

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125472Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 11 October, 2013
To: Administrative File, STN 125472/0
From: Reyes Candau-Chacon, PhD., Reviewer, OC/OMPQ/DGMPA/BMAB
Through: Patricia Hughes, Ph.D., Team Leader, OC/OMPQ/DGMPA/BMAB
Subject: Addendum to New Biologic License Application (BLA)
US License: 1048
Applicant: Genentech, Inc.
Facilities: [REDACTED] (b) (4)
(FEI # [REDACTED] (b) (4))
Product: ACTMERA® (tocilizumab)
Dosage: Prefilled syringe containing a sterile, preservative-free liquid solution containing 162 mg/0.9 mL tocilizumab for subcutaneous injection
Indication: Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs)
Due date: 21 October 2013

The purpose of this addendum is to review information submitted to the BLA after the primary review was completed.

Amendments Reviewed for Quality Microbiology

Information Request date	Question numbers	Amendment sequence	Amendment date
10-April-2013	9	0023	16-Sep-2013
20-June-2013			
15-July-2013			
02-October-2013	9	0030	04-Oct-2013
10-April-2013	15-e	0027	30-Sep-2013
20-June-2013			
15-July-2013			
08-October-2013	15-e	0034	10-Oct-2013

3.2. S.7 Stability

Proposed stability for commercial tocilizumab SC DS is (b) (4) months (b) (4) days) at (b) (4).

FDA Information Request 9 (included in the original review)

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

Sponsor Response in amendment 0023

Microbial quality of Actmera DS stored in the BDS for a cumulative hold time of (b) (4) days at (b) (4) was demonstrated at scale. A (b) (4) bottle (batch 531468) was held at (b) (4) days and transferred to (b) (4) days and analyzed for endotoxin and bioburden.

FDA Information Request in response to amendment 0023

Please submit microbiology data (endotoxin and bioburden) from the study included in amendment 0023 in support of (b) (4) storage of BDS.

Sponsor Response in amendment 0030

Microbial quality data for the study is included in Table S.7.3-21, included in Section S.7.3 of the BLA. Endotoxin was (b) (4) EU/mL at T=0 and T=32 ((b) (4) days at (b) (4); Specification (b) (4) EU/mL); Bioburden was (b) (4) CFU/mL at T=0 and T=32 ((b) (4) Specification (b) (4) CFU/mL).

Satisfactory

P.3.5.2 (b) (4) Validation

P.3.5.2.1 Microbial Retention Test

The microbial retention test conducted using the substitution method with microbial challenge in surrogate (b) (4) solution).

Reviewer Comments to sponsor response in amendment 0012 (included in the original review)

Inoculation of bacteria in (b) (4) is not adequate (b) (4)

[REDACTED] (b) (4)

Sponsor Response in amendment 0027

A microbial retention test of the [REDACTED] (b) (4) is included in the amendment. A viability study is included in the amendment (Attachment 3); the study showed that the product has no bactericidal effect, defined as ≤ 1 log reduction in viability relative to [REDACTED] (b) (4) control solution of the test organism *B. diminuta*, after 10 hours and 30 minutes of contact time; however, the product had bactericidal effect on the test organism after 12 hours and 30 minutes in comparison with [REDACTED] (b) (4) control solution. The study was conducted [REDACTED] (b) (4)

[REDACTED] (b) (4)
Acceptance criteria included:

- Bacterial challenge level [REDACTED] (b) (4) CFU/cm²
- No colonies observed [REDACTED] (b) (4)
- Growth of the test organism [REDACTED] (b) (4)
- Absence of contaminating organisms [REDACTED] (b) (4)
- Ability to measure the [REDACTED] (b) (4) after the test

The scale down study was conducted [REDACTED] (b) (4)
[REDACTED] (b) (4)

FDA Information Request in response to amendment 0027

Please justify [REDACTED] (b) (4) as effective [REDACTED] (b) (4)
[REDACTED] (b) (4)

Sponsor Response in amendment 0034

Although the total area of the [REDACTED] (b) (4)
[REDACTED] (b) (4)

Satisfactory

The results of the microbial retention study are shown in the Table below, duplicated from amendment 0027, Table 6.

