cite is supported by Observation 2 of the FDA 483, pages 17-18 of the EIR, and Exhibit Nos. 21-23 and 35-36.

VI. Observations Pertaining To Other Regulations

There are no observations pertaining to other regulations.

VII. Nonsupportable FDA 483 Observations

There are no nonsupportable FDA 483 observations.

VIII. CDRH Recommendation and Follow-up

CDRH has classified the inspection VAI based on the EIR dated July 22-25, 2013. CDRH defers to CDER, the lead Center for this inspection, to initiate any follow-up actions to the violations found during the inspection and to make a final decision on the overall classification of the inspection.



Emre Genca

Drafted: EGenca: 9/11/13

Reviewed: MITejero: 9/11/13

Reviewed: CFischer:  9/21/13

Final:

cc:

WO66-3513 (OC Division Chron. File)

HFR-CE4525 (BJDastoli)

WO66-3548 (EGenca)

CTS No.: ICC1300416

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/s/

PHILANTHA M BOWEN

09/30/2013

Entered in DARRTS on Behalf of CDRH/OC

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement A
General Hospital Devices Branch

DATE: September 11, 2013

TO: Philantha Bowen, Division of Pulmonary, Allergy, and Rheumatology Products, Office of Drug Evaluation II, Office of New Drugs, CDER

CC: Miya Paterniti, Division of Pulmonary, Allergy, and Rheumatology Products, Office of Drug Evaluation II, Office of New Drugs, CDER
Zhihao Peter Qiu, Biotech Manufacturing Assessment Branch, Division of Good Manufacturing Practice Assessment, Office of Manufacturing and Product Quality, Office of Compliance, CDER
Office of Combination Products at combination@fda.gov

THROUGH: Carl Fischer, Ph.D., Chief, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO66, Room 3526

 9/13/13

FROM: Emre Genca, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO66, Room 3548

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

INSPECTION SITE: F. Hoffmann-La Roche Ltd.
Wurmisweg, Kaiseraugst
Switzerland
FEI No. 3003973536

APPLICATION NO.: BLA 125472

PRODUCT NAME: Actemra Pre-filled Syringe with Needle Safety Device

CONSULT The request is to perform a post-inspection compliance review of F.

INSTRUCTIONS: Hoffmann-La Roche Ltd. (FEI No. 3003973536) in support of BLA 125472. Original classification of the inspection, which ended on July 25, 2013, was VAI. A 4-item Form FDA-483 was issued to the firm.

The Office of Compliance at CDRH received a consult request from CDER/OC/OMPQ/DGMPA/BMAB to perform a post-inspection compliance review of F. Hoffmann-La Roche Ltd. (FEI No. 3003973536) in support of BLA 125472.

Through BLA 125472, Genentech, Inc. requested that the Actemra Pre-filled Syringe with Needle Safety Device be approved for marketing and distribution. In a memorandum dated February 4, 2013 (attached), CDRH/OC recommended that F. Hoffmann-La Roche Ltd., the facility where final assembly of the finished combination product takes place, be inspected prior to approval of BLA 125472.

Application Documents Evaluation

Please see the attached Quality System EIR Review Memorandum.

Regulatory History Evaluation

Please see the attached Quality System EIR Review Memorandum for a review of the F. Hoffmann-La Roche Ltd. regulatory history.

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of the EIR, dated July 22-25, 2013, for the inspection that took place at the F. Hoffmann-La Roche Ltd., Kaiseraugst, Switzerland, facility, in support of BLA 125472, and recommends that the inspection be classified as VAI for the device Quality System regulations. CDRH defers to CDER to initiate any follow-up actions to the violations found during the inspection and to make a final decision on the overall classification of the inspection and on BLA approval.



Emre Genca

Attachments:

1. F. Hoffmann-La Roche Ltd. Quality System EIR Review Memorandum
2. CDRH/OC Memorandum for BLA 125472 dated February 4, 2013

Prepared: EGenca: 9/11/13

Reviewed: MITejero: 9/11/13

Reviewed: CFischer:

Final:

CTS No.: ICC1300416

BLA 125472

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/s/

PHILANTHA M BOWEN
09/30/2013



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: September 17, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID

TO: Philantha Bowen, Regulator Project Manager, CDER/OND/ODEII/DPARP

SUBJECT: BLA 125472
Applicant: Genetech, Inc
Drug: Actemra
Device: pre-filled syringe
Intended Use: treatment of rheumatoid arthritis
CTS Tracking: ICC1300018/CON131141

Overview and Recommendation

The Division Pulmonary, Allergy, and Rheumatology Products, Office of New Drugs, Center for Drug Evaluation and Research requested a human factors consultative review of a summative human factors report contained in BLA 125472 submitted by Genetech. The device is a pre-filled syringe for treatment of rheumatoid arthritis.

Genetech conducted two human factors validation study. The first study was conducted with 78 participants divided between two distinct user groups: 30 patients, 30 caregivers, and 18 healthcare professionals. The patient user group included needle-experience, and needle naïve patients, and all patients had a clinical diagnosis of Rheumatoid Arthritis. The study results showed task failures where injection site not pinched, injection at less than 45 degree angle and partially pushes down plunger. There were other non-critical use errors that were also observed during this study. Based on study results and root cause analysis, Genetech implemented changes to the Instructions for use and validated those changes in a supplemental validation study. The results of the supplemental study demonstrated that the IFU changes were effective in reducing the task failures and use errors seen in the previous study. **Therefore, this consultant finds the human factors data acceptable and has no outstanding concerns.**

Digitally signed by QuynhNhu Nguyen
Date: 2013.09.20 18:41:22 -04'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ronald D. Kaye

Digitally signed by Ronald D. Kaye
DN: c=US, ou=U.S. Government, ou=HHS, ou=FDA, ou=People
cn=Ronald D. Kaye, o=9 2342 19200300 100 1 1=1300110677
Date: 2013.09.23 09:33:12 -04'00'

Ron Kaye, Human Factors and Device Use-Safety Team Leader

Appendix 1: Summary of Human Factors Related Information

Genetech conducted a human factors validation study with 78 participants divided between two distinct user groups: 30 patients, 30 caregivers, and 18 healthcare professionals. The patient user group included needle-experienced, and needle naïve patients, and all patients had a clinical diagnosis of Rheumatoid Arthritis for greater than or equal to 6 months and a swollen joint count ≥ 4 and tender joint count of ≥ 4 with at least 1 joint in either hand is affected. Representative training was provided to patient users with the training decay of two to three weeks.

The following section provides a summary of the task failures seen in the study. Task failures were defined failures that have potential clinical impact and can result in patient harm.

1. Injection site not pinched

Injection site not pinched is the most frequently occurring error with potential clinical impact of loss in efficacy (14 errors or 81.8% success rate). Four of the 14 errors were determined to be due to the experimental artifact, and the remaining 10 errors were forgetting to pinch. Healthcare professionals appear less likely to make this error than needle-experienced patients and caregivers, or needle-naïve patients.

2. Injection at less than 45 degree angle

Three users injected at an angle less than 45 degrees, which the potential clinical impacts include pain, slower absorption rate and slight loss in efficacy. One forgot the correct angle for injection, and two others reverted to learned habits and preference from experience with other injections.

3. Partially pushes down plunger

Two participants failed to fully depress the plunger to activate the trigger fingers and needle-shield, which can result in potential loss in efficacy. Users may apply pressure with palm or index fingers, which compromises their ability to see or feel that they delivered the full dose and activated the trigger fingers. Video inspection showed that most of the medicine was injected into the pad.

There were other non-critical use errors that were observed such as participants not checking the expiration date, not inspecting the syringe, not inspecting the medicine in the syringe, not waiting for syringe to come to room temperature, not cleaning injection site, not letting the alcohol dry for 10 seconds, touching the injection site after wiping, unable to remove the needle cap, etc.

