

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125486Orig1s000**

**MICROBIOLOGY REVIEW(S)**



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

**Date:** October 21, 2013  
**To:** Administrative File, STN 125486/0  
**From:** Donald C. Obenhuber, Ph.D., CDER/OC/OMPQ/DGMPA/BMAB  
**Endorsement** Zhihao Peter Qiu, Ph.D., Branch Chief, CDER/OC/OMPQ/DGMPA/BMAB  
**Subject:** BLA: For the treatment of patients with previously untreated chronic lymphocytic leukemia.  
**Applicant:** Genentech, Inc.  
**US License:** 1048  
**Facility:** Roche Diagnostics GmbH  
Nonnenwald 2  
D-82377 Penzberg  
Germany  
FEI 3002806560  
**Product:** Gazyva (obinutuzumab, GA101)  
**Dosage:** Sterile solution for infusion, 1000mg/40mL (25 mg/mL)  
**Indication:** in combination with chlorambucil is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL)  
**PDUFA date:** November 22, 2013

**Recommendation:** The BLA, as amended, is recommended for approval from a product quality microbiology perspective.

PMC: Submit a protocol for [REDACTED] (b) (4)  
[REDACTED] The protocol should include bioburden and endotoxin limits to demonstrate continued microbial control [REDACTED] (b) (4).  
The protocol should be submitted as a CBE-30 by 31 Dec 2013. Execute the protocol and provide the results in the annual report following the approval of the CE-30.

## Summary

### INTRODUCTION

2.3.QOS.INT, introduction

Obinutuzumab is a recombinant, humanized, monoclonal, type II glycoengineered anti-CD20 monoclonal antibody (mAb) which is produced in Chinese hamster ovary (CHO) cells. The antibody targets CD20 + malignancies and is currently investigated in clinical trials for different indications, i.e., chronic lymphocytic leukemia (CLL), indolent non-Hodgkin's lymphoma (iNHL), diffuse large B-cell lymphoma (DLBCL).

Obinutuzumab is provided as a sterile liquid, and contains no preservatives. Each single-use 50 mL vial contains 1000 mg (nominal) obinutuzumab for intravenous (IV) infusion. The Drug Product is formulated as 25 mg/mL obinutuzumab in 20 mM L-histidine / L-histidine hydrochloride (b) (4) 240 mM trehalose, and 0.02% (w/v) poloxamer 188 at pH 6.0. Obinutuzumab is supplied as a clear (b) (4), colorless to pale brown, sterile liquid solution. The product is intended for IV administration.

Included here are product quality microbiology amendments reviewed in response to information requests.

Sequence number	Date	Description
Sequence No. 0010	July 18, 2013	Response to Request for Information dated July 12, 2013
Sequence No. 0013	July 25, 2013	Response to question 6 requested at the Pre-BLA meeting on March 5, 2013: Attachment 7
Sequence No: 0036	Sept 25, 2013	Final update to requests from March 5, 2013:

During the review of this BLA, Roche updated the BLA with product quality information as agreed during a CMC Pre-BLA meeting. Updates to the BLA in response to the pre-BLA meeting on March 5, 2013 were provided in Amendments e-CDT sequence 0010, 0013 and 0036. The data and information provided in these amendments were reviewed in this review.

## MANUFACTURERS [OBINUTUZUMAB]

3.2. S.2.1.MFR, manufacturer

### 1. MANUFACTURE AND BATCH RELEASE

#### FACILITY INFORMATION

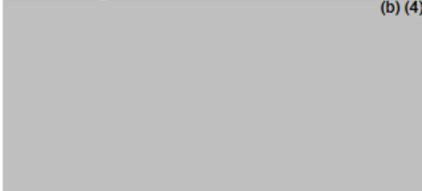
The Drug Substance is manufactured and released by:  
 Roche Diagnostics GmbH  
 Nonnenwald 2

D-82377 Penzberg  
Germany  
FEI 3002806560

An inspection of the Drug Substance manufacturer, Roche Diagnostics GmbH, Penzberg, Germany was conducted August 7-14, 2013 and found to be NAI.