(b) (4)



Reviewer Comments

The study supports microbial retention [redacted] (b) (4) at reduced [redacted] (b) (4) exposure of the organism.

Satisfactory

Conclusion

The information reviewed in this addendum to review of BLA 125472/0 supports the previous recommendation for approval from a microbial control, CMC sterility assurance and microbiology product quality perspective.

FDA Information Request in response to amendment 0023 submitted on October 2, 2013

Please submit microbiology data (endotoxin and bioburden) from the study included in amendment 0023 in support of (b) (4) storage of BDS.

FDA Information Request in response to amendment 0027 submitted on October 8, 2013

Please justify

(b) (4)

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/s/

REYES CANDAU-CHACON
10/11/2013

PATRICIA F HUGHES TROOST
10/11/2013



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 10 September 2013
To: Administrative File, STN 125472/0
From: Reyes Candau-Chacon, Ph.D., Reviewer, OC/OMPQ/DGMPA/BMAB
Through: Patricia Hughes, Ph.D., Team Leader, OC/OMPQ/DGMPA/BMAB
Subject: New Biologic License Application (BLA)
US License: 1048
Applicant: Genentech, Inc.
Facilities: [REDACTED] (b)(4)
Product: ACTMERA® (tocilizumab)
Dosage: Prefilled syringe containing a sterile, preservative-free liquid solution containing 162 mg/0.9 mL tocilizumab for subcutaneous injection
Indication: Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs)
Due date: 21 October 2013

Recommendation for Approvability: BLA 125472 is recommended for approval from a CMC sterility assurance and microbiology product quality perspective with the following post-marketing commitment:

Determine the (b)(4) volume necessary for a [REDACTED] (b)(4) and provide the report to the Agency in the by October 30, 2013.

Review Summary

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

BLA 125472 was submitted in eCTD on December 21, 2012. This review contains the assessment of the manufacturing process of tocilizumab from a microbial quality and sterility assurance perspective.

