

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125486Orig1s000

CHEMISTRY REVIEW(S)

SUMMARY BLA125486 obinutuzumab (Gazyva)



DEPARTMENT OF HEALTH & HUMAN SERVICES

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

The Quality Team Leader's Executive Summary

From: Marjorie A. Shapiro, Ph.D. (Lead)
Laurie Graham, M.S. (QbD)
Division of Monoclonal Antibodies (DMA)

Through: Kathleen A. Clouse, Ph.D., Director
Sarah Kennett, Ph.D., Review Chief
DMA/OBP/OPS/CDER

BLA Number: 125486
Product: Obinutuzumab (Gazyva™)
Sponsor: Genentech, Inc., a member of the Roche Group

Date of Review: September 27, 2013
Date of CDTL Memo: October 22, 2013

SUMMARY BLA125486 obinutuzumab (Gazyva)

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER, recommends approval of STN 125486 for obinutuzumab (Gazyva™) manufactured by Genentech. The data submitted in this application are adequate to support the conclusion that the manufacture of obinutuzumab (Gazyva™) is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use (under conditions specified in the package insert).

II. APPROVAL LETTER INFORMATION

Under this license, you are approved to manufacture the obinutuzumab drug substance at Roche Diagnostics GmbH in Penzberg, Germany. Obinutuzumab (Gazyva™) drug product will be manufactured at Roche Diagnostics GmbH in Mannheim, Germany.

The dating period for obinutuzumab drug product shall be 36 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as (b) (4)

The dating period for obinutuzumab drug substance shall be (b) (4) from the date of manufacture when stored at (b) (4)

Upon review of the supporting data, the design space as proposed in STN 125486 was found to be acceptable. The Agency would like to reiterate that in addition to the information described in the application, it is our expectation that plans for implementation of the design space for the commercial process are documented within the firm's Quality System. Such quality systems may include plans for handling movements within the design space (e.g., change control procedures, plans for updating batch records). Additionally, in accordance with ICH Q8(R2) the Agency does not expect any regulatory notification for movements within the design space; however movements outside of the design space should be reported to the Agency in concurrence with existing regulations

III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

PMC #1

A formal verification for hold times of (b) (4) from manufacturing scale samples for up to (b) (4) will be completed in December 2013. The final study report will be submitted to the Agency by February 28, 2014.

IV. LIST OF DEFICIENCIES TO BE COMMUNICATED

None

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V. EXECUTIVE SUMMARY

A. Description of Obinutuzumab (Gazyva™) drug substance and drug product

Obinutuzumab is a full length recombinant, humanized, immunoglobulin IgG1, κ monoclonal antibody (GA101, huMAb <CD20>, RO5072759) that is directed to CD20, a membrane protein expressed on B lymphocytes. Obinutuzumab is comprised of (b) (4)

The total molecular weight of obinutuzumab is approximately (b) (4)

Obinutuzumab drug product is supplied as a sterile, preservative-free liquid solution at 25 mg/ml in 50 mL single-dose vials. Obinutuzumab drug product is formulated in 20 mM L-histidine (L-histidine and L-histidine hydrochloride (b) (4), 240 mM trehalose (b) (4), and 0.02% (w/v) poloxamer 188, pH 6.0. The inclusion of 20 mM L-histidine (b) (4), while 240 mM trehalose (b) (4)

The (b) (4) poloxamer 188 at 0.02% (w/v) (b) (4)

As supplied, the solution of obinutuzumab drug product has a clear (b) (4) colorless to slightly brownish appearance (b) (4)

. It is supplied in single-use, 50 mL vials containing 1000 mg (nominal) obinutuzumab for intravenous (IV) infusion. The extractable volume of each vial is a minimum 40 mL.

The intended long term storage temperature for obinutuzumab drug product is 2-8°C.

The primary packaging components for obinutuzumab drug product consist of a USP/Ph. Eur./JP Type 1, 50 ml colorless (b) (4) glass vial that is sealed with a 20 mm (b) (4) rubber stopper (b) (4) and crimped with a 20 mm aluminum seal, then fitted with a slip off plastic cap.

