CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125326

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: August 20, 2009
To: Administrative File, STN 125326/0
From: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/BMT PFH 8/20/09
Endorsement: Barry Rothman, Actg. Branch Chief, CDER/OC/DMPQ/MAPCB/BMT BR 8/21/09
Subject: New Biologic License Application (BLA)
Applicant: GlaxoSmithKline
US License: 1809
Facilities: Drug Substance: Lonza Biologics plc, Slough, Berkshire, UK
FEI = 1000583959
Drug Product: Glaxo Operations UK Limited, Barnard Castle, UK
FEI = 3003722390
Product: ARZERRA (Ofatumumab)
Dosage: 100 mg (20 mg/mL), intravenous injection
Indication: Treatment of patients with chronic lymphocytic leukemia
PDUFA date: 31 October 2009

RECOMMENDATION FOR BLA APPROVABILITY:

CMC Microbiology Product Quality Assessment:

BLA 125326, as amended, is recommended for approval from a microbial control, sterility assurance and microbiology product quality perspective. Data and information supporting the recommendation for approval are presented in the review memos of Bo Chi, Ph.D., CDER/OC/DMPQ/BMT for the drug substance and Donald Obenhuber, Ph.D., CDER/OC/DMPQ/ NGDM for the drug product part of the application.

Two post marketing commitments will be communicated to the sponsor:

1. GSK has committed to update the bioburden test for cell culture, primary recovery and purification samples by changing from / / to filtration method. A study will be performed to establish the appropriate volume for each sample in the test. The validation information and data for the updated bioburden test should be provided at the end of the study by December 31, 2009. b(4)
2. GSK has committed to validate drug substance intermediate hold times for microbial control at commercial scale. Validation data should be submitted at the end of the study by December 31, 2010.

Establishment Assessment:

The manufacturing and testing facilities listed in the BLA have an acceptable compliance status.

1. A pre-approval inspection of the drug substance manufacturing and testing site at Lonza Biologics plc, Slough, Berkshire, UK (FEI = 1000583959) was conducted on 5/4-9/2009. A six item FDA 483 observation Form was issued to the manufacturer at the conclusion of the inspection on 5/9/2009. The inspection was classified VAI (Voluntary Action Indicated) and the facility has an acceptable compliance status.

2. A pre-approval inspection of the drug product manufacturing and testing site at Glaxo Operation UK Limited, Bernard Castle, UK (FEI = 3003722390) was conducted on 5/18-22/2009 and no 483 observations were presented to the drug product manufacturer. The inspection was classified as NAI (No Action Indicated) and the facility has an acceptable compliance status.

Review Summary

The drug substance, ofatumumab, is a recombinant monoclonal antibody produced from a murine NS0 cell line. The cell culture process at Lonza Biologics plc, Slough, Berkshire, UK uses chemically-defined

( ) b(4)

The drug product is a clear, colorless, aqueous solution for intravenous infusion. The drug product contains 20 mg/mL of ofatumumab in a mM citrate buffer, pH 6.5 and mM sodium chloride. It is supplied in a 10ml Type 1 glass vials sealed with a coated rubber stopper which is secured with a mm aluminum overseal and a flip-off cap. Each vial contains 5mL of a solution intended for intravenous infusion. Prior to administration, the product is diluted into an infusion bag containing isotonic pyrogen free 0.9% Sodium Chloride Injection. During administration of the intravenous infusion the product solution is filtered through an in-line sterile filter. The drug product is manufactured by processing and tested at Barnard Castle facility of GSK in the UK. No review issues were encountered during the review of the drug product part of this application and no inspectional observations were made during the inspection of the GSK processing and testing facility. b(4)

Conclusion

I. The BLA is recommended for approval from a microbial control, sterility assurance and product quality microbiology perspective.
II. Information and data in this submission not related to microbial control, sterility assurance and product quality microbiology should be evaluated by OBP reviewers.
III. All establishments involved in the manufacture and testing of the drug substance and drug product have an acceptable compliance status.

Cc: WO51: Obenhuber
WO 51: Chi
WO51: Hughes
WO22: Chiang
WO 51: Dillon

HFD-328, eCTD Blue Files (STN 125326)

Archived File: S:\archive\BLA\125326\125326.0.TL .rev.mem.BLA.8-21-2009.doc

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: **August 20, 2009**
To: Administrative File, **STN 125326/0**
From: Donald C. Obenhuber, PhD, CDER/OC/DMPQ/MAPCB/BMT DCO 8/31/09
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT PH 9/1/09
Subject: New Biologic License Application (BLA)
Applicant: GlaxoSmithKline
US License: **1809**
Facility: Glaxo Operations UK Limited, Barnard Castle, UK
FEI: 3003722390
Product: ARZERRA (Ofatumumab)
Dosage: 100 mg (20 mg/mL), intravenous injection
Indication: Treatment of patients with chronic lymphocytic leukemia
PDUFA date: October 31st, 2009

Recommendation: The drug product part of this application, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective.