Amendments Reviewed for Quality Microbiology

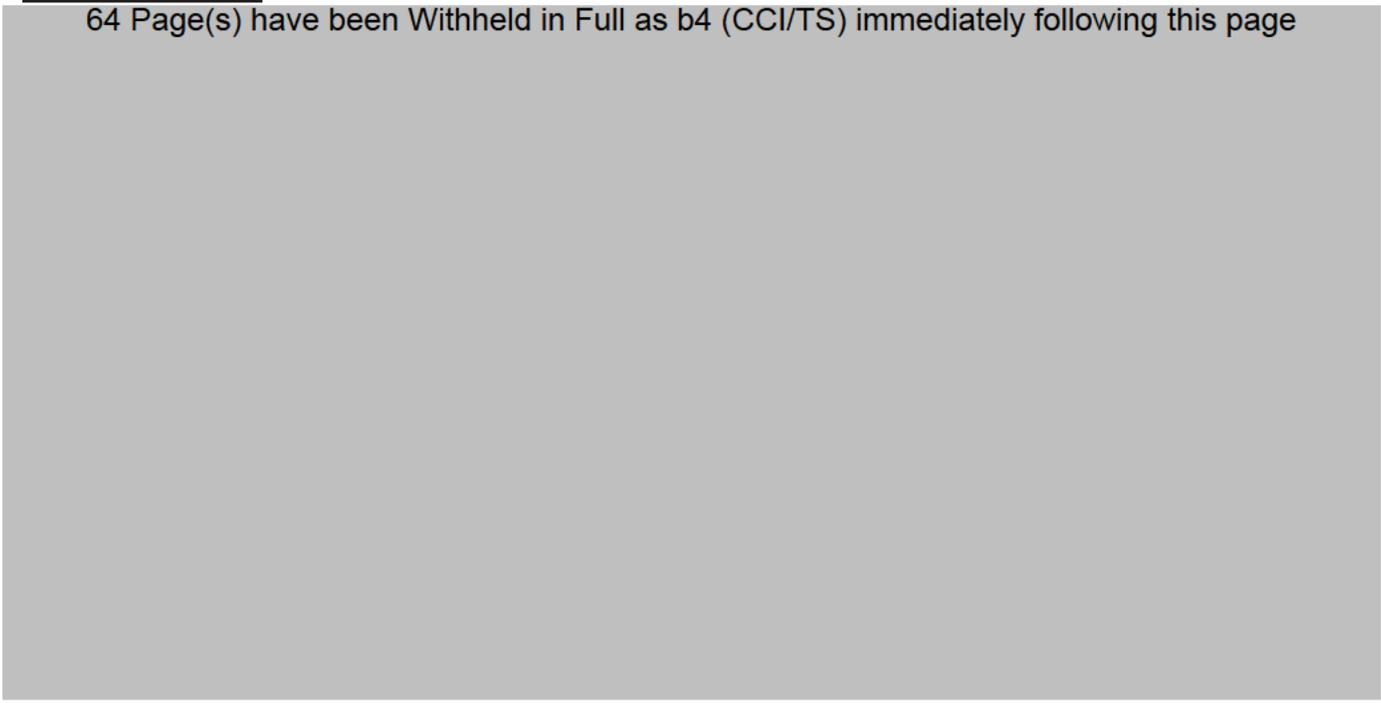
Information Request date	Question numbers	Amendment sequence	Amendment date
10-Apr-2013	All (1-25)	0006	23-Apr-2013
10-Apr-2013	15-e	0011	18-Jun-2013
24-May-2013	All (24.2)	0012	1-Jul-2013
20-June-2013	3, 9, 12d-e, 13b, 15e, 16, 20a, 24a	0012	1-Jul-2013
15-July-2013	3, 9, 15e. 16	0017	25-Jul-2013
10-Apr-2013	23d, 24a	0021	30-Aug-2013

Consults for Drug Product Quality Microbiology

Consult date	Type	Division	Response
30-Jan-2013	Devices Inspection	CDRH/OC	10-Apr-2013

Review Narrative

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/s/

REYES CANDAU-CHACON
09/16/2013

PATRICIA F HUGHES TROOST
09/16/2013

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

BLA Number:

Applicant:

Stamp Date:

STN 125472

Genentech/Roche

February 11, 2013

Established/Proper Name: BLA Type:

Standard

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

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed	Y	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y N	Not required
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling:	Y N	Defer to OBP
<input type="checkbox"/> PI –non-annotated	Y N	
<input type="checkbox"/> PI –annotated	Y N	
<input type="checkbox"/> PI (electronic)	Y N	
<input type="checkbox"/> Medication Guide	Y N	
<input type="checkbox"/> Patient Insert	Y N	
<input type="checkbox"/> package and container	Y N	
<input type="checkbox"/> diluent	Y N	
<input type="checkbox"/> other components	Y N	
<input type="checkbox"/> established name (e.g. USAN)	Y N	
<input type="checkbox"/> proprietary name (for review)	Y 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:	Y	
<input type="checkbox"/> legible	Y	
<input type="checkbox"/> English (or translated into English)	Y	
<input type="checkbox"/> compatible file formats	Y	
<input type="checkbox"/> navigable hyper-links	Y	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a	Y N	Not Applicable

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

Examples of Filing Issues	Yes?	If not, justification, action & status
shared or divided manufacturing arrangement		

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]		
Introduction to the summary documents (1 page) [2.2]		
Quality overall summary [2.3]	Y	
<input type="checkbox"/> Drug Substance	Y	(b)(4) Facilities and Equipment information in 3.2.A. Manufacturers in 3.2.S.2.1
<input type="checkbox"/> Drug Product	Y	
<input type="checkbox"/> Facilities and Equipment	Y	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y N	Defer to OBP
<input type="checkbox"/> Novel Excipients	Y N	Not Applicable
<input type="checkbox"/> Executed Batch Records	Y	
<input type="checkbox"/> Method Validation Package	Y	
<input type="checkbox"/> Comparability Protocols	Y N	Not Applicable