Obinutuzumab is diluted into 250 mL 0.9% saline PVC or non-PVC polyolefin infusion bags immediately prior to administration. The diluted infusion solution can be stored at 2-8°C for up to 24 hours.

The obinutuzumab drug product vial does not contain any overages.

A claim for a categorical exclusion from the Environmental Assessment (EA) requirement has been submitted under 21CFR section 25.31(c), which states that any application for marketing approval of a biologic product for substances that occur naturally in the environment, or supplement to such an application, is categorically excluded and ordinarily does not require an EA or an Environmental Impact Statement when there is not a significant alteration of the concentration or distribution of the substance, its metabolites or degradation product in the environment. The Sponsor states that no extraordinary circumstances exist with respect to this product. There is no

SUMMARY BLA125486 obinutuzumab (Gazyva)

indication that additional environmental information is warranted. The claim of categorical exclusion is deemed acceptable.

B. Clinical Trial Information

Obinutuzumab is intended to be used in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).

The route of administration of obinutuzumab is IV infusion. The recommended dosing is 1000 mg for up to 6 cycles. For cycle 1, the first infusion is carried out over two days with 100 mg administered on day 1 (25 mg/hour over 4 hours) and the remaining 900 mg administered on day 2 (50 mg/hour with escalation in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour). For days 8 and 15 of cycle 1 and cycles 2 – 6, 1000 mg are administered starting at 100 mg/hour, increasing by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

The pivotal clinical study (BO21004/CLL11) was a randomized, open-label, multi-center, international Phase III trial of obinutuzumab in combination with chlorambucil (GClb) versus rituximab in combination with chlorambucil (RClb) versus chlorambucil alone (Clb) in previously untreated CLL patients.

In Stage 1, patients were randomized in a 2:2:1 ratio to GClb, RClb, or Clb alone. In Stage 2, randomization continued in a 1:1 ratio in the RClb and GClb arms only.

In all three study arms, treatment was given for a maximum of 6 cycles, each cycle having a duration of 28 days.

The primary efficacy endpoint of progression free survival (PFS) was a median of 23 months in the GClb arm, ~15 months in the RClb arm and ~11 months in the Clb arm

Clinical trials are ongoing in NHL and B-cell malignancies. At this time, obinutuzumab is not under development for non-oncology indications.

This BLA was designated a Breakthrough Therapy and granted priority review status.

C. Stability

The BLA submission contained adequate stability data to support establishment of a drug substance and drug product shelf-life. Stability studies have been conducted in accordance with ICH Q1A(R2) and Q5C. Drug substance and drug product stability protocols, including specifications, conditions and testing intervals, were provided and found acceptable.

Note that drug substance lots manufactured for clinical studies were initially stored at (b) (4) (b) (4)

SUMMARY BLA125486 obinutuzumab (Gazyva)

(b) (4)
the storage temperature was changed to (b) (4)

