

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125472Orig1s000

CHEMISTRY REVIEW(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies

The Quality Team Leader's Executive Summary

From: Marjorie A. Shapiro, Ph.D. Chief LMDI
Division of Monoclonal Antibodies (DMA)

Through: Kathleen A. Clouse, Ph.D. Director, DMA

BLA Number: 125472
Product: Tocilizumab (Actemra)
Sponsor: Genentech

Date of Review: August 6, 2013
Due Date of TL Memo: September 30, 2012

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER, recommends approval of STN125472 for the subcutaneous formulation of tocilizumab (Actemra) manufactured by Genentech, a wholly owned subsidiary of Hoffman La Roche. The data submitted in this application are adequate to support the conclusion that the manufacture of tocilizumab is well controlled, and leads to a product that is pure and potent. It is recommended that this product be approved for human use (under conditions specified in the package insert).

II. APPROVAL LETTER INFORMATION

Tocilizumab (Actemra) for subcutaneous administration drug substance is manufactured at Genentech's facility in Oceanside, CA. The storage containers are (b) (4)

The drug product is presented in a pre-filled syringe sealed with a rigid needle shield (RNS) and a needle safety device (NSD). It is manufactured in pre-filled syringes by (b) (4). Labeling, assembly with the NSD and secondary packaging are performed by F. Hoffman-La Roche Ltd in Kaiseraugst, Switzerland.

Tocilizumab drug substance is stored (b) (4). We recommend approval of a shelf life of (b) (4) for (b) (4) storage of tocilizumab drug substance at (b) (4). The stability protocol is adequate to support the (b) (4).

Tocilizumab drug substance can be stored (b) (4) at 2-8°C. We recommend approval for (b) (4) storage of tocilizumab drug substance at 2-8°C for up to (b) (4).

Tocilizumab drug substance is (b) (4)

Tocilizumab drug product is stored (b) (4) at 2-8°C. We recommend approval of a cumulative shelf life of 30 months for tocilizumab drug product in pre-filled syringes plus pre-filled syringes with the needle safety devices when stored at 2-8°C.

III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

None

IV. LIST OF DEFICIENCIES TO BE COMMUNICATED

None

V. EXECUTIVE SUMMARY**A. Description of tocilizumab (Actemra) for subcutaneous administration**

- Tocilizumab (Actemra) is supplied as a sterile, colorless to slightly yellowish, preservative-free liquid solution in a single-use 1 mL prefilled syringe (PFS) for subcutaneous (SC) injection, delivering 162 mg tocilizumab/0.9 mL.
- The composition of Drug Product is 180 mg/mL tocilizumab in (b) (4) arginine, (b) (4) methionine, (b) (4) histidine and (b) (4) (w/v) polysorbate 80, pH 6.0.
- The primary container closure is a clear, (b) (4) 1 mL glass barrel with a staked-in 27G ½ in hypodermic needle, sealed with a rigid needle shield (RNS) comprised of (b) (4) a (b) (4) shell and a (b) (4) rubber plunger stopper with a (b) (4). A needle safety device is assembled with the PFS, but is not considered part of the primary container closure as it does not directly contact the Drug Product and interacts only with the external surface of the syringe.
- The target fill volume is (b) (4) mL to ensure delivery of a dose of 162 mg/0.9 mL.
- Pre-filled syringes and the assembled prefilled syringes plus needle safety device are stored at 2-8°C. It is sensitive to light and should be kept in the outer carton prior to use.
- The Claim Of Categorical Exclusion is acceptable

B. Clinical Trial Information

- Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
- subcutaneous
- Tocilizumab was approved for intravenous administration in the US in 2010 for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). It was subsequently approved in 2013 for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

This BLA describes tocilizumab for subcutaneous administration in adult patients in order to allow for more convenient dosing as a fixed dose given once every two weeks administration for patients weighing <100 kg followed by an increase to

once weekly based on the clinical response. For patients weighing ≥ 100 kg the dosing regimen is once weekly.

The supporting data are from two Phase III clinical trials (WA22762 and NA25220) in adult patients with RA, a supportive Phase II clinical trial exclusively in Japanese patients and six clinical pharmacology studies. WA22762 was a randomized, two-arm, double-blind, double-dummy, active-controlled, parallel-group multi-center study and NA25220 was a randomized, two-arm, double-blind, placebo-controlled, parallel-group study.

