CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES | Public Health Service

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

Date: December 9, 2009
To: Administrative File, SNT 125276/0/64
From: Patricia F. Hughes, Ph.D., Reviewer, CDER/OC/DMPQ/BMT PFH 12/9/09
Endorsement: Kalavati Suvarna, Ph.D., Peer Reviewer, CDER/OC/DMPQ/BMT KS 12/9/09
Subject: Review of a BLA amendment in response to a complete response letter
US License #: 1048
Applicant: Genentech, Inc.
Facility: Utsunomiya Plant, Chugai Pharma Manufacturing Co., Utsunomiya City, Tochigi, 321-3231, Japan (FEI: 3006942691)
Product: ACTEMRA (tocilizumab, MRA, recombinant humanized anti-human Interleukin-6 Receptor (IL-6R) monoclonal antibody)
Indication: Treatment for reducing signs and symptoms in adult patients with moderately to severely active RA
Dosage: Sterile injectable solution in single use vials b(4)
Due Date: January 8, 2010

Recommendation: BLA 125276, as amended, is recommended for approval from a CMC sterility assurance, microbiology product quality and CGMP perspective. Chugai Pharma Manufacturing Co., the manufacturing and testing establishment for the product, is acceptable from a CGMP perspective.

Review Summary

This amendment (64) to BLA 125276 addresses non-approval issues that were communicated to the sponsor in a complete response letter on 9/17/2008. The application was initially recommended for approval from a CMC sterility assurance and microbiology product quality perspective (review from Patricia F. Hughes, 9/16/2008). However, approval of the license application was pending from a GMP perspective as a result of 483 observations found during a pre-license inspection of Chugai Pharma Manufacturing Co. (FEI: 3006942691) conducted May 21-June 5, 2008. Upon further review of the firm's responses to 483 observations, the establishment is currently classified as acceptable with voluntary action indicated (VAI).

cGMP Status

A current TB-EER states:
"The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of Chugai Pharma Manufacturing Co. (FEI: 3006942691). There are no pending or ongoing compliance actions to prevent approval of STN 125276/0/64 at this time. The current status classification of the Chugai Pharma Manufacturing Co. site is VAI."

Conclusion

I. BLA 125276, as amended, is recommended for approval from a CMC sterility assurance, microbiology product quality, and a cGMP perspective.

II. All other BLA complete response items addressed in this amendment should be evaluated by the appropriate BLA reviewers.

III. There are no follow-up inspection items.

Cc:
OC/DMPQ/WO Bldg 51: Hughes
OC/DMPQ/WO Bldg 51: Dillon
OND/ODEII/DMEP/WO Bldg 22: Turner-Rinehardt
OC/DMPQ/WO Bldg 51: BMT eArchive

Archived File: S:\Archive\BLAs\125276\125276.0\125276.0.64.rev.mem.BLA.AD.12-09-09.pdf

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, NIH Bldg 29B, HFD-123
29B Lincoln Drive, Bethesda, MD 20892

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**

To: **Jeffrey Siegel, M.D. CDTL, DAARP, ODEII**

BLA Number: **127526**
Product: **Actemra™ (tocilizumab)**
Sponsor : **Hoffman La Roche**

Date of Review : **August 21 , 2008**

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The data submitted in this Biologics License Application support the conclusion that the manufacture of Actemra™ (tocilizumab) is well controlled, and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. The Division of Monoclonal Antibodies recommends that Actemra™ (tocilizumab) be approved for human use (under conditions specified in the package insert) based on the review of the Quality information submitted with the package (Module 3).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no CMC-related Phase 4 (post-marketing) commitments.

II. Summary of Quality Assessments

A. Description of the Drug Product(s) and Drug Substance

- Actemra™ (tocilizumab) Drug Product is supplied as a sterile, preservative-free, liquid that is colorless to pale yellow. It is pH buffered in an isotonic formulation for infusion into commercially available intravenous solutions, such as normal saline (0.9% NaCl). It is a sterile 20 mg/ml aqueous solution at pH 6.5 in a formulation that contains 15 mM sodium phosphate, 146 mM sucrose, 0.05% Polysorbate 80, and ——. Tocilizumab DP is filled in 10 or 20 cc type I ——— glass vials at 3 different target volumes (4 ml, 10 ml, and 20 ml), corresponding to 80 mg, 200 mg, and 400 mg dosage strengths, respectively. The container closure system consists of Type I glass vials that are stoppered with ——— rubber stoppers and sealed with aluminum seals with ——— flip-off caps. b(4)