- The data support a shelf life of (b) (4) from the date of manufacture for the obinutuzumab drug substance when stored at (b) (4). Although data are provided only through (b) (4) for the three registration batches at (b) (4) there are data for two additional representative drug substance batches demonstrating stability out to (b) (4) when stored at (b) (4).
- Stability tests for drug substance lots stored at either (b) (4) include content of protein, appearance, color, pH, Potency by Bioassay, IE-HPLC (b) (4), SE-HPLC (b) (4), and reducing CE-SDS (b) (4). All tests at both storage conditions are performed at 0, 3, 6, 9, 12, 18, 24, 36, and 48 months.
- The most sensitive stability-indicating assays for drug substance were shown to be IE-HPLC and SE-HPLC.
- The post-approval drug substance annual stability protocol will store samples at only (b) (4) and include tests for color, clarity and opalescence, content of protein, Potency by Bioassay and SE-HPLC (b) (4). Testing will be performed at 0, 12, 14, 36 and 48 months. Methods or quality attributes that will not be included in the post-approval stability protocol may be considered for stability in comparability exercises or may be included in the drug product post-approval stability protocol (b) (4).
- The data support a shelf life of 36 months from the date of manufacture for obinutuzumab (Gazyva™) drug product when stored at 2-8°C. The date of manufacture shall be defined as (b) (4) (b) (4).
- Stability tests for drug product lots stored at 2-8°C include color, clarity and opalescence, pH, osmolality, content of protein, SE-HPLC (b) (4), IE-HPLC (b) (4), non-reducing CE-SDS (b) (4), Potency by Bioassay, visible particles, subvisible particles and container closure integrity (CCI). All tests are performed at 0, 3, 6, 9, 12, 18, 24, and 36 months, except for CCI which is performed on an annual basis at 12, 24 and 36 months.
- The most sensitive stability-indicating assays for drug product were shown to be IE-HPLC, SE-HPLC and non-reducing CE-SDS.
- The post-approval annual drug product stability protocol will store samples at 2-8°C and include tests for color, clarity and opalescence, SE-HPLC (b) (4), IE-HPLC (b) (4), Potency by Bioassay, visible particles, subvisible particles and CCI. Testing will be performed at 0, 12, 24, and 36 months.
- Stressed studies included temperature excursion, freeze/thaw and photostability.
- Photostability studies indicated that obinutuzumab is light sensitive and should not be exposed to intense light for prolonged periods of time.

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- Freeze/thaw studies performed on obinutuzumab drug substance support up to [REDACTED] (b) (4)
- Drug product does not contain preservatives. Drug product vials are single-dose and should be discarded after use.

D. Complexity

Critical Quality Attributes (Written by LG)

Attributes that can impact the safety and/or efficacy of obinutuzumab (i.e., critical quality attributes or CQAs) are divided into different categories: product-variants, process-related impurities, raw materials, leachables, and obligatory. The approach to determining CQAs is category dependent.

- For product variants and process-related impurities, the sponsor used a risk based, risk ranking and filtering (RRF) tool to evaluate the impact and the uncertainty associated with each quality attribute's potential to affect product safety and/or efficacy. The evaluation was based on previous knowledge, scientific literature, experience with other related products and obinutuzumab-specific data, including clinical experience. The impact is the magnitude of the attribute's effect on bioactivity, PK, safety, and immunogenicity, while uncertainty is the degree of confidence that the impact has been correctly assessed. The impact and uncertainty scores were multiplied to calculate a final risk score for each attribute. Attributes with a risk score above a specified value (i.e., 13) were classified as critical quality attributes. The BLA contained sufficient information to explain and justify the RRF and scoring system used.
- For raw materials, estimated daily intake for raw materials, without clearance by the purification process (EDI_0) were calculated. These values were compared with acceptable daily exposure (ADE) levels. When the EDI_0 exceeds the ADE, the raw material is considered a CQA. For these raw materials, clearance by the purification process must be demonstrated. The levels after purification (EDI_{actual}) were calculated to determine the amount of the raw material in the maximum dose of obinutuzumab. This was compared to the ADE levels to confirm that the EDI_{actual} is $<$ ADE.
- Leachables' criticalities were based on exceeding trace levels of [REDACTED] (b) (4). No leachables were identified as CQAs for obinutuzumab.
- Obligatory CQAs (i.e., pH, excipient concentrations, protein concentration, osmolality, bioburden, endotoxin, leptospira, mycoplasma, potential viruses, appearance, particulates, sterility, and extractable volume) are based upon regulatory requirements.
- The proposed summary list of CQAs identified by the sponsor is shown in the table below, which was copied directly from the submission.

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Table 32 Summary of Obinutuzumab Critical Quality Attributes

Product Variants	Process-Related Impurities	Obligatory CQAs
(b) (4)	(b) (4)	<u>Adventitious Agents</u> Viral purity Microbiological purity (bioburden, mycoplasma, leptospira) Endotoxins <u>Drug Substance and Drug Product Composition and Strength</u> Protein content Osmolality pH Appearance (color, opalescence, clarity) L-Histidine content Trehalose content Poloxamer 188 content <u>Drug Product Specific</u> Subvisible particles Visible particles Extractable volume Sterility
		(b) (4)

- The specific raw materials that were identified as CQAs for obinutuzumab are (b) (4)

These were all assessed in removal studies and the final levels were found to be acceptable.