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		
<input type="checkbox"/> general info		Defer to OBP.
<input type="checkbox"/> nomenclature	Y	
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)	Y	
<input type="checkbox"/> properties	Y	
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	
<input type="checkbox"/> description of manufacturing process and process control	Y	OBP has the lead; bioburden and endotoxin for BMAB review.
<input type="checkbox"/> batch numbering and pooling scheme	Y	
<input type="checkbox"/> cell culture and harvest	N	Referred to STN 125276/50 (approved 4/20/12). (b)(4)
<input type="checkbox"/> purification	Y	(b)(4)
<input type="checkbox"/> filling, storage and shipping	N	(b)(4)
<input type="checkbox"/> control of materials	Y	OBP has the lead for this section.
<input type="checkbox"/> raw materials and reagents	Y	
<input type="checkbox"/> biological source and starting materials	Y	

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CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> ○ cell substrate: source, history, and generation 	Y	
<ul style="list-style-type: none"> ○ cell banking system, characterization, and testing 	Y	
<ul style="list-style-type: none"> □ control of critical steps and intermediates <ul style="list-style-type: none"> ○ justification of specifications ○ stability 	N	Defer to OBP; bioburden IPCs for BMAB review. Referred to 125276/6 (approved 6/24/10) and /50. (b) (4) bioburden/endotoxin limits included.
<ul style="list-style-type: none"> □ process validation (prospective plan, results, analysis, and conclusions) 	Y	OBP has the lead; (b) (4) for BMAB review.
<ul style="list-style-type: none"> □ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) 	Y	Defer to OBP.
<ul style="list-style-type: none"> □ characterization of drug substance 	Y	Defer to OBP.
<ul style="list-style-type: none"> □ control of drug substance 	Y	OBP has the lead; compendia or equivalent microbial analytical procedures are for BMAB review.
<ul style="list-style-type: none"> ○ specifications 	Y	BMAB specifications are unchanged.
<ul style="list-style-type: none"> ○ justification of specs. 	Y	OBP has the lead; bioburden & endotoxin evaluation in BMAB review.
<ul style="list-style-type: none"> ○ analytical procedures 	Y	Defer to OBP. Bioburden/endotoxin provided.
<ul style="list-style-type: none"> ○ analytical method validation 	Y	OBP has the lead; bioburden for BMAB review.
<ul style="list-style-type: none"> ○ batch analyses 	Y	Defer to OBP. (b) (4)
<ul style="list-style-type: none"> □ reference standards 	N	Defer to OBP.
<ul style="list-style-type: none"> □ container closure system 	Y	
<ul style="list-style-type: none"> □ stability 	Y	
<ul style="list-style-type: none"> □ summary 		
<ul style="list-style-type: none"> □ post-approval protocol and commitment 	Y	
<ul style="list-style-type: none"> □ pre-approval 		
<ul style="list-style-type: none"> ○ protocol 		
<ul style="list-style-type: none"> ○ results 		
<ul style="list-style-type: none"> ○ method validation 		
Drug Product [3.2.P] [Dosage Form]		
<ul style="list-style-type: none"> □ description and composition of DP 	Y	
<ul style="list-style-type: none"> □ pharmaceutical development 	Y	
<ul style="list-style-type: none"> ○ preservative effectiveness 	Y	N
<ul style="list-style-type: none"> ○ container-closure integrity 	Y	Not Applicable
<ul style="list-style-type: none"> □ manufacturers (names, locations, and responsibilities of all sites involved) 	Y	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> batch formula	Y	
<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)	Y	
<input type="checkbox"/> controls of critical steps and intermediates	Y	
<input type="checkbox"/> process validation including aseptic processing & sterility assurance:	Y	
<input type="checkbox"/> Filter validation	Y	
<input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation	Y	
<input type="checkbox"/> Validation of aseptic processing (media simulations)	Y	
<input type="checkbox"/> Environmental Monitoring Program	N	Environmental monitoring program not included. It will be requested
<input type="checkbox"/> Lyophilizer validation	Y	N Not Applicable
<input type="checkbox"/> Other needed validation data (hold times)	N	Hold times not validated for microbial quality. It will be requested.
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	N Defer to OBP
<input type="checkbox"/> control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	
<input type="checkbox"/> reference standards or materials	Y	N Defer to OBP
<input type="checkbox"/> container closure system [3.2.P.7]	Y	
<input type="checkbox"/> specifications (vial, elastomer, drawings)	Y	
<input type="checkbox"/> availability of DMF & LOAs	Y	
<input type="checkbox"/> administration device(s)	Y	
<input type="checkbox"/> stability		
<input type="checkbox"/> summary	Y	
<input type="checkbox"/> post-approval protocol and commitment	Y	
<input type="checkbox"/> pre-approval		
<input type="checkbox"/> protocol	Y	
<input type="checkbox"/> results	Y	
<input type="checkbox"/> method validation	Y	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