The release bioassay can alternatively be performed by:  
Roche Diagnostics GmbH  
Sandhofer Straße 116  
D-68305 Mannheim  
Germany  
FEI 3002806559

Testing for adventitious viruses of the preharvest cell culture fluid is performed by:

(b) (4)  


Drug product manufacturing and testing is performed by:  
Firm Name: Roche Diagnostics GmbH  
Address: Sandhofer Strasse 116, Mannheim, Germany  
FEI: 3002806559

Drug product labeling and secondary packaging is performed by:.  
Firm Name: F. Hoffmann-La Roche Ltd.  
Address: Wurmisweg, CH-4303 Kaiseraugst, Switzerland  
FEI: 3003973536

*Comment: A TB-EER listing of all facilities from the BLA was submitted in DARRTS. A final TB-EER will be submitted by the OND RPM 15-30 days before the action date.*

**DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS  
CELL CULTURE AND HARVEST**

3.2.S.2.2.DMP firm, manuf-process-and-controls-cellculture

Obinutuzumab manufacturing begins with  (b) (4)

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**Table 1 Obinutuzumab Drug Substance Release Specification**

Analytical Procedure	Acceptance Criteria
Color <sup>a</sup>	(b) (4)
Clarity/ Opalescence <sup>a</sup>	(b) (4)
pH	(b) (4)
Osmolality [mOsmol/kg]	(b) (4)
Content of Poloxamer 188 [mg/mL]	(b) (4)
Content of Protein by UV [mg/mL] <sup>a</sup>	(b) (4)
Potency by Bioassay [ $\times 10^4$ units/mg] <sup>a</sup>	(b) (4)
Identity of Obinutuzumab by Peptide Mapping	(b) (4)
Purity by SE-HPLC	(b) (4)
Sum of HMW Forms [area-%] <sup>a</sup>	(b) (4)
Sum of LMW Forms [area-%]	(b) (4)
Purity by CE-SDS (non-reduced)	(b) (4)
(b) (4)	(b) (4)
Purity by IE-HPLC	(b) (4)
(b) (4)	(b) (4)
Bioburden	(b) (4)
Bacterial Endotoxins [EU/mg]	(b) (4)
Content of Host Cell Protein [ppm]	(b) (4)

<sup>a</sup> Analytical procedures including acceptance criteria also applied for post-approval annual stability protocol.

*Comment: The bioburden and endotoxin specifications are acceptable.*

**Satisfactory**

**GMP Status:** See TB-EER in DARRTS

**Conclusion**

- I. This BLA, as amended, is recommended for approval from a product quality microbiology perspective.
- II. Information and data in this submission not related to the product quality microbiology was not evaluated and should be reviewed by an OBP reviewer.
- III. No additional inspectional follow-up items were identified.

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/s/  
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DONALD C OBENHUBER  
10/21/2013

ZHIHAO PETER QIU  
10/22/2013



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

**Date:** 15 October 2013  
**To:** Administrative File, STN 125486  
**From:** Colleen Thomas, Ph.D., Reviewer, CDER/OC/OMPQ/DGMPA/BMAB  
**Endorsed:** Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB  
**Subject:** Original BLA for obinutuzumab.  
**US License:** 1048  
**Applicant:** Genentech, Inc.  
**Facility:** Roche Diagnostics GmbH  
Sandhofer Strasse 116  
D-68305 Mannheim, Germany  
FEI: 3002806559  
**Product:** Gazyva (obinutuzumab)  
**Indication:** Treatment of patients with previously untreated chronic lymphocytic leukemia.  
**Dosage:** Sterile, preservative-free 25 mg/ml solution for infusion supplied in 50 ml single-use vials. The solution is diluted in 0.9% (w/v) sodium chloride prior to administration.  
**Action date:** 21 December 2013

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**Recommendation for approvability:** The BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval.