Review Summary

Ofatumumab Injection is a clear, colorless, aqueous solution containing 20 mg/mL of ofatumumab in a / mM citrate buffer, pH 6.5 containing / mM sodium chloride. It is supplied in a 10ml Type 1 glass vials sealed with a / / coated / / rubber stopper which is secured with a / mm aluminum overseal and a / / flip-off cap. Each vial contains 5mL of a solution intended for intravenous infusion. Prior to administration, the product is diluted into an infusion bag containing isotonic pyrogen free 0.9% Sodium Chloride Injection. During administration of the intravenous infusion the product solution is filtered through an in-line sterile filter. The drug product is manufactured by / / processing at Barnard Castle facility of GSK. The Drug Product part of this application, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective.

b(4)

A pre-approval inspection of the drug product manufacturing site at Glaxo Operations UK Limited, Harmire Road, Barnard Castle, Durham ,DL128DT, United Kingdom, FEI No 1809 was conducted May 18-22, 2009. No Form FDA observations were issued. The inspection was classified as NAI.

37 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

4 other Reviews

Statement of Categorical Exclusion For
Ofatumumab Solution for Infusion 20 mg/mL

April 7, 2008
GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

STATEMENT:
The proposed action is subject to the categorical exclusion listed in 21 CFR Part 25.31(c). As stated in 21 CFR Part 25.31(c), action on an application for marketing approval of a biologic product is categorically excluded from environmental assessment requirements if the action is for a substance which occurs naturally in the environment, when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. GlaxoSmithKline does not have knowledge of any extraordinary circumstances that might cause this action to have a significant affect on the quality of the human environment.

cGMP Status:

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the original request below to find the individual compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of BLA 125326/0 at this time.

Conclusion

I. The BLA is recommended for approval from a sterility assurance and product quality microbiology perspective.
II. Information and data in this submission not related to drug product sterility assurance was not evaluated and should be reviewed by an OBP reviewer.
III. The pre-approval inspection of the drug product manufacturer has been conducted and found that no action is indicated (NAI).

Cc: WO51: Obenhuber
WO51: Hughes
WO22: Chiang
HFD-328, eCTD Blue Files (STN 125326)

Archived File: S:\archive\BLA\125326\125326.0.rev.mem.BLA.8.19.2009.doc

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: **Barbara Rellahan, MS, PhD, Division of Monoclonal Antibodies (DMA), OPS, CDER**

Through: **Patrick Swann, PhD, Deputy Director, DMA\OPS\CDER**
Kathleen Clouse, PhD, Director, DMA\OPS\CDER

BLA Number: **125326/0**
Product: **Arzerra™**
Sponsor : **GlaxoSmithKline**

Date of Review : **August 12, 2009**

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The data submitted in this application support the conclusion that the manufacture of Ofatumumab 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).

The following should be communicated to sponsor in the approval letter:

The dating period for *Arzerra* drug product shall be 18 months from the date of manufacture when stored at 2° to 8°C. The date of manufacture shall be defined as the date of C) of the formulated drug product. The dating period for bulk drug substance shall be 24 months when stored at 2° to 8°C. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of drug product and drug substance under 21 CFR 601.12. b(4)

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

There are a number of deficiencies noted in the application which can be addressed as post-marketing commitments (PMCs) by the sponsor. They are outlined below.

The following are items the sponsor has committed to as PMCs.

1. To reassess release and stability specifications for ofatumumab drug substance and drug product through August 31, 2011. The assessment will be submitted in the 2011 Annual Report.
2. To develop and implement a quantitative specification for the icIEF assay used in the drug substance and drug product stability programs. The assessment will be submitted as a Change Being Effected-30 (CBE-30) to the BLA by October 31, 2011.
3. To develop and validate a semi-quantitative assay for measurement of visible particulates. The test method and specification should be incorporated into drug substance and drug product lot release and stability programs and a CBE-30 submitted by October 31, 2011.
4. To submit a Prior Approval Supplement for the introduction of a C) vial of Ofatumumab Injection, 20 mg/mL to reduce the number of vials needed for the 2000 mg dose by December 31, 2010. b(4)