- The excipients used in the formulation of Actemra™ (tocilizumab) as noted above are disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, polysorbate 80 and sucrose. A pH of 6.5 was determined to be optimal for tocilizumab,

b(4)

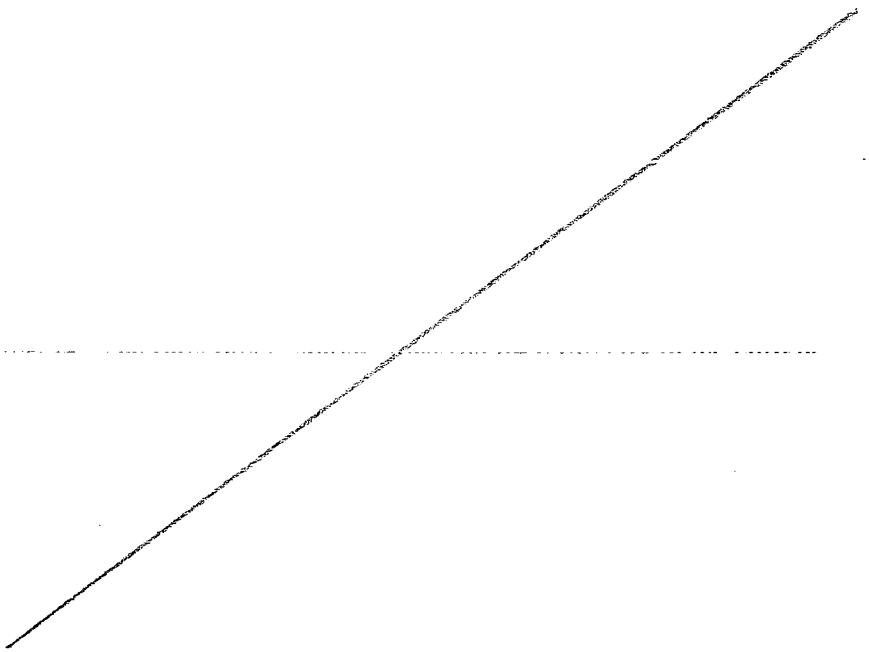
The concentration of polysorbate 80 was set at 0.5 mg/mL based on development data.

- Each vial of Actemra™/tocilizumab is a single use vial and is packaged in an individual carton.

- The stability of Actemra™ drug product (commercial DP 3 process) has been confirmed for up to 24 months at 2°-8° C (36°-46° F) stored in both the upright and inverted positions using multiple lots of each dosage form for validation. In addition, data available from multiple lots of the 200 mg dosage form manufactured by the DP2 process support the requested expiration dating of 24 months. Actemra™ (tocilizumab) drug product is to be stored refrigerated (2°-8° C) inside the original carton to protect it from light, since photostability studies have shown that it degrades when exposed to light under the conditions tested. The Actemra™ (tocilizumab) Drug Product stability b(4)

- Actemra™ (tocilizumab) is stable in 0.9% sodium chloride in a variety of containers (polypropylene, polyethylene, polyvinyl chloride, and glass) for up to — hours at ambient temperature while exposed to white fluorescent light. It was also demonstrated to be compatible with infusion sets and infusion bags. Stability data are provided in the BLA in support of this statement. Actemra™ (tocilizumab) does not contain preservatives, so any unused portion must be discarded. b(4)

- Actemra™ (tocilizumab) is expressed in the ⌜ ⌟ cell line. The cell bank system consists of a Master Cell Bank ——— and a Working Cell Bank ——— . Both cell banks were manufactured without ——— proteins and are stored at ——— and were appropriately qualified according to FDA and ICH Guidances. b(4)



b(4)

- The Actemra™ (tocilizumab) Drug Substance and Drug Product manufacturing processes have been modified a number of times during clinical development. Biochemical comparability study results between successive processes were reviewed. Based on biochemical, biophysical and biological data submitted, products produced by the different Drug Substance and Drug Product processes appear comparable.

- Actemra™ (tocilizumab) Drug Product used in the pivotal trial extension study WA17823 was produced by the commercial process (DP3). Actemra™ (tocilizumab) manufactured by the DP2 process (using Drug Substance produced by the commercial process) was used in the pivotal studies WA17822, WA17824, WA18062, WA1806.