The primary objective of WA22762 was to demonstrate the non-inferiority of tocilizumab sc versus tocilizumab iv for an ACR20 response rate at 24 weeks, in addition to comparing adverse events between the two arms.

The primary objective of NA25220 was to demonstrate the superiority of tocilizumab sc versus placebo for an ACR20 response rate at 24 weeks in addition to comparing adverse events between the two arms.

C. Stability

The recommended storage condition for tocilizumab sc drug substance is (b) (4) stored in (b) (4). Data are provided that support a shelf life of (b) (4). The stability protocol is adequate (b) (4).

The data supporting the (b) (4) month expiration date are derived from three clinical lots manufactured at Genentech's (b) (4). Data were provided out to 18 months for the registration batches.

(b) (4). The manufacture of tocilizumab DS for sc administration was moved to the Oceanside, CA facility. The only differences in the manufacturing processes between (b) (4) Oceanside were (b) (4).

ICH Q5C Stability Testing of Biotechnological/Biological Product states "The quality of the batches of drug substance placed into the stability program should be representative of the quality of the material used in preclinical and clinical studies and of the quality of the material to be made at manufacturing scale."

SUMMARY BLA125472 tocilizumab sc (Actemra)

The clinical trial DS materials are representative of the quality of the commercial DS material. In addition, there are ample data from iv tocilizumab lots, which uses the same container closure. Together, the data support a (b) (4) month expiration dating period.

In addition, data are provided to support (b) (4) storage of tocilizumab sc drug substance at 2-8°C for (b) (4).

The recommended storage condition for tocilizumab sc drug product is 2-8°C stored in prefilled syringes or the assembled prefilled syringes plus the needle safety device. Data are provided supporting a shelf life of 30 months, which represents the final time point of stability studies. The 30-month time period starts (b) (4). HLR is not requesting approval of the stability protocol to extend the expiration dating period for drug product beyond 30 months.

The data supporting the 30 month expiration date are derived from five clinical lots manufactured with (b) (4) DS lots. Data from these lots are available from 30-36 months. Data were provided out to 18 months for 4 DP registration batches where the DS was manufactured at Oceanside. The DP commercial process validation batches were manufactured at the same commercial facility as the Phase III clinical material: (b) (4). The same container was used as for Phase III clinical material. For the commercial DP manufacturing process, differences between the manufacturing of Phase III and process validation material were relate (b) (4). The (b) (4) manufacturing process for Phase III clinical supply is comparable to the commercial manufacturing process.

The clinical trial DP materials are representative of the quality of the commercial DP material. The data support a 30-month expiration dating period.

- Tocilizumab sc drug product should be stored protected from light.
- There are no preservatives in the formulation.
- Each prefilled syringe is intended for a single use.
- The tocilizumab sc formulation was optimized based on studies using different stress conditions (heat, freeze-thaw and agitation) and an assessment of aggregate and fragment formation. Stability testing of drug product under accelerated and stress conditions demonstrated that (b) (4)

(b) (4) There was no impact on product quality when samples were exposed to vibrations.

D. Complexity

- **Critical Quality Attributes**

- The activity is based on the ability to block IL6 from binding either membrane bound or soluble IL6R
- Antibody effector functions are not part of the tocilizumab mechanism of action
- Tocilizumab was fully characterized and reviewed for the intravenous formulation in the original BLA 125276 submission and 125276.50, which was approved for the manufacture of tocilizumab at the Oceanside facility. See the review of STN125276 and STN125276.50 for additional details.
- The (b) (4) formulation did not impact quality attributes such as potency, aggregates and other size variants, or charge variants. Levels of process-related impurities were also not impacted by the (b) (4) subcutaneous formulation.
- Release and stability methods are the same as those used for the intravenous formulation. Methods that could be impacted by the (b) (4) (SEC, IEC, KT-3 potency and US spectrophotometry) were revalidated with an additional dilution step.