5. To revise the system suitability criteria for the robotic format of the complement-mediated antibody cytotoxicity potency assay so that the coefficient of variation (CV) (%) for duplicates is consistent with validation limits and is less than or equal to 25%. The commitment will be completed by March 2010 and a revised potency assay SOP will be submitted in the 2010 Annual Report, or alternatively, the robot format of the potency assay will be removed from the BLA. b(4)
6. To perform leachables studies to characterize the potential presence of volatile leachables from the elastomeric stopper and the presence of ( ) under accelerated conditions (25°C) for 6 months and at the recommended storage temperature for 24 months as outlined in the June 5, 2009 submission. Information from this study will be submitted in the 2012 Annual Report (s). b(4)
7. To establish permanent control action limits for purification step yields. This information will be submitted in the 2010 Annual Report after 30 in-control points have been analyzed.
8. To undertake a study to identify the composition of visible particles observed in drug substance lots when particles are observed during ongoing stability studies of the drug substance conformance lots. The results of these studies will be submitted in the 2010 Annual Report.
9. To confirm the lack of impact of reprocessing at the ( ) step by monitoring the real-time stability of drug substance lot 09P01105 and performing accelerated stability studies on this lot at 25°C for 6 months and at 40°C for 3 months. The real time and accelerated studies will include the licensed drug substance stability program's tests and acceptance criteria. Real time stability data will be submitted in the Annual Report and the accelerated stability studies will be completed by 2010 and submitted in the 2010 Annual Report. b(4)

II. Summary of Quality Assessments

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

- Arzerra is supplied as a sterile, single use, 10 mL stoppered glass vial containing 100 mg (5 ml of 20 mg/ml) drug product. Arzerra does not contain preservative.
- Recommended dosing is an initial dose of 300 mg, followed 1 week later by 2,000 mg once weekly for 7 infusions, followed 4 — weeks later by 2,000 mg once every 4 weeks for 4 infusions. b(4)
- The composition per milliliter of Arzerra is 20 mg Ofatumumab, 5.85 mg sodium chloride, 8.55 sodium citrate, 0.195 mg citric acid monohydrate, — water for injection.
- Arzerra drug product is supplied in clear, colorless 10 mL (/ Type I glass vials. The vials are closed with ( ) rubber stoppers, secured with ( ) aluminum overseal with a ( ) flip-off cap (/ which does not come into contact with the drug product. Due to the photosensitivity of the drug product, vials should be stored in their original containers protected from light. b(4)
- The vials have intended (/ overage of the fill volume. The overage volume meets USP Chapter 1 'volume in container' recommendations. b(4)

- Arzerra should be stored at 2° to 8°C, protected from light. Arzerra should not be shaken or frozen. Arzerra does not contain preservatives; therefore, unused portions should be discarded.
- The 300 mg dosage form consists of a package with three 100 mg vials. The 2000 mg dosage form consists of a package with twenty 100 mg vials. Studies were conducted to verify that the packaging was sufficient to ensure vial integrity during shipment.
- Stability of Ofatumumab drug product has been established for up to 18 months at its recommended storage temperature of 2° to 8°C inside the original carton protected from light. Photostability studies have demonstrated Ofatumumab degrades when exposed to light under the tested conditions.
- Stability of Ofatumumab drug substance has been established for up to 24 months when stored at its recommended storage temperature of 2° to 8°C.
- Ofatumumab is an IgG1κ human monoclonal antibody that recognizes a combination epitope comprised of amino acids from the large and small extracellular loops of human CD20. b(4)
- The theoretical molecular mass of Ofatumumab is 148,837 Da.
- Ofatumumab binds to the extracellular region of CD20 which is expressed primarily by B lymphocytes. The primary mechanism of action of Ofatumumab is complement mediated cytotoxicity (CDC) of CD20+ tumor cells. Ofatumumab appears to be an efficient mediator of CDC and has been shown to achieve complete lysis of any cell line expressing >60,000 CD20 molecules/cell. Cell lysis in the range of / /, was also demonstrated with cell expressing relatively low levels of CD20 (~4,500 CD20 molecules/cell. Ofatumumab was also demonstrated to be relatively insensitive to the expression of complement defense molecules such as CD55 and CD59. b(4)
- Potency is defined as the percent activity relative to the reference standard.

b(4)

b(4)

b(4)

1 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

b(4)

b(4)

b(4)

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

- Ofatumumab is indicted for treatment of patients with chronic lymphocytic leukemia (CLL) refractory to alemtuzumab and fludarabine
- Ofatumumab drug product is provided as sterile, single-use, 10-mL glass vial configuration containing 100 mg/vial.
- Ofatumumab vials should be stored under refrigeration at 2° to 8°C inside the original carton to protect it from light until use. The recommended expiration dating period for Ofatumumab vials is 18 months from date of manufacture when stored under these conditions.
- The recommended dose and schedule is 12 doses administered as follows:

  300 mg initial dose, followed one week later by
  2,000 mg weekly for seven doses, followed four weeks later by
  2,000 mg every four weeks for four doses

- Ofatumumab is packaged as a single use presentation. Formulation does not include preservatives so any unused portion remaining in the vial must be discarded immediately.

C. Basis for Approvability or Not-Approval Recommendation

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

- Post-marketing commitments described in the recommendations section above will provide additional information to assure the continued safety of the product.