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## **Summary**

BLA 125486 was submitted in electronic format on 22 March 2013 to license obinutuzumab for treatment of patients with previously untreated chronic lymphocytic leukemia. Obinutuzumab is designated as a breakthrough therapy. Amendment 0040 was submitted on 9 October 2013 to provide additional microbial retention data for the (b) (4), as requested by the Agency. This memo covers amendment 0040 and is an addendum to the product quality microbiology review submitted to DARRTS on 27 September 2013.

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SATISFACTORY

### **Additional Information**

#### **Environmental Assessment**

A claim for a categorical exclusion from preparing an Environmental Assessment under 21 CFR 25.31(c) was provided by the firm on the grounds the substances associated with this submission occurs naturally in the environment and the actions associated with this submission do not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

#### **CGMP Status**

Please refer to the response to the TB-EER request in DARRTS.

#### **Conclusion**

- I. The BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval.
- II. Product quality aspects other than microbiology should be reviewed by OBP.
- III. No inspection follow-up items were identified.

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/s/  
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COLLEEN THOMAS  
10/15/2013

PATRICIA F HUGHES TROOST  
10/15/2013



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

**Date:** 26 September 2013  
**To:** Administrative File, STN 125486  
**From:** Colleen Thomas, Ph.D., Reviewer, CDER/OC/OMPQ/DGMPA/BMAB  
**Endorsed:** Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB  
**Subject:** Original BLA for obinutuzumab.  
**US License:** 1048  
**Applicant:** Genentech, Inc.  
**Facility:** Roche Diagnostics GmbH  
Sandhofer Strasse 116  
D-68305 Mannheim, Germany  
FEI: 3002806559  
**Product:** Gazyva (obinutuzumab)  
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**Dosage:** Sterile, preservative-free 25 mg/ml solution for infusion supplied in 50 ml single-use vials. The solution is diluted in 0.9% (w/v) sodium chloride prior to administration.  
**Action date:** 21 December 2013

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**Recommendation for approvability:** The BLA was reviewed from a product quality microbiology perspective. Approval cannot be recommended until acceptable microbial retention data for the (b) (4) has been provided. The study data will be submitted to the BLA the week of 7 October 2013. The study data will be reviewed in an addendum to this memo.

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## **Summary**

BLA 125486 was submitted in electronic format on 22-Mar-2013 to license obinutuzumab for treatment of patients with previously untreated chronic lymphocytic leukemia. Obinutuzumab is designated as a breakthrough therapy. Obinutuzumab is a recombinant, humanized, monoclonal, type II glycoengineered antiCD-20 monoclonal antibody which targets CD20+ malignancies. The drug substance is produced in CHO cells at Roche Diagnostics GmbH in Penzberg,

Germany. The drug product is manufactured (b) (4) at Roche Diagnostics in Mannheim, Germany. This review covers microbial control of the drug product manufacturing process, sterility assurance of the drug product, and microbiological specifications for the drug product. Aside from endotoxin testing validation for the drug substance (which also applies to the drug product), the drug substance module is covered in a separate review memo.

**Product Quality Microbiology Information Reviewed**

Sequence Number	Date	Description
0000	22 April 2013	Original BLA
0013	25 July 2013	Amendment (response to 25 July IR)
0019	14 August 2013	Amendment (response to 8 August IR)
0021	19 August 2013	Amendment (response to 25 July IR, question 9b)
0028	10 September 2013	Amendment (response to 26 August IR)
0035	24 September 2013	Amendment (response to 20 September IR)

**Drug Substance Review**

The hold time validation study for endotoxin testing is reviewed below. The remainder of the drug substance information in Module 3 is reviewed in a separate memo.