- Actemra™ (tocilizumab) Drug Substance was shown to exist primarily in a [redacted] with small amounts of [redacted] b(4)

- The process-related impurities validated to be effectively cleared during manufacturing include the following: [redacted] b(4)

- Analytical assays are in place for Actemra™ (tocilizumab) Drug Product to confirm the following: [redacted] b(4)

- The stability of Actemra™ (tocilizumab) Drug Substance has been confirmed for up to 24 months when stored at -50° C. The data support Roche's request for a 24 month DS expiration dating period. A stability protocol has been submitted for continued DS testing up to 42 months [redacted] b(4)

- The specifications proposed by Hoffmann La-Roche for Drug Substance and Drug Product are statistically valid and deemed appropriate; stability-indicating assays have been identified and are included among the lot release and stability tests.

B. Physical and Biological Properties

- Actemra™ (tocilizumab) is a 149,000 Da recombinant, glycosylated, humanized IgG1, kappa monoclonal antibody composed of two 448 amino acid heavy chains and two 214 amino acid light chains. [redacted] b(4)

b(4)

- b(4)

- b(4)

- The mechanism of action for tocilizumab is to block the interaction between the soluble and/or membrane bound IL6 receptor and IL6, thus inhibiting the IL6 signal transduction pathway.

- b(4)

C. Description of How the Drug Product is Intended to be Used

- Actemra™/tocilizumab is indicated for the treatment of patients with Adult Onset Rheumatoid Arthritis.

- Actemra™ is indicated for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who are naïve to treatment with, or who had an inadequate response to, one or more DMARDS or TNF antagonists. Actemra™ can be used alone or in combination with methotrexate or other DMARDS.

- Actemra™ (tocilizumab) Drug Product is provided in single-use vials as a sterile preservative-free concentrate (20 mg/mL) solution for intravenous infusion. The single-use vials are 10 or 20 cc type I ——— glass vials filled at 3 different target volumes (4 ml, 10 ml, and 20 ml), corresponding to 80 mg, 200 mg, and 400 mg dosage strengths, respectively. The concentration of Actemra™ (tocilizumab) is the same for each vial configuration - 20 mg/mL. The recommended expiration dating period for Actemra™ vials is 24 months from date of manufacture when stored under appropriate conditions. Stability studies were performed on Actemra™ filled at all three dosage strengths. b(4)

- The package insert states that Actemra™ (tocilizumab) vials should be stored under refrigeration at 2° C to 8° C in the original carton to protect it from light until the time of use. Vials should not be frozen. If visibly opaque particles, discoloration or other foreign particles are observed, the solution should not be used.
- The recommended dosage regimen for Actemra™ (tocilizumab) in adults is 8 mg/kg once every four weeks as a 60-minute intravenous drip infusion. Actemra™/ tocilizumab concentrate for intravenous infusion should be diluted to 100 mL using 0.9% Sodium Chloride Injection, USP.
- The fully diluted Actemra™ (tocilizumab) solutions for infusion may be stored at 2-8°C (36-46°F) or room temperature for up to 24 hours and should be protected from light. Actemra™/tocilizumab solutions do not contain preservatives; therefore, unused product remaining in the vials should be discarded.

D. Basis for Approvability or Not-Approval Recommendation

Tocilizumab is manufactured by a robust process with precautions for contamination by cell substrate or adventitious agents. Tocilizumab is manufactured consistently, leads to a safe and effective product, and approval is recommended for the proposed indication.

Quality unit Assessment

I. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

The review of module 3.2 is attached as a separate document that also includes a review of the product immunogenicity and pharmacokinetic assays.

II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

Hoffmann La-Roche claims categorical exclusion from the requirements of environmental assessment based on 21 CFR 25.31(c). Given that tocilizumab is composed of a protein, Hoffmann La-Roche contends that it meets the criteria for compounds that may be exempted from testing because of their chemical structure and constituents (amino acids and proteins), which should either degrade into their amino acid or constitutive elements in the environment.

III. LIST OF DEFICIENCIES TO BE COMMUNICATED

There are no CMC-related deficiencies precluding approval of this BLA.

IV. ADMINISTRATIVE

A. Reviewer's Signature

Product Quality Reviewer: Gerald M. Feldman, Ph.D.

B. Endorsement Block

Product Division Team Leader: Marjorie A. Shapiro, Ph.D.