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 review of the immunogenicity.

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

A. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

The proposed action is subject to the categorical exclusion listed in 21 CFR Part 25.31(c). As stated in 21 CFR Part 25.31(c), action on an application for marketing approval of a biologic product is categorically excluded from environmental assessment requirements if the action is for a substance which occurs naturally in the environment, when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. GlaxoSmithKline does not have knowledge of any extraordinary circumstances that might cause this action to have a significant affect on the quality of the human environment.

III. LIST OF DEFICIENCIES TO BE COMMUNICATED

None.

IV. ADMINISTRATIVE

A. Reviewer's Signatures

for Product Quality Reviewer: Subramanian Muthukkumar, Ph.D. Barbara Rellahan 8.17.09

Product Quality Reviewer: Rashmi Rawat, Ph.D. Rashmi Rawat 8.11.09

B. Endorsement Block

Product Division Team Leader: Barbara Rellahan, M.S., Ph.D. Barbara Rellahan 8/10/2009

Product Division Deputy Director: Patrick Swann, Ph.D. Patrick Swann 8-10-09

Product Division Director: Kathleen A. Clouse, Ph.D. Kathleen A. Clouse 08/10/09

C. CC Block

OBP Office Director: Steven Kozlowski, M.D.

Clinical Deputy Division Director: Joseph Gootenberg, M.D.

Clinical Division Director: Patricia Keegan, M.D.

Division of Monoclonal Antibodies File: BLA STN 125326

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: 8/10/2009
To: Administrative File, STN **125326/0**
From: Bo Chi, Ph.D., CDER/OC/DMPQ/MAPCB/BMT BC 8/10/09
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT PH 8/10/09
Subject: New Biologic License Application (BLA)
Applicant: GlaxoSmithKline
US License: 1809
Facility: Lonza Biologics plc, Slough, Berkshire, UK
FEI: 1000583959
Product: ARZERRA (Ofatumumab)
Dosage: 100 mg (20 mg/mL), intravenous injection
Indication: Treatment of patients with chronic lymphocytic leukemia
PDUFA date: October 31st, 2009

Recommendation: The drug substance part of this application is recommended for approval from product quality microbiology perspective with the following two post-market commitments:

1. GSK has committed to update the bioburden test for cell culture, primary recovery, and purification samples from [redacted] to filtration method. A study will be performed to establish the appropriate volume of each sample in the test. The validation information and data for the updated bioburden test should be provided at the end of the study by December 31, 2009. b(4)
2. GSK has committed to validate drug substance intermediate hold times for microbial control at commercial scale. Validation data should be submitted at the end of the study by December 31, 2010.

The pre-approval inspection of the drug substance manufacturing site at Lonza Biologics plc at Slough, UK was conducted on 5/4-9/2009. Six Form FDA 483 observations were issued at the conclusion of the inspection on 5/9/2009. The inspection was recommended to be classified as voluntary action indicated (VAI). The BLA is recommended for approved.

Review Summary

GlaxoSmithKline has submitted this Biologics License Application (BLA) for ofatumumab, a monoclonal antibody against CD20, for the treatment of chronic lymphocytic leukemia (CLL). The drug substance (DS) is manufactured at Lonza Biologics plc, Slough, Berkshire, UK. The

drug product (DP) is manufactured at Glaxo Operations UK Limited, Barnard Castle, UK. The application contains CMC information in an eCTD format.

The pre-license inspection of the drug substance manufacturing site at Lonza Biologics plc, Slough, Berkshire, UK was conducted by BMT (Bo Chi and Mary Farbman), OBP/DMA (Subramanian Muthukkumar) on 5/4-9/2009. The inspection was recommended to be classified as voluntary action indicated (VAI). The implementation of the corrective actions should be evaluated during the next surveillance inspection. The application is recommended for approval.

Assessment

Drug Substance (3.2.S)

General Information (3.2.S.1)

Ofatumumab is an IgG1κ human monoclonal antibody (mAb) that specifically recognizes an epitope on the human CD20 molecule on B-cells. It is produced in a murine cell line (NS0),

b(4)

Manufacture (3.2.S.2)

Manufacturer(s) (3.2.S.2.1)

The manufacture and testing of ofatumumab drug substance and cell bank storage are performed by Lonza Biologics, UK.