**Module 3.2**

**S.4.3 Validation of Analytical Procedures**



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/s/  
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COLLEEN THOMAS  
09/27/2013

PATRICIA F HUGHES TROOST  
09/27/2013



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Compliance  
Office of Manufacturing and Product Quality  
Biotech Manufacturing and Assessment Branch

## PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

**REVIEWER:** Kalavati Suvarna, Ph.D.  
**TEAM LEADER:** Patricia Hughes, Ph.D.

<b>BLA</b>	125486/0
<b>APPLICANT</b>	Genentech, Inc.
<b>US LICENSE NUMBER</b>	1752
<b>SUBMISSION REVIEWED</b>	Original BLA
<b>PRODUCT</b>	Gazyva (obinutuzumab)
<b>MANUFACTURING FACILITY</b>	Drug Substance: Roche Diagnostics GmbH, Nonnenwald 2, D-82377 Penzberg, Germany, Inc. (FEI No. 3002806560).
<b>INDICATION</b>	For the treatment of patients with previously untreated chronic lymphocytic leukemia
<b>DOSAGE FORM</b>	Liquid for intravenous infusion (1000 mg/40 mL i.e. 25 mg/ml in single use vial)
<b>CDER RECEIPT DATE</b>	April 22, 2013
<b>REVIEW ASSIGN DATE</b>	July 16, 2013
<b>REVIEW COMPLETE DATE</b>	August 26, 2013
<b>GRMP GOAL DATE</b>	October 22, 2013
<b>PDUFA GOAL DATE</b>	November 22, 2013
<b>PROJECT MANAGER</b>	Kallungal, Beatrice
<b>DIVISION</b>	Division of Hematological Products
<b>TO</b>	S:\archive\BLA\125486\STN125486.rev.mem.BLA.08-26-2012.doc

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**SATISFACTORY****CONCLUSION:**

The real time *Leptospira* PCR assay was validated to detect (b) (4) *Leptospira* in (b) (4). Appropriate positive and negative controls were used. The validation assessed the specificity, sensitivity, and robustness of the assay. Overall, the real time qualitative PCR assay is acceptable for the detection of *Leptospira* in the Obinutuzumab (b) (4) samples.

**SIGNATURES/DISTRIBUTION LIST**

Primary BMAB Reviewer: Kalavati Suvarna, Ph.D.

Date:

Concurring BMAB Team leader: Patricia. F. Hughes, Ph.D.

Date:

cc:

OND/OHOP/DHP/ Kallungal, Beatrice

Building 51/OC/OMPQ/DGMPA/BMAB Hughes, Patricia

OND/OHOP/DHP/CDTL/ Kwitkowski, Virginia

OND/OHOP/DHP/MO/Hyon-Zu Lee

Information Request dated 7/23/2013:

Leptospira PCR assay:

1. Please provide the raw data obtained for the Leptospira PCR assay validation and calculations of Cp values.
2. Please clarify if the PCR products were sequenced.
3. Please provide the Leptospira assay results for all obinutuzimab (b) (4) lots tested.
4. Please explain your choice of internal control for the assay.
5. Please explain how you assessed matrix interference for the Leptospira PCR assay. The (b) (4) used in the matrix interference studies should be specified.
6. Please explain how the (b) (4) instrument performance is assessed and the frequency of the assessment.

Information request dated 8/12/2013:

With regards to the Leptospira PCR assay, please provide the following information:

1. Please provide the acceptance criterion used for the internal control to ensure consistent DNA recovery from sample using the (b) (4). Information on the impact of spiked sample storage on DNA recovery should be provided.
2. Please clarify which of the assay validation activities used more than one analyst.
3. Please clarify how false positive Cps are assessed.
4. Please explain how cycle threshold was determined for the Leptospira PCR assay.
5. Please commit to evaluate the matrix interference and sensitivity of the Leptospira assay if used to test samples of obinutuzumab (b) (4) where the (b) (4)

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/s/  
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KALAVATI C SUVARNA  
08/28/2013

PATRICIA F HUGHES TROOST  
08/29/2013