Based on the results of this study and root cause analysis, Genetech determined to implement changes to the Instructions for Use and validated those changes in a supplemental validation study. The results of this supplemental study demonstrated that the changes made to the IFU were effective in reducing the use errors seen in the previous study.

The following table shows a summary of use performance in the supplemental study and shows how they are compared to the previous study:

Task	Assessment Type	NA25656 Result (Success Rate, %)	20831D013 Result (Success Rate, %)
Check expiration date	Observed and Interview (knowledge based task)	50	100
Check medicine and syringe	Observed and Interview (knowledge based task)	77 (check medicine) 78 (check syringe)	100
Wait for medicine to come to room temperature	Interview (knowledge based task)	71	100
Remove needle cap	Observed	97	100
Pinch skin before needle insertion	Observed	82	100
Fully insert needle into injection site	Observed	97	100
Inject at 45-90 degree angle	Observed	96	100
Depress plunger completely	Observed	97	100

Appendix 2: CDRH HF Filing Review

DATE: February 14, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID
CC: Molly Story, Human Factors and Accessible Medical Technology Specialist, DAGID

TO: Philantha Bowen, Project Manager, CDER/OND/ODEII/DPARP
SUBJECT: BLA 125472
Company: Genetech
Drug: Actemra (Tocilizumab)
Device: Prefilled Syringe
CDRH CTS Tracking: ICC1300018/CON131141

CDRH Human Factors Review and Filing Memo

The Division of Pulmonary, Allergy, and Rheumatology Products, Office of Drug Evaluation II, Office of New Drugs, Center for Drugs Evaluation and Research requested a Human Factors consultative review of the BLA 125472 submitted by Genetech, Inc for the Actemra (Tocilizumab) prefilled syringe.

The Actemra prefilled syringe is single use disposable device with a fixed, or “staked-in” needle (SIN) that is assembled within the needle-safety device (NSD) unit to form a drug device combination product. The SIN is ½-inch long, 27 gauge needle that is covered by a needle cap (rigid needle shield) prior to use. The needle-cap must be removed to expose the needle and prepare the syringe for injection. Administration occurs by inserting the needle into the injection pad provided for the study (normally the skin for actual administration), and depressing the plunger until it stops. After completion of the injection, the needle is removed from the injection pad, and as the plunger is released, the needle shield (driven by the spring) moves into place to cover the needle. In its final position, the needle-shield locks in place to help prevent needlestick injuries.

The BLA contains necessary information to perform the review of the Human Factors component of the submission. It includes a Human Factors validation study report, and a supplemental Human Factors study report that was conducted based on changes as a result of the validation study. We recommend that from a CDRH Human Factors standpoint, the submission be filled for substantive review.

Appendix 3: Device Information

Actemra/RoActemra Pre-Filled Syringe

The unit used for the evaluation is a sterile, drug-filled syringe as shown in Figure 1.

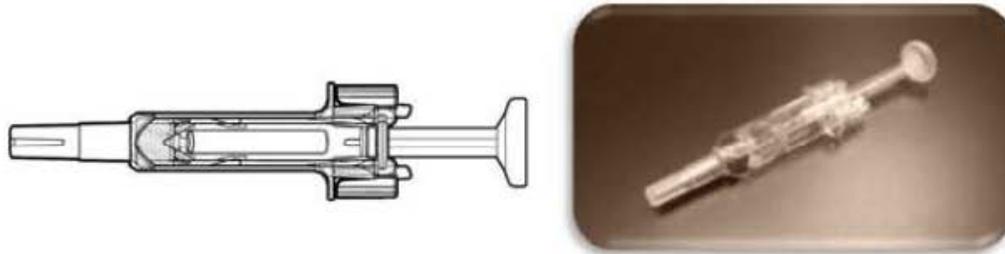


Figure 1. Pre-filled Syringe Unit

The single-use disposable device consists of a PFS with a fixed or “staked-in” needle (SIN) that is assembled within the needle-safety device (NSD) unit to form a drug-device combination product. The SIN is a ½-inch long, 27-gauge needle that is covered by a needle-cap (also referred to as the *rigid needle shield*) prior to use. The needle-cap must be removed to expose the needle and prepare the syringe for injection. Administration occurs by inserting the needle into the injection pad provided for the study (normally the skin for actual administration), and depressing the plunger until it stops. After completion of the injection, the needle is removed from the injection pad, and as the plunger is released, the needle shield (driven by the spring) moves into place to cover the needle. In its final position, the needle-shield locks in place to help prevent needle stick injuries.

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/s/

PHILANTHA M BOWEN

09/23/2013

Entered in DARRTS on Behalf of CDRH (Human Factors)

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

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 manufacturing 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: October 21, 2013

Applicant Name: Genentech, Inc.
U.S. License #: 1048
STN(s): 125472/0
Product(s): Tocilizumab (Actemra[®])

Short summary of application: BLA for the use of tocilizumab PFS for the treatment of Rheumatoid Arthritis.

FACILITY INFORMATION (DRUG SUBSTANCE)

Manufacturing Location: Oceanside, CA
Firm Name: Genentech, Inc.
Address: 1 Antibody Way, Oceanside, CA, 92056
FEI: 3006129086

Short summary of manufacturing activities performed: Drug substance (DS) manufacture, batch release testing [REDACTED]^{(b) (4)}, stability testing, raw materials testing

Manufacturing Location: SSF, CA
Firm Name: Genentech, Inc.
Address: 1 DNA Way, South San Francisco, CA 94080
FEI: 2017923

Short summary of manufacturing activities performed: [REDACTED]^{(b) (4)} testing

Manufacturing Location: Singapore
Firm Name: Roche Singapore Technical Operations Pte. Ltd.
Address: 10 Science Park Road, Singapore 117684
FEI: 3007164129

Short summary of manufacturing activities performed: [REDACTED]^{(b) (4)} testing for batch release.

Manufacturing Location: (b) (4)
Firm Name: Genentech, Inc.
Address: (b) (4)
FEI: (b) (4)

Short summary of manufacturing activities performed: Raw materials testing

FACILITY INFORMATION (DRUG PRODUCT)

Manufacturing Location: (b) (4)
Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)

Short summary of manufacturing activities performed: Drug Product manufacturing, sterility and endotoxin testing

Manufacturing Location: Switzerland
Firm Name: F. Hoffmann-La Roche Ltd.
Address: Wurmisweg; 4303 Kaiseraugst
FEI: 3003973536

Short summary of manufacturing activities performed: Labeling, assembly with needle safety device, secondary packaging, (b) (4); release testing with exception of sterility and endotoxin

Manufacturing Location: Germany
Firm Name: Roche Pharma AG
Address: Emil-Barell-Strasse 1; 79639 Grenzach-Wyhlen
FEI: 3002807206

Short summary of manufacturing activities performed: release testing with exception of sterility and endotoxin.

Manufacturing Location: (b) (4)
Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)

Short summary of manufacturing activities performed: Sterility and endotoxin testing

Manufacturing Location: (b) (4)
Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)

Short summary of manufacturing activities performed: Sterility and endotoxin. testing

³ The 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.”

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/s/

REYES CANDAU-CHACON
09/20/2013

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PHILANTHA M BOWEN
09/20/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: September 19, 2013

Reviewer: Teresa McMillan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD, M.S.
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Actemra (Tocilizumab)
Injection
162 mg/0.9 mL

Application Type/Number: BLA 125472

Applicant/Sponsor: Genentech

OSE RCM #: 2013-1208

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the Summative and Supplemental Human Factors study results for the proposed pre-filled syringe, container label, carton labeling, professional labeling, Instructions for Use, and (b) (4) submitted by Genentech, for BLA 125472, for Tocilizumab. The proposed proprietary name, Actemra (Tocilizumab) for this product is currently being evaluated in a separate review (OSE# 2013-1208).