While it was determined that the overall system used for identifying CQAs was acceptable, there were concerns that the RRF tool used for the assessment of product variants and process-related impurities may have underestimated the impact of attributes on safety, immunogenicity, and PK. When evaluating the immunogenicity and safety impact of a number of quality attributes, the sponsor appeared to rely heavily on data from clinical studies in which the attributes were present in very small amounts. These clinical studies, therefore, were not designed to be able to detect safety or immunogenicity signals for product variants. It was not clear if the sponsor considered all of the available information with regard to the risk of a variant to impact safety and immunogenicity. In addition, there were concerns about the suitability of the *in vitro* FcRn assays used to assess the impact of product variants on PK.

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While there may have been an underestimation of the risk related to safety, immunogenicity and PK for some quality attributes, these attributes were classified as CQAs for other reasons. Therefore, it was not thought that any of the identified non-CQAs should have been CQAs. In addition, all CQAs are appropriately included in the control strategy and the sponsor cannot change the control strategy without Agency approval. Future changes to the control strategy should include consideration for whether the impact of variants on safety, immunogenicity, and PK were underestimated.

F. Mechanism of Action

- Obinutuzumab is a Type II anti-CD20 monoclonal antibody, distinct from Type I antibodies, such as rituximab. Obinutuzumab differs from rituximab in its CD20 epitope and relative to rituximab, has enhanced antibody dependent cytotoxicity (ADCC) activity, enhanced induction of direct cell death and reduced complement dependent cytotoxicity (CDC) activity.

(b) (4)



G. Manufacturing Process

(b) (4)



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(b) (4)

Quality by Design (QbD) Elements (Written by LG)

The sponsor used QbD principles to establish an overall control strategy for the process. It was determined that sufficient information was provided to recommend approval of a design space and post-approval lifecycle management (PALM) plan.

The QbD elements in the submission included the following:

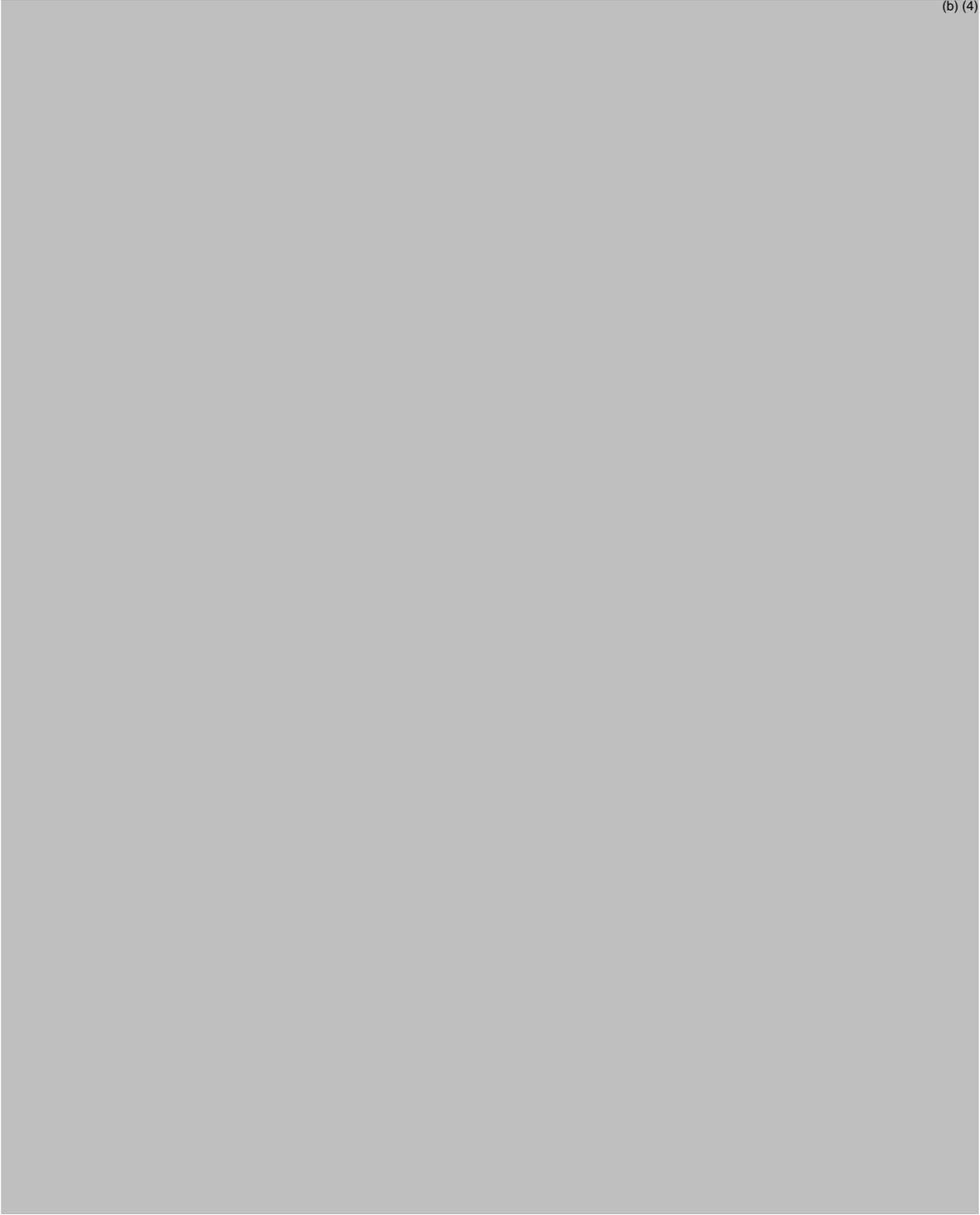
(b) (4)