Product Division Director: Kathleen A. Clouse, Ph.D.

C. CC Block

OBP Office Director: Steven Kozlowski, M.D.
Clinical Deputy Division Director: Rigoberto Roca, M.D.
Clinical Division Director: Bob Rappaport, M.D.
Division of Monoclonal Antibodies File: BLA STN 127526

Review Cover Sheet

BLA STN 125276/0

ACTEMRA (tocilizumab)

Hoffmann La Roche, Inc.

Gerald M. Feldman, Ph.D.
Division of Monoclonal Antibodies; HFD-123

Product Quality Review Data Sheet

1. **BLA#** STN 125276/0

2. **REVIEW #:** 1

3. **REVIEW DATE:** 26-June-08

4. **REVIEWERS:** Gerald M. Feldman, Ph.D.
Marjorie Shapiro, Ph.D. – Team Leader

5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS:**

Communication/Document	Date
Type C pre-approval CMC meeting	28-Jun-2007
Planned BLA submission feedback	09-Oct-2007
Telecon	17-Dec-2007
Filing Review memo (45 days)	01-Feb-2008
Chugai Inspection	18-May-2008
Information Request Letter	03-Aug-2008

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

Submission(s) Reviewed	Document Date	
STN 125276/0/Original Submission–CMC RU	20-Nov-2007	
STN 125276/1/Initial response to IR	20-Dec-2007	
STN 125276/2/G2-G4 comparability	04-Jan-2008	
STN 125276/4/sterility and mycoplasma validation	31-Jan-2008	
STN 125276/7/UT2 facility update	28-Feb-2008	
STN 125276/8/batch analytical records/CoAs	19-Mar-2008	
STN 125249/9/validation updates	20-Mar-2008	
STN 125249/12/batch record update	08-Apr-2008	
STN 125249/13/rabbit endotoxin validation	11-Apr-2008	
STN 125249/16/alternative trade name	23-May-2008	
STN 125249/17/Risk assessments – [redacted]	12-Jun-2008	b(4)
STN 125249/20/bulk sterility exemption req	01-Jul-2008	
Response to Chugai 483	03-Jul-2008	
STN 125249/23/revised validation studies	11-Jul-2008	
STN 125249/28/updated stability data	18-Jul-2008	
STN 125249/33/Response to IR	08-Aug-2008	

7. **NAME & ADDRESS OF APPLICANT:**
Name: Hoffmann La Roche, Inc.

Address:	340 Kingsland Street Nutley, New Jersey 07110-1199 USA FDA registration number:	
Representative:	Deborah Savuto	
Telephone:	973-562-3705	

8. **DRUG PRODUCT NAME/CODE/TYPE:**
   a) Proprietary Name: Actemra
   b) Non-Proprietary/USAN: Tocilizumab
   c) Code name: CAS registry number is 375823-41-9
   d) Common name: anti-IL-6R, MRA
   e) Drug Review Status: Normal
   f) Chemical Type: recombinant monoclonal antibody G1, humanized

9. **PHARMACOL. CATEGORY:** Therapeutic (blocking) monoclonal antibody to the interleukin-6 receptor

10. **DOSAGE FORM:** Sterile solution for IV administration

11. **STRENGTH/POTENCY:**
    a) The concentration of Actemra (tocilizumab) Drug Product is 20 mg/ml
    b) Potency is defined as percent IC_{50} 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 ——— Potency specification is ⌜ ⌟ based on comparative data against the reference standard. b(4)
    c) Dating period for vialed drug product is 24 months when stored at 2°C -8°C and protected from light.
    d) Actemra is filled into either 10 ml (containing 80 mg of active ingredient) or 20 mL glass vials (containing 200 or 400 mg of active ingredient).

12. **ROUTE OF ADMINISTRATION:** Intravenous administration.

13. ⌜ b(4)

process:

Raw Material:
Vendor:
Subcomponent
Vendor

b(4)

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

b(4)

In addition to the properties listed in the table above, the following characterization of tocilizumab is supported from the contents of the quality section (section 3.2.S.3):

- Despite its glycosylation, tocilizumab has no Fc functionality or effector function *in vitro*, and its mechanism of action is solely mediated by its direct binding to the IL-6 receptor (soluble or membrane-bound) and thus interfering with their ability to bind IL-6.
- Tocilizumab is glycosylated to a similar extent found with most other antibodies. There is limited ——— present on the molecule. b(4)
- Post-translational modifications of both the heavy and light chains result in multiple ——— of tocilizumab. All retain full biological activity.
- b(4)
- LMW species levels do not interfere with the biological activity of tocilizumab, based on potency assay assessments.