1.1 PRODUCT INFORMATION

The following product information is provided in the December 21, 2012 submission. The Applicant intends to create a combined professional labeling insert for the proposed syringe and vial.

Table 1.

	<i>Actemra (approved)</i>	<i>Actemra (proposed)</i>
Active Ingredient	Tocilizumab	Tocilizumab
Indication of Use	Treatment of Adult Rheumatoid Arthritis (RA) and Systemic Juvenile Idiopathic Arthritis (SJIA),	Treatment of Adult Rheumatoid Arthritis (RA)
Route of Administration	Intravenous	Subcutaneous
Dosage Form	Injection (Single-use) vial	Injection (Single-use) Pre-filled syringe
Strength	80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL	162 mg/0.9 mL
Dose and Frequency	<ul style="list-style-type: none">• RA- 4 mg/kg once every 4 weeks followed by an increase to 8 mg/kg once every 4 weeks based on clinical response• SJIA-12 mg/kg once every 2 weeks if patient less than 30 kg or 8 mg/kg once every 2 weeks if patient is at or above 30 kg	<ul style="list-style-type: none">• RA patients less than 100 kg- 162 mg every other week, followed by an increase to every week based on clinical response• RA patients at or above 100 kg- 162 mg every week
How Supplied	Sterile concentrate, preservative-free single-use vial (20 mg/mL) solution for intravenous infusion. Supplied individually or in box of 4 single-use vials.	Sterile preservative-free liquid solution in a single-use pre-filled syringe
Storage	Refrigerated at 2°C to 8°C (36° to 46° F). Do not freeze. Store in the original container to protected from light.	Refrigerated at 2°C to 8°C (36° to 46° F). Do not freeze. Store in the original container to protected from light.

2 MEDICATION ERROR RISK ASSESSMENT

DMEPA searched the FDA Adverse Event Reporting System (FAERS) and ISMP databases for Actemra (Tocilizumab) medication error reports (See Appendix A for a description of the databases). Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, we also evaluated the container labels, carton labeling, and instructions for use, (b) (4) and insert labeling (See Appendices B, C, E, and F for images). Additionally, the currently approved Actemra (Tocilizumab) labels and labeling were reviewed (See Appendix D).

2.1 SELECTION OF MEDICATION ERROR CASES AND LITERATURE SEARCH

DMEPA conducted a recent FAERS, ISMP, and literature search as part of a FDAAA Section 915 New Molecular Entity (NME) Postmarketing Safety Evaluation.² Although we identified errors in this review, our evaluation noted that the Prescribing Information, carton labeling, and the container labels for the currently marketed Actemra formulation were adequate to help mitigate the medication errors observed. We have also ensured that the proposed pre-filled syringe is also adequately labeled to help mitigate these errors.

2.2 PACKAGING, LABELS, AND LABELING DEFICIENCIES

This product is the first Tocilizumab subcutaneous injectable pre-filled syringe formulation intended to deliver a fixed dose of 162 mg. This dose is supported by the dosage and administration section and is appropriate for this packaging configuration.

Actemra (Tocilizumab) is currently marketed as an intravenous injectable formulation (vial) and is dosed in mg/kg, whereas the proposed formulation is a subcutaneous injectable formulation (pre-filled syringe) that has a fixed dose. Although there are differences amongst the two formulations, it is common for different dosage formulations and dosages to exist together in the market within the same product line (i.e. Orencia). Postmarketing experience with similar products show that there is always a risk of wrong route and wrong frequency medication errors with marketing multiple dosage forms under the same product line. Therefore, it is important that these differences are adequately highlighted in the labels and labeling for this product to help mitigate these types of medication errors

The route of administration does appear on the labels and labeling of Tocilizumab, but it is not overly prominent. This statement should be more prominent to help further mitigate wrong route medication errors because the device design does afford administration by other routes. The frequency of administration is adequately presented in the insert labeling and thus no recommendations are warranted.

Subcutaneous Tocilizumab will be marketed as one strength (162 mg/0.9 mL), whereas the marketed intravenous injectable formulations are available in three different strengths. The carton labeling for the proposed strength is not adequately differentiated from the currently marketed 80 mg/4 mL

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

² OSE Review #2010-601 dated March 5, 2013.

strength. This is problematic because the lack of label differentiation can lead to selection errors of the wrong strength.

We also note the insert labeling uses dangerous abbreviations such as “IV” and “SC”. The Agency discourages the use of these dangerous abbreviations because they may be interpreted as “four”, “ill” or “intravertebral” and “SL” or “sublingual”.

In addition, the Applicant did not bold and highlight the headings for each section of the IFU as shown in both tested versions of the IFU. We recommend the marketed version include the same bolded and highlighted headings as the tested versions.

2.3 SUMMATIVE AND SUPPLEMENTAL HUMAN FACTORS STUDY

The Summative Human Factors study assessing the usability of the single-use pre-filled syringe and its instructions for use was previously evaluated by DMEPA and CDRH as part of a pre-BLA meeting package (see Appendix G). Table 2 lists the critical and essential task failures noted in the study.

The supplemental Human Factors study protocol was not submitted to the protocol prior to conducting the study. This study assessed whether revisions made to the IFU and training were effective in improving the critical/essential task failures listed in Table 2 and to ensure the revisions did not introduce any new errors. The supplemental study design is discussed in Appendix H.

Table 2. Summative and Supplemental Study Results

Critical/Essential Tasks	Summative Study Results Success Rates%	Supplemental Study Results Success Rates%
	[N=75 30 RA patients 30 caregivers 15 HCP] *Majority of the errors occurred with the RA patients and caregivers	[N=15 RA patients]
Check expiration date	50	100
Check medicine and syringe	77 (check medicine) 78 (check syringe)	100
Wait for medicine to come to room temperature	71	100
Remove needle cap	97	100
Pinch skin before needle insertion	82	100
Fully insert needle into injection site	97	100
Inject at 45-90 degree angle	96	100
Depress plunger completely	97	100

Two limitations to the study design were noted: the different decay time and lack of testing for the (b) (4).

There was a 30-60 minute decay time between training and self-injection and therefore the study did not capture how a user would perform under “real world” use. This product is given once weekly to every other week, so it is conceivable that a significant time may pass from the time a patient receives training on the use of the product and when they administer their medication. After seeking clarification from the Applicant, (b) (4)

(b) (4). However, we disagree with their rationale. Due to the limited decay time, this study design only tested that this device can be successfully used immediately following training and did not test if users can successfully use the device when considerable time has passed.

In regards to the Applicant not testing the (b) (4)

We refer to the summative human factors results listed in Table 2 for validation of this device. We are not recommending the summative human factors test be retested because the failures observed in the summative HFS are known failures for this type of device and the recommendations made for the IFU and (b) (4) in Section 4.2 Comments to the Applicant do not change the context of the instructions that were previously tested.

In addition, Table 3. list the task failures identified in the summative study that may have potential for clinical impact. We note that these failures are common for pre-filled syringes and not unique to the proposed syringe and therefore find that these failures pose no new risks from a medication error prospective. However, we defer to clinical to determine if these critical task failures will have any clinical significance for users.

Table 3. Summative Study Task Errors with Potential Clinical Impact

Critical Task Error	Potential clinical impact
Injection site not pinched	Potential loss in efficacy
Injection at less than a 45 degree angle	Pain, slower absorption rate and loss of efficacy
Failure to Depress plunger	Potential loss in efficacy
Failure to Depress plunger after completing injection	Potential for needle stick injury or infection or transmission of bloodborne/ Significant pathogen

3 CONCLUSIONS

The Human Factors Study confirmed that users may encounter difficulties while administering this product. However, these difficulties are common for pre-filled syringes and not unique to the proposed syringe. In addition, DMEPA concludes that the proposed label and labeling can be improved to increase the prominence of important information on the label to promote the safe use of the product. We provide recommendations in section 4.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this BLA:

4.1 COMMENTS TO THE DIVISION

Based on this review, DMEPA provides the following comments for consideration by the review division prior to the approval of this BLA:

A. General Comments

The Applicant lists the following critical task failures: injection site not pinched, injection at less than a 45 degree angle, failure to depress plunger and failure to depress plunger after completed injection as potential clinical significant failures. We note that these failures are common for pre-filled syringes and not unique to the proposed syringe. We defer to clinical to determine if these critical task failures will have any clinical significant impact towards users.