E. Homology to Other Products

Not Applicable

F. Mechanism of Action

- Tocilizumab binds both soluble and membrane bound IL6 receptor and inhibits IL6 mediated signaling through these receptors.
- IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis.
- Potency is defined as percent IC₅₀ value relative to the reference standard, using a proprietary chemiluminescent cell-based assay dependent on the ability of Actemra to inhibit IL-6 mediated proliferation of KT-3 cells. Potency specification is (b) (4) U/ml (or (b) (4) U/mg), based on comparative data against the reference standard.

G. Manufacturing Process

- The tocilizumab sc drug substance manufacturing process (b) (4)

SUMMARY BLA125472 tocilizumab sc (Actemra)

(b) (4)

- [REDACTED] (b) (4)
[REDACTED]. Appropriate in-process controls are in place for sterility assurance.

H. Comparability

The initial drug substance manufacturing campaigns were conducted at Genentech's [REDACTED] (b) (4) the manufacture of tocilizumab sc drug substance was transferred to Genentech's Oceanside, CA facility. Comparability between tocilizumab [REDACTED] (b) (4) and Oceanside was established. The main changes between the processes were [REDACTED] (b) (4) lots manufactured at both facilities were used in the Phase 3 studies that support this BLA. There have been no major manufacturing changes in the process since the implementation of the [REDACTED] (b) (4) process at Oceanside.

I. Immunogenicity

The immunogenicity assays used in the tocilizumab sc clinical trials are the same as those used to support licensure (STN125276.00) and the efficacy supplement for juvenile idiopathic arthritis (126276.64) The assays were reviewed for both BLAs and were not re-reviewed for the current BLA.

VI. SIGNATURE BLOCK (BLA ONLY)

Name and Title	Signature and Date
Kathleen A. Clouse, Ph.D. Director Division of Monoclonal Antibodies	
Marjorie A. Shapiro, Ph.D. Laboratory Chief, Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies	

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/s/

MARJORIE A SHAPIRO
09/16/2013

KATHLEEN A CLOUSE STREBEL
09/16/2013

BLA STN 125472

USAN name: Tocilizumab

**Manufacturer:
Genentech Inc.
1 Antibody Way
OCN, CA 92056-5802**

**Reviewer: Gerald M Feldman, Ph.D.
LC Reviewer: Marjorie Shapiro, Ph.D.
Division of Monoclonal Antibodies**

OBP CMC Review Data Sheet

1. **BLA#: STN 125472**

2. **REVIEW DATE: May 31, 2013**

3. **PRIMARY REVIEW TEAM:**

Medical Officer: Dr. Miya Paterniti
Pharm/Tox: Dr. Asoke Mukherjee
Product Quality: Dr. Gerald Feldman
BMT or Facilities: Dr. Maria Candauchacon
Clinical Pharmacology: Dr. Liang Zhao
Statistics: Dr. David Hoberman
OBP Labeling: Capt. Kimberly Raines
RPM: Capt. Philantha Bowen

4. **MAJOR 21st Century Review DEADLINES**

Filing Meeting: February 19, 2013
Mid-Cycle Meeting: May 8, 2013
Wrap-Up Meeting: September 16, 2013
Primary Review Due: September 16, 2013
Secondary Review Due: September 30, 2013
CDTL Memo Due: September 30, 2013
PDUFA Action Date: October 21, 2013

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
Filing Review Memo	02/05/2013
Request for CMC information	06/04/2013
Request for CMC information	08/07/2013

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
125472.00 (Original Submission)	12/21/2012	Yes
125472.06 Response to BMAB IR	04/24/2013	Yes
125472.08 Nomenclature request	05/16/2013	Yes
125472.11 Response to BMAB IR	06/19/2013	Yes
125472.12 Response to BMAB IR	07/02/2013	Yes
125472.14 Response to CMC IR	07/15/2013	Yes
125472.21 Response to CMC IR	08/14/2013	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: Actemra
- b. Trade Name:
- c. Non-Proprietary/USAN: Tocilizumab
- d. CAS name: 375823-41-9
- e. Common name: RO4877533, MRA
- f. INN Name: Tocilizumab
- g. Compendial Name:
- h. OBP systematic name: MAB HUMANIZED (IGG1) ANTI (b)(4)
(IL6RA_HUMAN) [RO4877533]
- i. Other Names: Recombinant humanized anti-IL-6 receptor monoclonal antibody