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5. Development of a post-approval lifecycle management (PALM) plan, which presents the sponsor's intended overall control strategy, including how process and product monitoring will be performed post approval and how changes to the design space will be managed and reported to the Agency

A more detailed summary description of the QbD elements is provided below.

(b) (4)



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The PALM plan specifies how the sponsor will monitor the process and product quality post-approval, manage changes within the design space, and update the control system based on additional process and product knowledge.

The PALM plan includes such things as

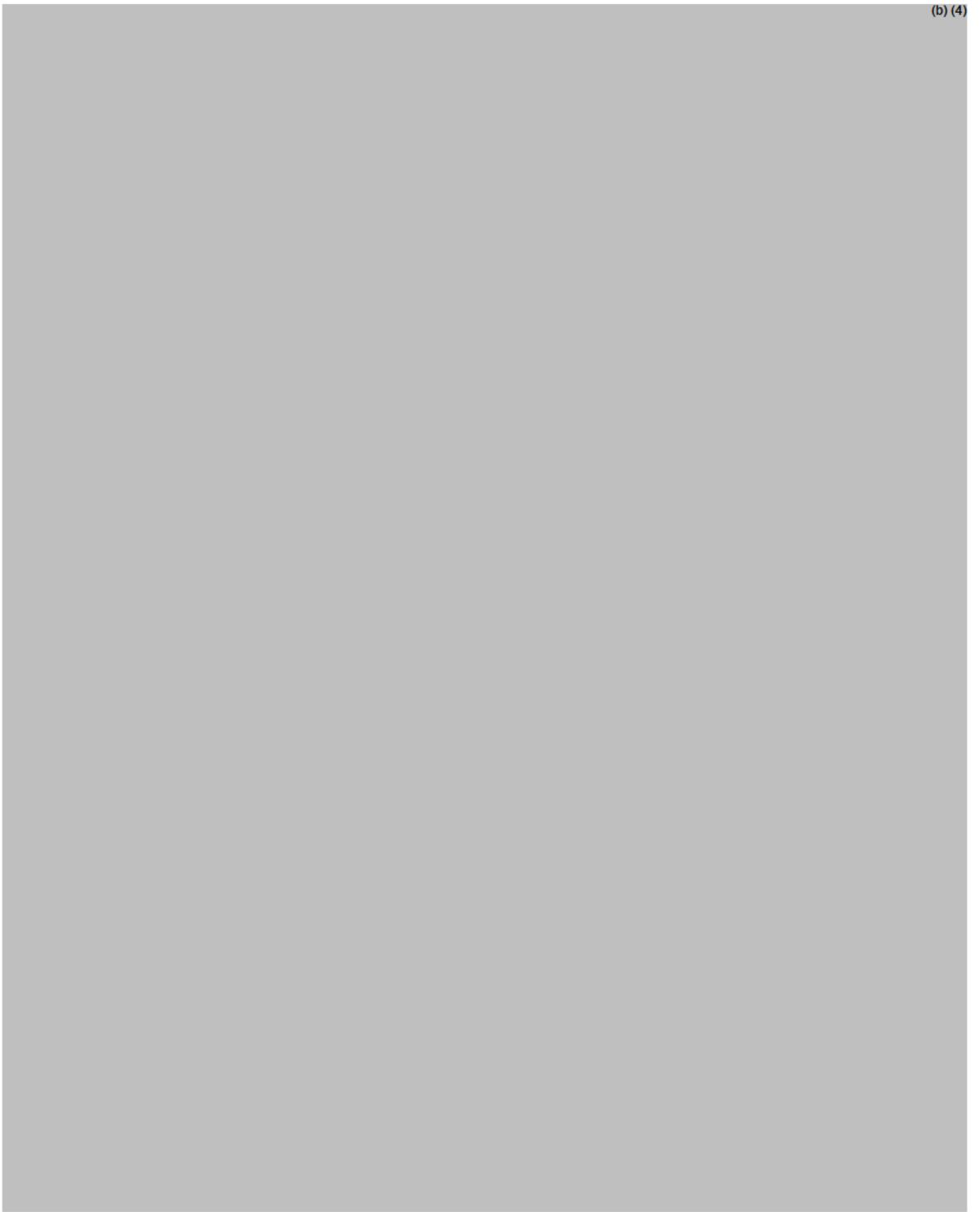
- The final testing strategies for DS and DP
- A list of the relevant sections of the BLA (e.g., sections that define the design space and in-process control testing)
- A description of the key process indicators (KPIs)
- A description of how CPPs, non-CPPS, KPIs, in-process controls, and CQAs are routinely monitored and the potential outcomes of that monitoring
- A table defining the preliminary trend limits for attributes
- A description of how changes to process parameters will be managed
- A description of how the design space will be verified when changes are made within the design space.
- A description of how changes outside of the design space will be managed.