The amino acid sequence of the Heavy and Light chains used can be found in the primary review.

15. **STATUS:** The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Establishment Status	Approve		
Environmental Assessment	Approve		Gerald M. Feldman
DMPQ – memo for Drug Substance facilities review	Approve		
DMPQ – memo for Drug Product facilities review	Approve		
DDMAC Carton and vial labeling	Approve		
DMA Carton and vial labeling	Approve	August 4, 2008	Jessica Dement-Brown
DMETS/DDMAC – tradename review	Approve		
EIR for Actemra	VAI		

16. **Inspectional Activities**

A pre-approval inspection (PAI) of Chugai Pharma Manufacturing Co. (CPMC) in Utsunomiya-city, Tochigi, Japan in support of BLA STN 125276 for ACTEMRA™ (tocilizumab) from Hoffmann-La Roche was conducted May 21 –June 5, 2008. Chugai Utsunomiya is responsible for the manufacture of tocilizumab drug substance, formulated drug substance, QC testing of drug substance, formulated drug substance, drug product and final QA review and approval. This was the first US inspection of Utsunomiya. A 14 item Form FDA 483 was issued to the responsible head at the conclusion of the inspection. Three systems were found to have an unacceptable GMP status: Facilities and Equipment, Quality, and Production and Control Systems:

- Facilities and Equipment observations included inadequate validation of the tocilizumab drug substance production process, insect infestation of buildings in controlled areas, inadequate environmental monitoring and cleaning program, inadequate design of the ——— system in the tocilizumab production area, inadequate testing of ——— failure to follow QA approved protocols in drug substance manufacturing, and inadequate equipment cleaning processes. b(4)
- Observations for the Quality System included, inaccurate data and information in the BLA submitted to the Agency for approval and general ignorance of the US GMPs and ICH guidances (specifically Q7) among Chugai production personnel.
- Observations for the Production and Process Controls System included inadequate sterilization validation data for ——— and stopper loads for the drug product ——— process, inadequate ——— , lack of validation data for buffers, column storage solutions and drug substance intermediates, and inadequate record keeping. b(4)

In addition, 10 recommendations were made to the firm:

1. Conduct the concurrent validation of the — system in UT-1 production area to establish reuse and cleaning procedures under approved protocol. Include an appropriate monitoring regime that includes — and microbial monitoring of the system (Exhibit 10). b(4)
2. Amend the protocol for — reuse studies in UT-2 to include monitoring for microbial control and —
3. Develop a scientifically sound approach to demonstrate sterile hold time for ——— small equipment. The use of ——— is inadequate. b(4)
4. Equipment validation documentation should be reviewed to determine gaps in the validation data and amended where necessary. The documentation often lacks sufficient detail and the studies conducted were not adequate. For example, [redacted] were not adequate by current industry standards; [redacted] in the bioreactors were minimal [redacted] there were no ——— and determinations of cold spots. Overall summaries of the validation status might be useful in subsequent inspections. An English translation might be useful to have on file (Exhibit 7). b(4)
5. The equipment re-qualification and calibration programs need to be managed in a more formal and comprehensive manner. These programs should be managed by engineering and validation groups, not by production personnel (Exhibit 9).
6. A reassessment of the facility insect and rodent control program should be conducted and modified as appropriate. The facility appears to be clean and shiny, but there are insect traps everywhere and mice have gotten into the production facility. The facility is not as tight as it would appear at a glance and rodents and insects should not be entering the controlled areas.
7. The SOP for reprocessing should be revised to clarify when reprocessing should take place. The SOP was not followed for lot M8E21 when it failed the in line integrity test 5 times and the lot was not reprocessed.
8. [redacted] b(4)

b(4)

9. A microbiologist trained in mold identification should be available to identify molds from the facility.
10. Roche, the license holder, should provide more input and oversight to GMP related operations.

The inspection is classified as a non concur with approval of the BLA pending resolution of GMP issues observed.

17. **Recommendations on BLA Approvability**

The data submitted in this application support the conclusion that the manufacture of Actemra (tocilizumab) is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents in a way that meets the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. It is recommended that this product be approved for human use under conditions specified in the package insert.