B. Insert Labeling

The insert labeling uses dangerous abbreviations such as “IV” and “SC”. The Agency discourages the use of these dangerous abbreviations because they may be interpreted as “four”, “ill” or “intravertebral” and “SL” or “sublingual”. Revise all instances of the abbreviations “IV” and “SC” to state subcutaneously and intravenously, respectively.

4.2 COMMENTS TO THE APPLICANT

Based on this review, DMEPA recommends the following be implemented prior to approval of this BLA:

A. Instructions for Use

The IFU submitted to the Agency is not the same as what was tested in the summative human factors study. The IFU does not contain the bolded paragraph and instructional headings. Bold all paragraph and instructional headings so that the reader is aware of what each paragraph and instruction step references.

B.



C. Carton Labeling and Container Labels

1. The dosage form has been omitted. Revise the labels and labeling to read as follows:

Actemra
(tocilizumab)
Injection

2. Increase the font size of the “For Subcutaneous Injection Only” statement to increase its prominence.

3. The container label and the carton labeling for proposed strength is not adequately differentiated from the marketed 80 mg/4 mL strength. The trade dress colors used for the label are similar (shades of green) across both these strengths thereby minimizing the strength differentiation. To prevent selection errors, revise this label to provide more color contrast between all strengths within this product line.

D. Carton Labeling

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

Single Dose Prefilled Syringe – Discard Unused Portion

E. Container Labeling

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

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

ISMP DATABASES

ISMP

The Institute for Safe Medication Practices (ISMP) operates two national error-reporting programs—the National Medication Errors Reporting Program (ISMP MERP) and the National Vaccine Errors Reporting Program (ISMP VERP). Both are confidential, practitioner-based voluntary reporting programs that provide expert analysis of system-based causes of medication and vaccine errors.

QUANTROS MEDMARX DATABASE

MEDMARX® is a national, Internet-accessible database that hospitals and health care systems use to track and trend adverse drug reactions and medication errors. Hospitals and health care systems participate in MEDMARX voluntarily and subscribe to it on an annual basis. MEDMARX is a quality improvement tool, which facilitates productive and efficient documentation, reporting, analysis, tracking, trending, and prevention of adverse drug events.

PA-PSRS

The Pennsylvania Patient Safety Authority developed the Pennsylvania Patient Safety Reporting System, known as PA-PSRS, a secure, web-based system that permits healthcare facilities to submit reports of what Act 13 of 2002, Act 30 of 2006 and Act 52 of 2007 defines as "Serious Events" and "Incidents." The Authority analyzes the collected data to identify trends and recommend changes in healthcare practices and procedures that may be instituted to reduce the number and severity of future serious events and incidents. More than 525 healthcare facilities are subject to Act 13 of 2002 and Act 30 of 2006 requirements.

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in Full as b4 (CCI/tS) immediately following this
page

Appendix G: Meeting Comments

2.1. Human Factors

Question 1:

Does the Agency agree

(b) (4)

CDRH Response to Question 1:

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

(1) Two participants who had hand impairment were not able to perform their first injection. Ensure that this difficulty for hand impaired users is communicated to healthcare providers so that the patient's caregivers will understand the need to assist the patients in performing the injection at home.

(2) Some participants failed essential tasks necessary to insure proper injection. Of most importance were:

- pinching the skin*
- injecting at a 45 degree angle*
- completely depressing the plunger*
- visually checking the drug and the syringe*
- waiting for the drug to come to room temperature and*
- releasing the plunger.*

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

Discussion:

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

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

(b) (4)

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

(b) (4)

Page 4

Roche summarized the meeting discussion regarding the device use errors [REDACTED] (b) (4) as follows:

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

- [REDACTED] (b) (4)

Appendix H: Summary of the Supplemental Human Factors Study Design

Study Objective

The Supplemental Human Factors Study was conducted to assess whether revisions made to the IFU and training were effective in improving the critical/essential task failures and to ensure the revisions did not introduce any new errors.

Study Participants

This simulated use study consisted of 15 Rheumatoid Arthritis (RA) patients only [6 naïve and 9 injection experienced].

Study Design: Training and Test sessions

The RA patients were trained by registered nurses to administer an injection using the commercial version of the IFU. The training consisted of one-on-one training sessions on all the steps of the IFU. After training, the nurse trainers directed and coached the participants in the first simulated use injection with the pre-filled syringe. After the assisted use, there was training decay time of 30-60 minutes followed by the second unassisted simulated use injection with the pre-filled syringe.

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/s/

TERESA S MCMILLAN
09/19/2013

LUBNA A MERCHANT
09/19/2013

CAROL A HOLQUIST
09/19/2013



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: September 4, 2013

From: Jason To, Biomedical Engineer
CDRH/ODE/DAGRID/General Hospital Devices Branch (GHDB)

To: Philantha Bowen
CDER/OND/ODEII/DPARP

Subject: CDRH Consult Request, ICC1300412
Combination Product Review: BLA 125472, PFS

Firm: Genentech, Inc.
1 DNA Way MS# 241B
South San Francisco, CA 94080-4990

1. Consult Request

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH). The device constituent of this combination product is a prefilled syringe from Genentech Inc. CDER has requested that CDRH provide a consult to evaluate the firm's responses to initial questions posed by CDRH in the previous consult GEN1300014.

2. Documents

FDA Response 7-1-13_BL125472 (Dated 07/01/2013)

3. Device Description

Please see document "P.7 Container Closure System [Actemra SC, PFS + NSD 162 mg/0/9 mL]"

4. CDRH Review and Comments

CDRH's review consisted of assessing the firm's response to CDRH's initial questions.

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

Reviewer Assessment of Firm's Response: The sponsor has updated the DMF references for (b) (4) listed in Table P.7-1 to include the correct reference numbers of (b) (4) and (b) (4). This appears to be adequate.

Sincerely,

Jason To -S

Digitally signed by Jason To -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Jason To -S,
0.9.2342.19200300.100.1.1=2000489354
Date: 2013.09.10 12:06:45 -04'00'

Jason To
Biomedical Engineer

Concurred By:



Richard C. Chapman
2013.09.10 15:20:54
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Richard Chapman
Chief, General Hospital Devices Branch

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/s/

PHILANTHA M BOWEN

09/16/2013

Entered in DARRTS on behalf of CDRH/GHDB



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center

FINAL LABEL AND LABELING REVIEW

Date: September 5, 2013

Reviewer: Kimberly Rains, Pharm.D.
Office of Biotechnology Products

Through: Gerry Feldman, Ph.D.
Division of Monoclonal Antibodies

Marjorie Shapiro
Division of Monoclonal Antibodies

Application: BLA 125472

Product: Actemra (tocilizumab)

Applicant: Genentech Inc.

Submission Date(s): December 21, 2012

Executive Summary

The carton and container labels for Actemra (tocilizumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, USP 36/ NF 31 (5/1/13-12/31/13). Labeling deficiencies were identified. Comments are listed in the conclusions section. The carton and container labeling submitted on December 21, 2012 are acceptable.

Background and Summary Description

STN 125476 for Actemra has been submitted to introduce a 162 mg/ 0.9 mL prefilled syringe configuration. The product is currently approved under STN 125276 on January 8, 2010 in single-use vials in the following concentrations: 80 mg/ 4 mL, 200 mg/ 10 mL, and 400 mg/ 20 mL.