Lonza Biologics plc
228 Bath Road
Slough
Berkshire
SL1 4DX
UK
FEI: 1000583959

Additional cell bank storage is performed by:
Lonza Biologics Inc.,
101 International Drive,
Portsmouth,
NH 03801
USA.
FEI: 3001451441

Testing for Visual Inspection, pH, Osmolality, Protein Concentration, icIEF, HPLC, SDS-PAGE, Endotoxin and Bioburden and release of commercial ofatumumab drug substance are performed at:

b(4)

Lonza Biologics plc
228 Bath Road
Slough
Berkshire

19 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

5 Other Reviews

b(4)

Environmental Assessment:
A claim for a categorical exclusion from preparing an Environmental Assessment under 21 CFR 25.31(c) was provided by the firm. GlaxoSmithKline does not have knowledge of any extraordinary circumstances that might cause this action to have a significant affect on the quality of the human environment.

cGMP Status:
The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the original request below to find the individual compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of BLA 125326/0 at this time (Response to TB-EER attached).

Conclusion

I. The drug substance section of the BLA is recommended for approval from a product quality microbiology perspective with the following two post-market commitments:

   i. GSK has committed to update the bioburden test for cell culture, primary recovery, and purification samples from [redacted] to filtration method. A study will be performed to establish the appropriate volume of each sample in the test. The validation information and data for the updated bioburden test should be provided at the end of the study by December 31, 2009. b(4)

   ii. GSK has committed to validate drug substance intermediate hold times for microbial control at commercial scale. Validation data should be submitted to the agency at the end of the study by December 31, 2010.

II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by an OBP reviewer.

III. The pre-approval inspection of the drug substance manufacturing site Lonza, Slough, UK was conducted on 5/4-9/2009. Six Form FDA 483 observations were issued at the conclusion of the inspection on 5/9/09. The inspection was recommended to be classified as voluntary action indicated (VAI). The BLA is recommended for approved.

Cc: WO51: Chi
WO51: Hughes
WO22: Chiang
HFD-328, eCTD Blue Files (STN 125326)

Archived File: S:\archive\BLA\125326\125326.0.rev.mem.BLA.8.10.2009.doc

Review Cover Sheet

BLA STN 125326

Antibody Name: Ofatumumab

Manufacturer Name: GlaxoSmithKline

Subramanian Muthukkumar, PhD
Rashmi Rawat, PhD
Division of Monoclonal Antibodies; HFD-123

Product Quality Review Data Sheet

1. **BLA#** STN 125326
2. **REVIEW #:** 1

3. **REVIEW DATE:** 10-Aug-2009
4. **REVIEWERS:** Subramanian Muthukkumar, PhD and Rashmi Rawat, PhD
   Barbara Reilahan, MS, PhD Team Leader

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

Communication/Document	Date
Filing Review Memo	02/27/2009
Information Request Letter #1	03/06/2009
Information Request Letter #2 (74 day letter)	04/14/2009
Information Request Letter #3	05/11/2009
Information Request Letter #4	06/18/2009
Information Request Letter #5	06/19/2009
Information Request Letter #6	07/13/2009
483	05/09/2009
CMC Teleconference #1	05/21/2009
CMC Teleconference #2	08/03/2009

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

Submission(s) Reviewed	Document Date
STN 125326/0	01/30/2009
STN 125326/0.9 (eCTD 0008)	03/17/2009
STN 125326/0.15 (eCTD 0014)	05/14/2009
STN 125326/0.18 (eCTD 0017)	05/22/2009
STN 125326/0.19 (eCTD 0018)	06/05/2009
STN 125326/0.20 (eCTD 0019)	06/22/2009
STN 125326/0.21 (eCTD 0020)	07/02/2009
STN 125326/0.22 (eCTD 0021)	07/20/2009
STN 125326/0.23 (eCTD 0022)	07/30/2009
STN 125326/0.25 (eCTD 0025)	08/10/2009

7. **NAME & ADDRESS OF APPLICANT:**
   Name: Glaxo Group Limited d/b/a GlaxoSmithKline
   Address: Glaxo Wellcome House, Berkeley Avenue,
   Greenford, Middlesex, UB6 0NN UK
   FDA registration number: 1821
   Representative: Philip A. Witman
   Telephone: 1-888-825-5249

8. **DRUG PRODUCT NAME/CODE/TYPE:**
   a) Proprietary Name: ARZERRA injection
   b) Non-Proprietary/USAN: Ofatumumab
   c) Code name: GSK1841157 (HuMax-CD20) CAS # 679818-59-8
   d) Common name: HuMax-CD20, GSK1841157 and 2F2

e) Drug Review Status: Original Application
f) Chemical Type: Immunoglobulin G1, anti-(Human CD20 (antigen)) (Human monoclonal HuMax-CD20 heavy chain), disulfide with human monoclonal HuMax-CD-20 κ-chain, dimer
g) CAS index/registry number: 679818-59-8

9. **PHARMACOL. CATEGORY:** Fully human IgG1 kappa immunoglobulin molecule.

10. **DOSAGE FORM:** Sterile parenteral solution.