8. PHARMACOLOGICAL CATEGORY: Therapeutic monoclonal antibody directed against the IL6 receptor

9. DOSAGE FORM: Pre-filled syringe (PFS) containing 0.9 ml

10. STRENGTH/POTENCY: 180 mg/ml; 162 mg/dose

11. ROUTE OF ADMINISTRATION: Sub Cutaneous

12. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
		(b)(4)	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA

13. INSPECTIONAL ACTIVITIES: NONE

14. CONSULTS REQUESTED BY OBP: NONE

15. QUALITY BY DESIGN ELEMENTS: NONE

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
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	Design of Experiments
	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. PRECEDENTS: NONE

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Marjorie A Shapiro, Ph.D. Chief, Laboratory of Molecular and Developmental Immunology Division of Monoclonal Antibodies, OBP, CDER	
Gerald M. Feldman, Ph.D. Primary Reviewer Division of Monoclonal Antibodies, OBP, CDER	

B. CC Block

Recipient	Date
Clinical Division BLA RPM	
Division of Monoclonal Antibodies/Therapeutic Proteins File/BLA STN 125472	

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/s/

GERALD M FELDMAN
09/10/2013

MARJORIE A SHAPIRO
09/10/2013

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

BLA/NDA Number: 125472 **Applicant:** Genentech Inc **Stamp Date:** December 21, 2012

Established/Proper Name: Tocilizumab(TCZ)/Actemra **BLA/NDA Type:** BLA

On initial overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	<input checked="" type="radio"/> Y <input type="radio"/> N	
Form 356h completed	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	<input checked="" type="radio"/> Y <input type="radio"/> N	
Comprehensive Table of Contents	<input checked="" type="radio"/> Y <input type="radio"/> N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	<input checked="" type="radio"/> Y <input type="radio"/> N	
Labeling:	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> PI –non-annotated	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> PI –annotated	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> PI (electronic)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Medication Guide	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Patient Insert	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> package and container	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> diluent	<input checked="" type="radio"/> Y <input checked="" type="radio"/> N	Not Applicable
<input type="checkbox"/> other components	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> established name (e.g. USAN)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> proprietary name (for review)	<input checked="" type="radio"/> Y <input type="radio"/> N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> English (or translated into English)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	<input checked="" type="radio"/> Y <input type="radio"/> N	
Companion application received if a shared or divided manufacturing arrangement	<input type="radio"/> Y <input checked="" type="radio"/> N	Not Applicable