Materials Reviewed:

<http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea681153e0c>

Sequence: 0000

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

Start of Sponsor Material



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

- (1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]. **Conforms**
- (2) The name, address, and license number of manufacturer; **Conforms**
- (3) The lot number or other lot identification; **Conforms**

(4) The expiration date; **Conforms**

(5) The recommended individual dose, for multiple dose containers. **Not Applicable.**

(6) The statement: “Rx only” for prescription biologicals. **Conforms**

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. **Conforms.** Syringe label cannot accommodate a medication guide statement. However, a medication guide statement appears on the carton.

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. **Not Applicable**

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label.

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. **Not Applicable**

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – This conforms to the regulation per CMC visual inspection. **Conforms**

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; **Conforms. NDC number provided on the carton.**

C. 21 CFR 201.5 Drugs; adequate directions for use; **Conforms**

D. 21 CFR 201.6 Drugs; misleading statements; **Conforms**

E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence]. **Conforms**

F. 21 CFR 201.15 Drugs; prominence of required label statements; **Conforms**

G. 21 CFR 201.17 Drugs; location of expiration date; **Conforms**

H. 21 CFR 201.25 Bar code; **Conforms**

I. 21 CFR 201.50 Statement of identity; **Conforms**

J. 21 CFR 201.51 Declaration of net quantity of contents; **Conforms**

K. 21 CFR 201.55 Statement of dosage; **Conforms**

L. 21 CFR 201.100 Prescription drugs for human use; **Conforms**

Start of Sponsor Material

(b) (4)



End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label

a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]. **Conforms**

- b) The name, addresses, and license number of manufacturer; **Conforms**
- c) The lot number or other lot identification; **Conforms**
- d) The expiration date; **Conforms**
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative”. **Conforms**
- f) The number of containers, if more than one; **Not Applicable**
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; **Conforms**
- h) The recommended storage temperature; **Conforms**
- i) The words “Do not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product; **Conforms**
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; **Conforms**
- k) The route of administration recommended, or reference to such directions in and enclosed circular; **Conforms**
- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; **Not Applicable**
- m) The type and calculated amount of antibiotics added during manufacture; **Not Applicable**
- n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; **Conforms**
- o) The adjuvant, if present; **Not Applicable**
- p) The source of the product when a factor in safe administration; **Not Applicable**

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; **Not Applicable**

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency”; **Conforms**

s) The statement “Rx only” for prescription biologicals; **Conforms**

B. 21 CFR 610.62 Proper name; package label; legible type [*Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of “specified” biological products listed in 21 CFR 601.2(a)*]

a) Position. The proper name of the product on the package label shall be placed above any trademark or trade name identifying the product and symmetrically arranged with respect to other printing on the label. **Not Applicable**

b) Prominence. The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name. **Not Applicable**

c) Legible type. All items required to be on the container label and package label shall be in legible type. “Legible type” is type of a size and character which can be read with ease when held in a good light and with normal vision. **Not Applicable**

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; **Not Applicable**

D. 21 CFR 610.64 Name and address of distributor

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: “Manufactured for _____”, “Distributed by _____”, “Manufactured by _____ for _____”, “Manufactured for _____ by _____”, “Distributor: _____”, or “Marketed by _____”. The qualifying phrases may be abbreviated. **Not Applicable**

- E. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter; **Conforms**
- F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35]. **Conforms**
- G. 21 CFR 201.5 Drugs; adequate directions for use; **Conforms**
- H. 21 CFR 201.6 Drugs; misleading statements; **Conforms**
- I. 21 CFR 201.10 Drugs; statement of ingredients;[Placement and Prominence] **Conforms**
- J. 21 CFR 201.15 Drugs; prominence of required label statements; **Conforms**
- K. 21 CFR 201.17 Drugs; location of expiration date; **Conforms**
- L. 21 CFR 201.25 Bar code label requirements; **Conforms**
- M. 21 CFR 201.50 Statement of identity; **Conforms**
- N. 21 CFR 201.51 Declaration of net quantity of contents; **Conforms**
- O. 21 CFR 201.55 Statement of dosage; **Conforms**
- P. 21 CFR 201.100 Prescription drugs for human use; **Conforms**

Conclusions

The labels submitted on December 21, 2012 meet regulatory requirements and are acceptable. However, there are CDER preferences that may be recommended by the Division of Medication Error and Prevention.

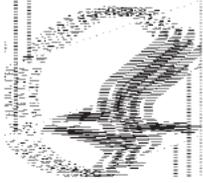
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/s/

KIMBERLY M RAINS
09/10/2013

GERALD M FELDMAN
09/10/2013

MARJORIE A SHAPIRO
09/10/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Pediatric and Maternal Health Staff Review

Date: August 23, 2013

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne P. Yao, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Drug: ACTEMRA[®] (tocilizumab) subcutaneous injection

BLA: 125472\0

Subject: Restructuring of the pregnancy and nursing mothers sections of labeling

Applicant: Genentech

Materials Reviewed: December 21, 2012, package insert submitted by sponsor.

Consult Question: “Requesting a review of sections 8.1 and 8.3 of the PI to access compliance regarding the new labeling standards for pregnancy and lactation that will be implemented in 2014. The present application is for subcutaneous administration using a pre-filled syringe. The label will cover administration by both the IV and SC routes. Current label for SC administration is attached.”

INTRODUCTION

On December 21, 2012, Genentech, submitted an original Biologics License Application (BLA) for the use of Actemra (tocilizumab) subcutaneous injection for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). Actemra (tocilizumab) for intravenous injection was approved on January 8, 2010, for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies.

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and update the Pregnancy and Nursing Mothers information in the Actemra labeling.

This review provides suggested revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Actemra (tocilizumab)

Actemra is a recombinant, interleukin 6 (IL-6) receptor monoclonal antibody.¹ Actemra inhibits IL-6-mediated signaling through receptors by binding specifically to soluble and membrane-bound IL-6 receptors. IL-6 is involved in t-cell activation, induction of immunoglobulin secretion and initiation of hepatic acute phase protein synthesis. In addition, IL-6 plays a role in the inflammatory processes such as those that occur in rheumatoid arthritis through the production of IL-6 by synovial and endothelial cells leading to the local production of IL-6 in joints affected by the inflammatory process.¹

Rheumatoid arthritis (RA) and pregnancy

Rheumatoid arthritis is a chronic, autoimmune disease that affects more women than men and usually manifests between the ages of 30 to 50.² RA causes arthritis of the large and small joints and causes joint stiffness, swelling, synovial effusion and pain. Patients with RA are typically treated with a disease modifying anti-rheumatic drug (DMARDs) such as cyclosporine, methotrexate, leflunomide, azathioprine, cyclophosphamide, sulfasalazine or hydroxychloroquine or a biological agent such as Actemra, Cimzia, Enbrel, Humira, Kineret, Orencia, Remicade, Rituxan or Simponi. Management of RA can be challenging in pregnant women. While some women experience an improvement in RA symptoms during pregnancy many others require continuous medication management.²

¹ ACTEMRA (tocilizumab), April 29, 2013, approved package insert.

² Al-Shakarchi, I., Gullick, N., Scott, D. (2013). Current perspectives on tocilizumab for the treatment of rheumatoid arthritis: a review. *Patient Preference and Adherence*,7:653-666.

DISCUSSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

The Drugs and Lactation Database (LactMed)³ was searched for available lactation data on with the use of Actemra, and no information was found. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

CONCLUSION

The pregnancy subsection of Actemra labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of the Actemra labeling was revised to comply with current labeling recommendations.

The PMHS-MHT discussed labeling recommendations with the review team during a labeling meeting on August 7, 2013. The following PMHS- MHT recommendations reflect the discussions with the Division at that meeting.