CTD Module 3 Contents	Present?	If not, justification, action & status
Diluent (vials or filled syringes) [3.2P']		Not applicable
<input type="checkbox"/> description and composition of diluent	Y N	
<input type="checkbox"/> pharmaceutical development	Y N	
<input type="checkbox"/> preservative effectiveness	Y N	
<input type="checkbox"/> container-closure integrity	Y N	
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
<input type="checkbox"/> batch formula	Y N	
<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)	Y N	
<input type="checkbox"/> controls of critical steps and intermediates	Y N	
<input type="checkbox"/> process validation including aseptic processing & sterility assurance:	Y N	
<input type="checkbox"/> Filter validation		
<input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation	Y N	
<input type="checkbox"/> Validation of aseptic processing (media simulations)		
<input type="checkbox"/> Environmental Monitoring Program	Y N	
<input type="checkbox"/> Lyophilizer sterilization validation	Y N	
<input type="checkbox"/> Other needed validation data (hold times)		
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
<input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
<input type="checkbox"/> reference standards	Y N	
<input type="checkbox"/> container closure system	Y N	
<input type="checkbox"/> specifications (vial, elastomer,		

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> drawings) <ul style="list-style-type: none"> ○ availability of DMF & LOAs <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 	Y N	
Other components to be marketed (full description and supporting data, as listed above): <ul style="list-style-type: none"> <input type="checkbox"/> other devices <input type="checkbox"/> other marketed chemicals (e.g. part of kit) 	Y N Y N	Not Applicable
Appendices for Biotech Products [3.2.A] <ul style="list-style-type: none"> <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production <input type="checkbox"/> novel excipients 	Y Y N Y Y Y N Y N	Reference to 125276 (for DS) Other products not included. It will be requested. Defer to OBP Defer to OBP
USA Regional Information [3.2.R] <ul style="list-style-type: none"> <input type="checkbox"/> executed batch records <input type="checkbox"/> method validation package <input type="checkbox"/> comparability protocols 	Y N Y Y N	Defer to OBP Defer to OBP Not Applicable
Literature references and copies [3.3]	Y	Defer to OBP

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	Defer to OBP
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	Defer to OBP
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	Defer to OBP
Certification that all facilities are ready for inspection	Y	
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.	Y N	Defer to OBP
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 Y N Y	Rabbit pyrogen test not included. It will be requested Defer to OBP
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	Defer to OBP
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA (OBP & BMAB/OC)**

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

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.

Michelle Clark-Stuart	February 1, 2013
Product Quality Microbiology Reviewer (Drug Substance)	Date
Reyes Candau-Chacon, PhD	February 8, 2013
Product Quality Microbiology Reviewer (Drug product)	Date
Patricia Hughes, PhD	February 11, 2013
Team Leader	Date

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/s/

REYES CANDAU-CHACON
02/11/2013

MICHELLE Y CLARK STUART
02/12/2013
BMAB reviewer for DS.

PATRICIA F HUGHES TROOST
02/12/2013