11. **STRENGTH/POTENCY:**
a) The concentration of Arzerra Drug Product is 20 mg/ml.
b) Potency is defined as the percent activity relative to the reference standard, b(4)
c) Dating period for vialed drug product is (18?) months when stored at and protected from light. b(4)
d) Ofatumumab is filled into 10 mL glass vials containing 5 ml of a 20 mg/ml antibody solution.

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

13. **ACID (Animal Component Information Database)**
Refer to BLA 125326 review for animal/human derived component information.
Also see section 3.2.S.2.3.1 Control of Source and Starting Materials of Biological Origin.

14. **RELATED/SUPPORTING DOCUMENTS:**

DMF #	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
		DS manufacturing facility		N/A		Information for facilities and process is in the BLA. A PAI was conducted at the facility as part of the approval mechanism.
CBER MF		media components	1	Adequate	7-29-09 by Rashmi Rawat	Pertinent sections reviewed and found acceptable
MF			4	Adequate	Not assessed (N/A)	No review required as all the relevant information related to compatibility with the product was in the BLA
			4	Adequate	N/A	No review was required as relevant

b(4)

b(4)

b(4)

				information is provided in the BLA.
	4	Adequate	N/A	No review was required as relevant information is provided in the BLA.
	4	Adequate	N/A	No review was required as relevant information is provided in the BLA.
	4	Adequate	N/A	No review was required as relevant information is provided in the BLA.

b(4)

b(4)

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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			
Environmental Assessment	Approval	06/09/2009	B. Rellahan
DMPQ – memo for Drug Substance facilities review	Approval	08/2009	Bo Chi
DMPQ – memo for Drug Product facilities review	Approval	08/2009	Bo Chi
OBP Carton and vial labeling			K. Rains
DMETS/DDMAC – tradename review			
EIR for Lonza Biologics plc, Slough, UK	VAI	05/11/2009	B. Chi, S. Muthukkumar, M. Farbman
EIR for Glaxo Operations Barnard Castle, UK	VAI		D. Obenhumber, K. Zielny

(1) DMPQ review date states VAI has not been changed since EIR

16. **Inspectional Activities**

A pre-approval inspection (PAI) of this biologics final product manufacturing facility was conducted following a request by the Biotech Manufacturing Team, Office of Compliance, CDER, under FACTS assignment # 1053606 (Inspection No.TFRB-09-06). The inspection covered the manufacturing operations for BLA STN 125326/0 for the Arzerra (Ofatumumab) drug substance at Lonza Biologics plc, Slough, Berkshire, UK. An additional pre-approval inspection of the testing laboratories of Lonza Biologics plc, in Winnersh Triangle, Berkshire, UK, was conducted following a request by the Biotech Manufacturing Team, Office of Compliance, CDER, under FACTS assignment # 1053608 (Inspection No. TFRB-09-07).These inspections were conducted on May 4-9, 2009 by TFRB inspectors, Bo Chi and Mary Farbman and product reviewer Subramanian Muthukkumar in accordance with applicable sections of CP 7356.002M, Inspections of Licensed Therapeutic Drug Products and ICH Q7A. This inspection was limited to the manufacturing and testing of Ofatumumab. This PAI covered the following five Quality Systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. Lonza Biologics, Slough is responsible for manufacturing of ofatumumab drug substance, formulated drug substance, QC testing of drug substance, and final QA review and approval. Lonza Biologics, Winnersh Triangle is responsible for QC testing of drug substance,

FDA form 483 with 6 observations was issued at the end of this inspection. As noted below 483 item # 3 is associated with product quality review.

3. Verification of the suitability of certain testing methods is deficient. Specifically, the subvisible particle assay used in ofatumumab drug product stability studies is not appropriately qualified for the conditions of its use. Reference: 21CFR 211.194(a) (2)

Description of above 483 citation: Ofatumumab drug product stability testing carried out by Lonza includes <USP> 788 subvisible particle assay. During the inspection, Lonza informed that <USP> 788 assay is contracted out to ( ) Review of the SOPs (SOP-10-1 and APSS SOP) provided by Lonza during inspection revealed that <USP> 788 subvisible particle assay used in drug product stability studies has not been appropriately qualified to measure particles in ofatumumab drug product. Specifically, unlike indicated on page 1 of ( ) SOP (SOP-10-1) **"Prepare sample by procedure agreed with client", Lonza failed to provide procedure or details** regarding how ofatumumab samples are prepared for the test or what has agreed upon with ( ) regarding sample preparation (e.g., number of vials pooled, dilutions, etc) to measure subvisible particles. This deficiency of verification of the suitability of testing method for subvisible particles in ofatumumab DP stability studies resulted in a 483 citation (#3). To resolve this issue GSK moved testing for subvisible particles to the Barnard Castle facility which has a qualified product specific assay. This was deemed an acceptable approach.

b(4)

The following product quality items were identified and communicated verbally to the firm during the closeout meeting:

1. Review of batch records for ( ) revealed that viable cell concentration reached well below ( ) cells/mL prior to day 14 for batches 48885 and 89662. Nevertheless cells were ( )

b(4)

Though drug substance from these batches were said to be met all critical quality attributes, it was brought to the attention of the firm that not harvesting cells within the validated time and especially ( ) b(4)

2. Between drug substance lots, there were discrepancies in the assays used for lot release and stability testing (e.g. ( ) . Therefore, revised tables listing all updated lot release and stability assays and specifications should be submitted to the BLA. b(4)

3. Stability data to support reprocessing at ( ) step was provided neither in the BLA nor during the DS inspection. The firm was unable to provide information whether reprocessing at this step was carried out within the validated hold time. Supporting stability data should be submitted to agency for concurrence prior to performing reprocessing at this step. b(4)

Firm management promised to implement the recommendations.

Inspection at Drug Product manufacturing facility, Bernard Castle, UK: It was concluded in the drug product inspection conducted at GSK, Bernard Castle, UK that the method used to measure subvisible particulates is carried out in accordance with USP in combination with their standard operating procedure for the ( ) (the instrument used for the analysis). Inspectors also concluded that this is a basic Compendial test ( ) ( ) As per inspectors there are no dilutions and the method indicates the number of vials to be pooled to generate the volume as recommended in the USP. b(4)

( ) b(4)

Reviewer's Comment: It should be noted that unlike GSK SOP, the SOP followed by ( ) for subvisible particle analysis indicated that samples should be prepared by procedure agreed with client but this procedure was not in place. A statement that the method is carried out in accordance with USP <788> does not address some method parameters which are critical to the accuracy and reliability of the method when applied to biotechnology products. For example, <788> states that elimination of gas bubbles can be done by allowing a sample to stand for 2 minutes or sonication. Sonication of a protein could lead to increased protein particulates. Therefore, the procedure for elimination of gas bubbles needs to be specified. b(4)

17. Quality Assessment

a) Review of Module 3.2: Body of Data

The review of module 3.2 is attached as a separate document that also includes review of the immunogenicity assay and the assay to detect neutralizing antibodies.

b) Module 1: Environmental Assessment

Statement of Categorical Exclusion for Ofatumumab Solution for Infusion 20 mg/mL: The proposed action is subject to the categorical exclusion listed in 21 CFR Part 25.31(c). As stated in 21 CFR Part 25.31(c), action on an application for marketing approval of a biologic product is categorically excluded from environmental assessment requirements if the action is for a substance which occurs naturally in the environment, when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. GlaxoSmithKline does not have knowledge of any extraordinary circumstances that might cause this action to have a significant affect on the quality of the human environment.

c) List of Deficiencies: None.

18. Recommendations on Approvability

The data submitted in this application support the conclusion that the manufacture of Arzerra 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.

IV Administrative

A. Reviewers' Signature

for Product Reviewer: Subramanian Muthukummar, Ph.D. Barbara Rellahan 8.17.09

Product Reviewer: Rashmi Rawat , Ph.D. Rashmi Rawat 8.11.09

B. Endorsement Block

Product Division Team Leader: Barbara Rellahan, MS, Ph.D. Barbara Rellahan 8/10/2009

Product Division Deputy: Patrick Swann, Ph.D. Patrick Swann 8/14/09

Product Division Director: Kathleen A. Clouse, Ph.D. Kathleen A. Clouse 08/13/09

C. CC Block

ONDOODP/DBOP Project Manager: Raymond Chiang
Division of Monoclonal Antibodies File/BLA STN 125326/0

161 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry-1

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	N/a
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	Not Applicable
❑ 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	Not provided
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	Y	N	

CTD Module 3 Contents	Present?	If not, justification, action & status
plan, results, analysis, and conclusions)	Y N	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	
❑ characterization of drug substance	Y N	(not included. This is a review issue.) b(4)
❑ control of drug substance		
o specification		
o justification of specs.		
o analytical procedures		
o analytical method validation		
o batch analyses		
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 other needed validation data		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	
❑ control of drug product	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
(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	
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 ❑ container closure system o specifications (vial, elastomer,	 Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N	N/a Product administered after dilution in 0.9% sodium chloride infusion bags.

CTD Module 3 Contents	Present?	If not, justification, action & status
drawings) o availability of DMF o closure integrity ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results	Y N	
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	 Y N Y N	N/a
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	BMT assessment N/a
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y N Y N Y N	
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?	Y N	
❑ legible	Y N	
❑ English (or translated into English)	Y N	
❑ compatible file formats	Y N	
❑ navigable hyper-links	Y N	Some major sections do not have links to their sub-sections. These sections are therefore very hard to navigate through.
❑ interpretable data tabulations (line listings) & graphical displays	Y N	
❑ summary reports reference the location of individual data and records	Y N	
❑ all electronic submission components usable	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	BMT assessment - VAI not OAI
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	
❑ LAL instead of rabbit pyrogen	( )	b(4)

Examples of Filing Issues	Yes?	If not, justification, action & status
☐ mycoplasma ☐ sterility ☐ ☐	/ /	
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	N/a
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	BMT assessment
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y N	BMT assessment
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	N/a

b(4)

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).