PMHS LABELING RECOMMENDATIONS

PMHS-MHT labeling recommendations (label excerpts) appear below.

HIGHLIGHTS

-----USE IN SPECIFIC POPULATIONS-----

Pregnancy: Based on animal data, may cause fetal harm. (b) (4) (8.1)

Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother. (8.3)

³ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

Pregnancy Category C

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ACTEMRA during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

Reviewer comment: PMHS-MHT is currently reviewing a request by the sponsor (b) (4) . The information in the above paragraph may change pending the outcome of that review.

Risk Summary

Adequate and well controlled studies with ACTEMRA have not been conducted in pregnant women. In animal reproduction studies, administration of tocilizumab to cynomolgus monkeys during organogenesis caused abortion/embryo-fetal death at dose exposures 1.25 times the human dose exposure of 8 mg per kg every 2 to 4 weeks. The incidence of malformations and pregnancy loss in human pregnancies have not been established for ACTEMRA. However, all pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. ACTEMRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

In general, monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Animal Data

An embryo-fetal developmental toxicity study was performed in which pregnant cynomolgus monkeys were treated intravenously with tocilizumab (daily doses of 2, 10, or 50 mg per kg from gestation day 20-50) during organogenesis. Although there was no evidence for a teratogenic/dysmorphogenic effect at any dose, tocilizumab produced an increase in the incidence of abortion/embryo-fetal death at 10 mg per kg and 50 mg per kg doses (1.25 and 6.25 times the human dose of 8 mg per kg every 2 to 4 weeks based on a mg per kg comparison).

Testing of a murine analogue of tocilizumab in mice did not yield any evidence of harm to offspring during the pre- and postnatal development phase when dosed at 50 mg per kg intravenously with treatment every three days from implantation until day 21 after delivery (weaning). There was no evidence for any functional impairment of the development and behavior, learning ability, immune competence and fertility of the offspring.

Reviewer comment: The animal data section above may receive further edits by the Division's pharmacology/toxicology reviewer.

8.3 Nursing Mothers

(b) (4)

It is not known whether tocilizumab is present in human milk or if it would be absorbed systemically in a breastfed infant after oral ingestion. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ACTEMRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Reviewer comments:

- *PMHS-MHT recommends the Division request a lactation study in women using Actemra therapeutically and who are nursing an infant. The Division is considering the recommendation.*
- *PMHS-MHT refers to the final BLA action for final labeling.*

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

/s/

CARRIE M CERESA
08/23/2013

JEANINE A BEST
08/23/2013

LYNNE P YAO
08/23/2013

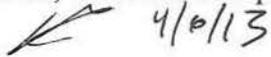
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement A
General Hospital Devices Branch

DATE: February 4, 2013

TO: Miya Paterniti, OND/ODEII/DPARP, CDER, WO-22, Room 3343
Maria Candauchacon, OMPQ/DGMPA/BMAB, CDER, WO-51, Room 2252

CC: Theresa Michele, OND/ODEII/DPARP, CDER, WO-22, Room 3232
Patricia Hughes, OMPQ/DGMPA/BMAB, CDER, WO-51, Room 4328
Philantha Bowen, OND/ODEII/DPARP, CDER, WO-22, Room 3326
Office of Combination Products at combination@fda.gov

THRU: Carl Fischer, Chief, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO-66, Room 3526 

FROM: Emre Genca, General Hospital Devices Branch, Division of Enforcement A, Office of Compliance, CDRH, WO-66, Room 3533

SUBJECT: Inter-Center consult requested by OND/ODEII/DPARP/CDER. This is a premarket consult for Actemra, BLA 125472, submitted by Genentech Inc.

CONSULT INSTRUCTIONS: Evaluate the information provided and advise on the need for inspection.

Objective

The Office of Compliance at CDRH received a consult request from CDER regarding the device manufacturing information provided in support of this submission from Genentech, Inc.

Product Description

Actemra (tocilizumab) is a recombinant, humanized, anti-human interleukin-6 receptor (IL-6R) monoclonal antibody of the immunoglobulin G1 subclass (IgG1). It is indicated for the treatment of adult patients with moderately to severely acute rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies. Actemra can be used alone or in combination with methotrexate (MTX) and/or other disease-modifying anti-rheumatic drugs (DMARDs).

Actemra is supplied in a 1 mL ready-to-use, single-use prefilled syringe (PFS) (b) (4) for subcutaneous (SC) injection. (b) (4) device delivers 0.9 mL (162 mg) of tocilizumab. The recommended dose of tocilizumab for adult patients is 162 mg given once every week as a SC injection.

(b) (4) is the site where drug product manufacturing as well as sterility/endotoxin testing activities take place. The most recent inspection of this site was OAI.

F. Hoffmann-La Roche Ltd., Wurmisweg, 4303 Kaiseraugst, Switzerland, FEI No. 3003973536, is the site where labeling, final assembly with needle safety device, secondary packaging, (b) (4) and release testing (except sterility/endotoxin testing) activities take place.

Consult Evaluation

CDRH Office of Compliance reviewed the inspectional history of F. Hoffmann-La Roche Ltd. All previous inspections were drug-related and did not cover devices. Drug manufacturing information was provided in IND 11972 dated October 1, 2012.

CDRH Recommendation

CDRH recommends that the approval of BLA 125472 be deferred until the time when a satisfactory preapproval inspection pertaining to applicable device manufacturing regulations has been conducted at F. Hoffmann-La Roche Ltd. Attached to this review is an inspection guidance document.



Emre Genca

Prepared: EGenca: 2/4/13
Reviewed: CFischer: *CF* 2/6/13
Final:

cc:
WO66-3523 (Division Firm File)
WO66-3513 (Division Chron. File)
WO66-3533 (EGenca)

CTS No.: ICC1300011

ASSIGNMENT

F. Hoffmann-La Roche Ltd.
Wurmisweg, 4303 Kaiseraugst
Switzerland
FEI No. 3003973536

Please conduct a “For-Cause” inspection of this firm in order to assess its compliance with the Quality System regulation (21 CFR Part 820), Medical Device Reporting regulation (21 CFR Part 803), and the Corrections and Removals regulation (21 CFR Part 806). This inspection should specifically focus on Design Controls, Purchasing Controls, Acceptance Activities, MDRs, Complaint Handling, Corrective and Preventive Actions, and Corrections and Removals.

INSPECTIONAL GUIDANCE

Perform a directed inspection based on the recommendations of this Inspectional Guidance and the Quality System Inspection Technique (QSIT) Guide.

Note: As per usual inspection, please use your discretion to determine which documentation should be collected to support the observations.

21 CFR 820.30 Design Controls

Each manufacturer shall establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met.

1. Determine if the firm has established and maintained design control records for Actemra. Determine if design changes were implemented, including those related to corrective actions. Determine if the design changes have been verified, validated, and do not adversely affect the finished device.
2. Records reflecting design development, design input and output, design review, design verification, validation, and transfer as well as design changes for Actemra should be reviewed and collected.
3. Determine if the firm has a Risk Management Program. Does the Risk Management Program extend through the various Quality System processes such as Design Controls, CAPA, and Complaint Handling and integrated with Purchasing Controls and Acceptance Activities?

21 CFR 820.50 Purchasing Controls

Each manufacturer shall establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements.

1. Evaluation of the manufacturer's purchasing control over its suppliers.
 - a. Identify the sources of raw materials for Actemra and its components.
 - b. Are these components purchased sterile, sterilized in-house, or sterilized by a contract sterilizer?
 - c. Review the Purchasing Control procedures for Actemra and its components.
 - i. Evaluate the agreement between the supplier and the manufacturer, taking note whether the supplier is required to notify the manufacturer of changes in the product that may affect the quality of the finished device.
 - ii. Collect documentation regarding audit procedures the manufacturer has on its suppliers.
 - d. Does Genentech, Inc. have a written purchasing agreement with F. Hoffmann-La Roche Ltd.? Does Genentech, Inc. audit this supplier?