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Quality overall summary [2.3]	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Drug Substance	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Drug Product	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Facilities and Equipment	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Novel Excipients	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Executed Batch Records	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Method Validation Package	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Comparability Protocols	<input checked="" type="radio"/> Y <input type="radio"/> N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Drug Substance [3.2.S]	<input type="radio"/> Y <input checked="" type="radio"/> N	
<input type="checkbox"/> general info <ul style="list-style-type: none"> <input type="radio"/> nomenclature <input type="radio"/> structure (e.g. sequence, glycosylation sites) <input type="radio"/> properties 	<input type="radio"/> Y <input checked="" type="radio"/> N	
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	<input type="radio"/> Y <input checked="" type="radio"/> N	Much of Module 3 (Drug Substance manufacturing process and process controls) for this BLA (b) (4)
<input type="checkbox"/> description of manufacturing process and process control <ul style="list-style-type: none"> <input type="radio"/> batch numbering and pooling scheme <input type="radio"/> cell culture and harvest <input type="radio"/> purification <input type="radio"/> filling, storage and shipping 	<input type="radio"/> Y <input checked="" type="radio"/> N	
<input type="checkbox"/> control of materials <ul style="list-style-type: none"> <input type="radio"/> raw materials and reagents <input type="radio"/> biological source and starting materials <input type="radio"/> cell substrate: source, history, and generation <input type="radio"/> cell banking system, characterization, and testing 	<input type="radio"/> Y <input checked="" type="radio"/> N	
<input type="checkbox"/> control of critical steps and intermediates <ul style="list-style-type: none"> <input type="radio"/> justification of specifications <input type="radio"/> stability 	<input type="radio"/> Y <input checked="" type="radio"/> N	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> <input type="checkbox"/> process validation (prospective plan, results, analysis, and conclusions) <input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> <input type="checkbox"/> specifications <ul style="list-style-type: none"> <input type="checkbox"/> justification of specs. <input type="checkbox"/> analytical procedures <input type="checkbox"/> analytical method validation <input type="checkbox"/> batch analyses <input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results <input type="checkbox"/> method validation 	<p align="center">Y N</p> <p align="center">Y N Y N</p> <p align="center">Y N Y N Y N</p>	
<p>Drug Product [3.2.P] [Dosage Form]</p> <ul style="list-style-type: none"> <input type="checkbox"/> description and composition <input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> <input type="checkbox"/> preservative effectiveness <input type="checkbox"/> container-closure integrity <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) <input type="checkbox"/> batch formula <input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) <input type="checkbox"/> controls of critical steps and intermediates <input type="checkbox"/> process validation including aseptic processing & sterility assurance: 	<p align="center">Y N Y N</p> <p align="center">Y N</p> <p align="center">Y N Y N</p> <p align="center">O</p> <p align="center">Y N Y N</p>	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> ○ Filter validation ○ Component, container, closure depyrogenation and sterilization validation ○ Validation of aseptic processing (media simulations) ○ Environmental Monitoring Program ○ Lyophilizer validation ○ Other needed validation data (hold times) <input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin) <input type="checkbox"/> control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities) <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system [3.2.P.7] <ul style="list-style-type: none"> ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs ○ administration device(s) <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> ○ protocol ○ results ○ method validation 	<p align="center"> <input checked="" type="radio"/> Y <input type="radio"/> N <input checked="" type="radio"/> Y <input type="radio"/> N <input checked="" type="radio"/> Y <input type="radio"/> N <input checked="" type="radio"/> Y <input type="radio"/> N </p>	
<p>Diluent (vials or filled syringes) [3.2P']</p> <ul style="list-style-type: none"> <input type="checkbox"/> description and composition of diluent <input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> ○ preservative effectiveness ○ container-closure integrity <input type="checkbox"/> manufacturers (names, locations, 	<p align="center"> Y N Y N Y N Y N Y N </p>	<p align="center">Not Applicable</p>

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?		If not, justification, action & status
and responsibilities of all sites involved)	Y	N	
□ batch formula			
□ description of manufacturing process for production through finishing, including formulation,	Y	N	
filling, labeling and packaging (including all steps performed at	Y	N	
outside [e.g., contract] facilities)	Y	N	
□ controls of critical steps and intermediates	Y	N	
□ process validation including aseptic processing & sterility assurance:			
○ Filter validation			
○ Component, container, closure depyrogenation and sterilization validation	Y	N	Not Applicable
○ Validation of aseptic processing (media simulations)	Y	N	
○ Environmental Monitoring Program	Y	N	
○ Lyophilizer sterilization validation	Y	N	
○ Other needed validation data (hold times)	Y	N	
□ control of excipients (justification of specifications; analytical method validation; excipients of	Y	N	
human/animal origin, other novel excipients)			
□ control of diluent (justification of specifications; analytical method	Y	N	
validation, batch analysis, characterization of impurities)	Y	N	
□ reference standards			
□ container closure system			
○ specifications (vial, elastomer, drawings)	Y	N	
○ availability of DMF & LOAs			
□ stability			
□ summary			
□ post-approval protocol and commitment			
□ pre-approval			

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes data demonstrating consistency of manufacture	<input checked="" type="radio"/> Y N	
Includes complete description of product lots and manufacturing process utilized for clinical studies	<input checked="" type="radio"/> Y N	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	<input checked="" type="radio"/> Y N	
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	<input checked="" type="radio"/> Y N	
Certification that all facilities are ready for inspection	<input checked="" type="radio"/> Y N	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	<input checked="" type="radio"/> Y N	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	Y N Y N Y N	Not Applicable
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	Not Applicable
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	<input checked="" type="radio"/> Y N	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	<input checked="" type="radio"/> Y N	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?

Yes **No**

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None so far

Gerald M Feldman, Ph.D.	February 5, 2013
Product Quality Reviewer(s)	Date

Branch Chief/Team Leader/Supervisor	Date
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Division Director	Date
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/s/

GERALD M FELDMAN
02/05/2013

MARJORIE A SHAPIRO
02/05/2013

KATHLEEN A CLOUSE STREBEL
02/05/2013