1. Provide a Table of Contents for Module 3 with links to all documents in this section.
2. In Section 3.2.S.2.5, Table 2, please insert links to the referenced section.
3. In Section 3.2.S.2.3, please insert a Table with links to the cited sections or Bookmarks to the major sections of this document.
4. In Section 3.2.S.2.3 in Tables 3, 5 and 7, please insert links from the specified tests to the actual test reports.

Recommendation (circle one): (File) RTF

Reviewer: [signature] 2/27/09 (signature/ date) Type (circle one): (Product) (Chair) Facility (DMPQ)

[signature] 2/27/09

Concurrence:

~~Branch/Lab Chief~~ Team Leader: [signature] 02/27/2009 (signature/ date)

Division. Director: [signature] (signature/ date) 02/27/09

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

BLA/NDA Number: STN125326/0

Applicant: GlaxoSmithKline

Stamp Date:

Established/Proper Name: Ofatumumab/ (HuMax-CD20)

BLA/NDA Type: Original BLA

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

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

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

Examples of Filing Issues	Yes?	If not, justification, action & status
Companion application received if a shared or divided manufacturing arrangement	Y	

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

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	N	The firm will provide it.
Drug Substance [3.2.S]		
❑ general info	Y	
o nomenclature		
o structure (e.g. sequence, [redacted] sites)		
o properties		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process and process control	Y	
o batch numbering and pooling scheme		
o cell culture and harvest		
o purification		
o filling, storage and shipping		
❑ control of materials	Y	
o raw materials and reagents		
o biological source and starting materials		
o cell substrate: source, history, and generation		

b(4)

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

CTD Module 3 Contents	Present?	If not, justification, action & status
○ cell banking system, characterization, and testing ❑ control of critical steps and intermediates ○ justification of specifications ○ stability ❑ process validation (prospective plan, results, analysis, and conclusions) ❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) ❑ characterization of drug substance ❑ control of drug substance ○ specifications ○ justification of specs. ○ analytical procedures ○ analytical method validation ○ batch analyses ❑ reference standards ❑ container closure system ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	Y Y Y Y Y Y Y Y	
Drug Product [3.2.P] [Dosage Form] ❑ description and composition ❑ pharmaceutical development ○ preservative effectiveness ○ container-closure integrity ❑ 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	Y Y Y Y Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
outside [e.g., contract] facilities)		
❑ controls of critical steps and intermediates	Y	
❑ process validation including aseptic processing & sterility assurance: o Filter validation o Component, container, closure depyrogenation and sterilization validation o Validation of aseptic processing (media simulations) o Environmental Monitoring Program o Lyophilizer validation o Other needed validation data (hold times)	Y	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	Under OBP's purview.
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	
❑ reference standards or materials	Y N	Under OBP's purview.
❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF & LOAs o administration device(s)	Y	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y	
Diluent (vials or filled syringes) [3.2P']		Not applicable.
❑ description and composition of diluent	Y N	
❑ pharmaceutical development	Y N	
o preservative	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
effectiveness o container-closure integrity	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	Y N	
(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 Filter validation o Component, container, closure depyrogenation and sterilization validation	Y N	
o Validation of aseptic processing (media simulations)	Y N	
o Environmental Monitoring Program	Y N	
o Lyophilizer sterilization validation o Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards	Y N	
❑ container closure system	Y N	
o specifications (vial, elastomer, drawings) o availability of DMF & LOAs		
❑ stability	Y N	

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

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results		
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	 Y Y N	 Not 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, sterilization and storage 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 Y N	 Under OBP's purview.
	Y N	Not applicable.
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y Y Y N	 Under OBP's purview.
Literature references and copies [3.3]	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status

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

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	Under OBP's purview.
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	Under OBP's purview.
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	Under OBP's peuview.
Certification that all facilities are ready for inspection	Y	The firm has indicated that all the facilities are ready for inspection.
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	Under OBP's Purview.
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: □ LAL instead of rabbit pyrogen □ mycoplasma □ sterility	Y	b(4) Under OBP's Purview.
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	Under OBP's purview. b(4)
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/NDA (OBP & DMPQ)

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.

Bo Chi	Bo Chi	3/4/09
Product Quality Reviewer(s)		Date
Patricia Hughes		3/4/09
Branch Chief/Team Leader/Supervisor		Date
Rick Friedman		3/5/07
Division Director		Date