21 CFR 820.70 Production and Process Controls

Each manufacturer shall develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications. Where deviations from device specifications could occur as a result of the manufacturing process, the manufacturer shall establish and maintain process control procedures that describe any process controls necessary to ensure conformance to specifications.

1. Review and collect the SOPs and methods that define and control the assembly processes, including packaging, of Actemra.
2. If automated processes are used in the final assembly of Actemra, review and collect the results of software validation for its intended use and SOPs.

21 CFR 820.75 Process Validation

Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures.

1. Review and collect the firm's procedures for monitoring and control of process parameters for any validated process taking place during the assembly, including packaging, of Actemra.

21 CFR 820.80 Acceptance Activities

Each manufacturer shall establish and maintain procedures for acceptance activities. Acceptance procedures include inspections, test, or other verification activities.

1. Review the firm's acceptance process for purchased supplies and services and document how the firm handles deviations from its established acceptance criteria.
 - a. Review the firm's qualification of its component supplier and associated acceptance testing.
 - b. Review documentation of the firm's audit checks on its suppliers.
2. Identify and review the firm's acceptance criteria and any acceptance testing performed on purchased supplies or services specifically for the components of Actemra.
 - a. What type of testing is done as part of the final release criteria for Actemra?
 - b. Are incoming products tested and the functionality verified prior to final release?
 - c. What is the firm's procedure for receipt of nonconforming products from suppliers?
 - d. Are device constituents ever rejected on incoming inspection? Is there a written procedure for this activity? What is the rejection rate – if any?

21 CFR 820.100 Corrective and Preventive Action (CAPA)

Each manufacturer shall establish and maintain procedures for implementing corrective and preventive action to include analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems.

1. In addition to the normal QSIT CAPA review, please review any CAPAs performed specifically for this combination product or any other substantially equivalent.
2. Review and collect the firm's final release testing procedures and results.

21 CFR 820.198 Complaint Files

Each manufacturer shall maintain complaint files. Each manufacturer shall establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit.

1. Collect a copy of the firm's written complaint handling procedures and document in the inspection report any deviations from the firm's written SOP. Determine if there are any complaints reviewed which relate to an adverse event which should

have been reported under the Medical Device Reporting (MDR) regulation (21 CFR 803) even if the initial complaint was an AER.

- a. If the review of the firm's complaint files identifies complaints that were not reported under MDR but appear to be reportable, please collect a copy of the complaint records. If the complaints include reports of malfunctions that would be likely to cause or contribute to a death or serious injury, provide an explanation of how the malfunction could cause or contribute to a death or serious injury and obtain the firm's rationale for considering the event to be not reportable.

21 CFR 806 Medical Device Reports of Corrections and Removals

1. Collect the firm's procedures for Recalls and/or Voluntary Corrections and Removals.

Recommendations:

CDRH recommends the following:

1. The Office of Regulatory Affairs (ORA) should be consulted regarding the participation of a Medical Device and Drug Expert to assist with the inspection.
2. The CDRH inspectional guidance will serve as an attachment to the inspection assignment written and routed by CDER's Office of Compliance for the Actemra device.

REGULATORY STRATEGY

The establishment inspection report (EIR) for F. Hoffmann-La Roche Ltd. should be shared with CDRH. If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Emre Genca
Consumer Safety Officer
General Hospital Devices Branch
Division of Enforcement A
Office of Compliance, WO-66, Room 3533
Phone: 301-796-5324

Secondary Contact (if Primary is unavailable and a timely answer is required):

Carl Fischer
Chief

General Hospital Devices Branch
Division of Enforcement A
Office of Compliance, WO-66 Room 3526
Phone: 301-796-5489

**THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN
TO IT DURING THE INSPECTION. THIS ATTACHMENT CONTAINS
PREDECISIONAL INFORMATION.**

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

/s/

PHILANTHA M BOWEN

04/10/2013

Entered in DARRTS on behalf of CDRH/OC

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 125472
Application Type: BLA
Name of Drug: Actemra (Tocilizumab) via prefilled syringe
Applicant: Genentech, A Member of the Roche Group
Submission Date: December 21, 2012
Receipt Date: December 21, 2012

1.0 Regulatory History and Applicant's Main Proposals

Actemra is currently approved in an intravenous (IV) formulation for the treatment of rheumatoid arthritis (RA) for patients who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs. This BLA does not provide for a new indication. This submission provides for a change in the formulation in order to support the new route of administration (the subcutaneous use of tocilizumab, via a pre-filled syringe) for the treatment of adult patients with RA.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 60 day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by March 12, 2013. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required

Selected Requirements of Prescribing Information (SRPI)

• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

YES

12. All text must be **bolded**.

Comment:

YES

Selected Requirements of Prescribing Information (SRPI)

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- YES** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- YES** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- YES** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- YES** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- NO** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Selected Requirements of Prescribing Information (SRPI)

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY

Selected Requirements of Prescribing Information (SRPI)

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- NO** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- YES** 42. All text is **bolded**.

Comment:

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information (SRPI)

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

PHILANTHA M BOWEN
02/15/2013

LADAN JAFARI
02/19/2013



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: February 14, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID
CC: Molly Story, Human Factors and Accessible Medical Technology Specialist, DAGID

TO: Philantha Bowen, Project Manager, CDER/OND/ODEII/DPARP

SUBJECT: BLA 125472
Company: Genetech
Drug: Actemra (Tocilizumab)
Device: Prefilled Syringe
CDRH CTS Tracking: ICC1300018/CON131141

CDRH Human Factors Review and Filing Memo

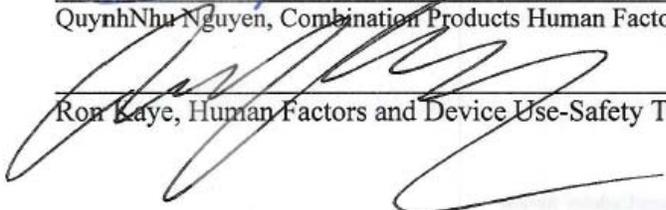
The Division of Pulmonary, Allergy, and Rheumatology Products, Office of Drug Evaluation II, Office of New Drugs, Center for Drugs Evaluation and Research requested a Human Factors consultative review of the BLA 125472 submitted by Genetech, Inc for the Actemra (Tocilizumab) prefilled syringe.

The Actemra prefilled syringe is single use disposable device with a fixed, or “staked-in” needle (SIN) that is assembled within the needle-safety device (NSD) unit to form a drug device combination product. The SIN is ½-inch long, 27 gauge needle that is covered by a a needle cap (rigid needle shield) prior to use. The needle-cap must be removed to expose the needle and prepare the syringe for injection. Administration occurs by inserting the needle into the injection pad provided for the study (normally the skin for actual administration), and depressing the plunger until it stops. After completion of the injection, the needle is removed from the injection pad, and as the plunger is released, the needle shield (driven by the spring) moves into place to cover the needle. In its final position, the needle-shield locks in place to help prevent needlestick injuries.

The BLA contains necessary information to perform the review of the Human Factors component of the submission. It includes a Human Factors validation study report, and a supplemental Human Factors study report that was conducted based on changes as a result of the validation study. We recommend that from a CDRH Human Factors standpoint, the submission should be considered fillable.