Administrative

A. Reviewers' Signatures

Product Reviewer: Gerald M. Feldman, Ph.D.

B. Endorsement Block

Product Division Team Leader: Marjorie Shapiro, Ph.D.

Product Division Director: Kathleen A. Clouse, Ph.D.

C. CC Block

OBP Office Director: Steven Kozlowski, M.D.

DAARP Deputy Division Director: Rigoberto Roca, M.D.

DAARP Division Director: Bob Rappaport, M.D.

Division of Monoclonal Antibodies File/BLA STN 125276/0

190 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

Part B – Product/CMC/Facility Reviewer(s)

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

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y N	
Drug Substance [3.2.S]		
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ description of manufacturing process o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	Y N	
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	Y N	
❑ control of critical steps and intermediates o justification of specifications o analytical method validation o reference standards o stability	Y N	
❑ process validation (prospective plan, results, analysis, and	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
conclusions)		
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y✓ N	
❑ characterization of drug substance	Y✓ N	
❑ control of drug substance	Y✓ N	
o specification		
o justification of specs.		
o analytical procedures		
o analytical method validation		
o batch analyses		
o consistency (3 consecutive lots)		
o justification of specs.		
❑ reference standards	Y✓ N	
❑ container closure system	Y✓ N	
❑ stability	Y✓ N	
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		
o results		
o method validation		
Drug Product [3.2.P]		
❑ description and composition	Y✓ N	
❑ pharmaceutical development	Y✓ N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y✓ N	
❑ batch formula	Y✓ N	
❑ 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	
❑ controls of critical steps and intermediates	Y✓ N	
❑ process validation including aseptic processing & sterility assurance:	Y✓ N	
o 3 consecutive lots		
o other needed validation data		
❑ control of excipients (justification of specifications; analytical method validation; excipients of	Y✓ N	

CTD Module 3 Contents	Present?	If not, justification, action & status
human/animal origin) ❑ control of drug product (justification of specifications; analytical method validation) ❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity o administration device(s) ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y ✓ N Y ✓ N Y ✓ N	
Diluent (vials or filled syringes) [3.2P'] ❑ description and composition of diluent ❑ pharmaceutical development ❑ manufacturers (names, locations, and responsibilities of all sites involved) ❑ batch formula ❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) ❑ controls of critical steps and intermediates ❑ process validation including aseptic processing & sterility assurance: o 3 consecutive lots o other needed validation data ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) ❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) ❑ reference standards	Y N Y N Y N Y N Y N Y N Y N Not Applicable Y N Y N Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results	Y N Not Y N	Applicable
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	Not Y N Y N	Applicable
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation and storage o sterilization of equipment and materials o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	 Y✓N Y✓N Y✓N	
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y✓N Y✓N Y✓N	Comparability between G1-G4 product was assessed in IND [redacted] b(4) Protocol provided addresses future product

CTD Module 3 Contents	Present?	If not, justification, action & status
Literature references and copies [3.3]	Y ☑ N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review? ❑ legible ❑ English (or translated into English) ❑ compatible file formats ❑ navigable hyper-links ❑ interpretable data tabulations (line listings) & graphical displays ❑ summary reports reference the location of individual data and records ❑ all electronic submission components usable	Y ☑ N Y ☑ N Y ☑ N Y ☑ N Y ☑ N Y ☑ N Y ☑ N Y ☑ N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	Y ☑ N	
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 ☑ N	
includes data demonstrating consistency of manufacture	Y ☑ N	
includes complete description of product lots and manufacturing process utilized for clinical studies	Y ☑ N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	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)	Y ☑ N	
certification that all facilities are ready for inspection	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.	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:	Y N ☑	

Examples of Filing Issues	Yes?	If not, justification, action & status
☐ LAL instead of rabbit pyrogen ☐ mycoplasma ☐ sterility ☐ ☐	Y N ✓ Y N ✓ Y N ✓	Some of the tests used reference the USP or Ph. Eur standards - Roche needs to provide the comparative validation to the BLA
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	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	Y ✓ N	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y ✓ N	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N Not	Applicable

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

Recommendation (circle one): File ✓ RTF

Reviewer: [signature] 12/17/07 Type (circle one): Product (Chair) ✓ Facility (DMPQ)
(signature/ date)

Concurrence:
Branch/Lab Chief: [signature] Division. Director: Kathleen A Clouse 12/17/07
(signature/ date) (signature/ date)
12/17/07