QuynhNhu Nguyen, Combination Products Human Factors Specialist



Ron Kaye, Human Factors and Device Use-Safety Team Leader

2/14/2013

Date

2/14/2013

Date

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/s/

PHILANTHA M BOWEN

02/15/2013

Entered in DARRTS on Behalf of CDRH/ODE/DAGID



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: February 19, 2013

From: Jason To, Biomedical Engineer
CDRH/ODE/DAGRID/General Hospital Devices Branch (GHDB)

To: Philantha Bowen
CDER/OND/ODEII/DPARP

Subject: CDRH Consult Request, GEN1300014
Combination Product Review: BLA 125472, PFS

Firm: Genentech, Inc.
1 DNA Way MS# 241B
South San Francisco, CA 94080-4990

1. Consult Request

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH). The device constituent of this combination product is a prefilled syringe from Genentech Inc. CDER has requested that CDRH provide a consult to determine if there is enough information provided in the submission to review the device.

2. Documents

- 1) P.7 Container Closure System [Actemra SC, PFS + NSD 162 mg/0/9 mL]
- 2) Letters of Authorization: Drug Master File # (b) (4),
(b) (4)

3. Device Description

Please see document “P.7 Container Closure System [Actemra SC, PFS + NSD 162 mg/0/9 mL]”

4. CDRH Review and Comments

CDRH's review consisted of assessing the documents provided above pertaining to this device.

Reviewer Assessment: It should be noted that on page 2 of the document “P.7 Container Closure System [Actemra SC, PFS + NSD 162 mg/0/9 mL]”, Table P.7-1 [PFS+NSD] “Container Closure Component Description” provides the following information:

Components	Supplier	DMF Number ^a	Description	Sterilization Method
1 mL Glass Barrel Syringe, 27G ½ in SIN	(b) (4)	(b) (4)	Colorless (b) (4) glass barrel (b) (4)	(b) (4)
Rigid Needle Shield	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Plunger Stopper	(b) (4)	(b) (4)	(b) (4)	(b) (4)

This shows that the Drug Master File (DMF) numbers for the supplier (b) (4), which are identical to the DMF numbers for the supplier (b) (4). This is contradictory to the DMF numbers listed in the document “Letters of Authorization: Drug Master File # (b) (4)”, which provides the following information:

1.4.1 Letter of Authorization

The following Letters of Authorization are provided in this section:

- Drug Master File No. (b) (4) Letter of Authorization, (b) (4)
- Drug Master File No. (b) (4) : Letter of Authorization, (b) (4)
- Drug Master File No. (b) (4) Letter of Authorization, (b) (4)
- Drug Master File No. (b) (4) Letter of Authorization, (b) (4)
- Drug Master File No. (b) (4) : Letter of Authorization (b) (4)
- 510(k) File Nos. (b) (4) Letter of Authorization, (b) (4)
(b) (4)

In this document, it states that the DMF numbers for the supplier (b) (4) are (b) (4). This should be raised to the sponsor to verify and assure the correct usage of the referencing of DMF numbers.

Based on the review of the documents provided for this consult, the information submitted by the sponsor for the device appears to be complete. However, CDRH may request for more additional data concerning the validity, accuracy, and sufficiency of the information submitted by the sponsor in order to further effectively evaluate the safety and/or efficacy of the device.

Sincerely,

Jason To -S Digitally signed by Jason To S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Jason To S
092342.19200300.100.1.1=2000489354
Date: 2013.02.14 09:50:56 -05'00'

Jason To
Biomedical Engineer

Concurred By:

Jacqueline S. Ryan Digitally signed by Jacqueline S. Ryan
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=200057029
3, cn=Jacqueline S. Ryan
Date: 2013.02.14 09:54:36 -05'00'

Dr. Jacqueline Ryan
Combination Products Team Leader

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/s/

PHILANTHA M BOWEN

02/14/2013

Entered in DARRTS on behalf of CDRH/ODE/GHDB

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 125472	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: <i>Actemra</i> Established/Proper Name: <i>Tocilizumab</i> Dosage Form: <i>Prefilled syringe</i> Strengths: <i>162 mg/0.9 mL</i>		
Applicant: <i>Genentech, A Member of the Roche Group</i> Agent for Applicant (if applicable):		
Date of Application: <i>December 21, 2012</i> Date of Receipt: <i>December 21, 2012</i> Date clock started after UN:		
PDUFA Goal Date: <i>October 21, 2013</i>		Action Goal Date (if different):
Filing Date: <i>February 19, 2013</i>		Date of Filing Meeting: <i>January 23, 2013</i>
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): <i>Subcutaneous administration of tocilizumab via a prefilled syringe for the treatment of rheumatoid arthritis</i>		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input checked="" type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 11972				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	✓			Under review by Biological NP Naming Work Group since this product is already approved as an IV formulation with the same names
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	✓			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>				
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below:</p>				
<p>Application No.</p>	<p>Drug Name</p>	<p>Exclusivity Code</p>	<p>Exclusivity Expiration</p>	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>		<p>✓</p>		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>				
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>				
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	✓			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	✓			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	✓			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?		✓		
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?				
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?				
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	✓			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?				
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	✓			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	✓			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	✓			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>				

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	✓			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		✓		
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	✓			
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>	✓			
<p><u>BPCA (NDAs/NDA efficacy supplements only):</u></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>				
<p><u>Proprietary Name</u></p> <p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>		✓		
<p><u>REMS</u></p> <p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>	✓			
<p><u>Prescription Labeling</u></p> <p>Check all types of labeling submitted.</p>	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	✓			
Is the PI submitted in PLR format? ⁴	✓			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	✓			CDRH (Device, Compliance, Human Factors) 1-7-13
<i>If yes, specify consult(s) and date(s) sent: CDRH(1-7-13)</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		✓		
Other Meetings: <i>Type C meeting: 10/24/12</i> <i>Written Responses: 2/6/12</i>	✓			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>10-31-12</i>	✓			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		✓		SPA No Agreement Letter issued <i>Type A meeting 9/2/10</i>
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT
MEMO OF FILING MEETING

DATE: January 23, 2013

BLA/NDA/Supp #: 125472

PROPRIETARY NAME: Actemra

ESTABLISHED/PROPER NAME: Tocilizumb

DOSAGE FORM/STRENGTH: Prefilled syringe/ 162mg/0.9ml

APPLICANT: Genentech

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Subcutaneous administration of tocilizumab via a prefilled syringe

BACKGROUND: Actemra (tocilizumab) is currently approved for intravenous infusion in the treatment of rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis (sJIA). This BLA proposes the aforementioned change for the approved indication of RA.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Philantha Bowen	Y
	CPMS/TL:	Ladan Jafari	N
Cross-Discipline Team Leader (CDTL)	Theresa Michele		Y
Clinical	Reviewer:	Miya Paterniti	Y
	TL:	Theresa Michele	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Liang Zhao	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	David Hoberman	Y
	TL:	Joan Buenconsejo	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Asoke Mukherjee	Y
	TL:	Timothy Robison	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	CMC	Y
	TL:		
Product Quality (CMC)	Reviewer:	Gerald Feldman	Y
	TL:	Majorie Shapiro	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:	Kimberly Rains	N
	TL:		
Facility Review/Inspection	Reviewer:	Maria Candauchacon	Y
	TL:	Patricia Hughes	Y
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	Carolyn L. Yancey	Y
	TL:	Kendra Worthy	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Jacqueline Ryan (Device) Quynh Nhu Nguyen (Human Factors) Emre Genca (OC)		
Other attendees	Nichelle Rashid, OSE PM		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: None</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: <i>This product is currently approved as an IV formulation and the applicant did not request any new indications.</i></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments: <i>This application is not an "original" BLA.</i></p> <p>If no, for an NME NDA or original BLA, include the</p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<p><i>reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: <i>Sarah Yim, Associate Director</i>	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day

	<p>filing letter; For NDAs/NDA supplements: see CST for choices)</p> <ul style="list-style-type: none"> • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 60-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

Drafted: Bowen/1-30-13

Clearance/Review: Jafari/1-31-13

Finalized: Bowen/2-4-13

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

/s/

PHILANTHA M BOWEN
02/04/2013