Of particular note, changes to the design space or control strategy will require Agency approval. Specifically:

(b) (4)



After multiple changes during the review cycle, the final PALM plan as described above was found to be acceptable.



I. Immunogenicity

The current screening immunogenicity assay is a ^{(b) (4)}bridging ELISA where _{(b) (4)}



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(b) (4)

[Redacted]

[Redacted]

This assay has sufficient sensitivity (18.4 ng/mL) and it has acceptable drug tolerance (500 ng/mL HAHA can be determined to be positive in a sample containing up to 47.8 µg/mL drug).

The immunogenicity assay is adequately validated. No inconclusive HAHA results were obtained in assessment of clinical samples with both the first and second generation HAHA assay.

[Redacted] (b) (4) neutralizing potential is evaluated using a complex approach based on correlation of several parameters.

The review of module 3.2 is attached as a separate document and includes review of the human anti-drug antibody immunogenicity assay (DMA only).

VI. SIGNATURE BLOCK (BLA ONLY)

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

SUMMARY BLA125486 obinutuzumab (Gazyva)

Laurie Graham, M.S. Team Leader, Division of Monoclonal Antibodies	
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/s/

MARJORIE A SHAPIRO
10/01/2013

LAURIE J GRAHAM
10/01/2013

SARAH B KENNETT
10/01/2013

KATHLEEN A CLOUSE STREBEL
10/01/2013

BLA STN 125486/0

GAZYVA (Obinutuzumab)

Genentech, Inc.

**Mate Tolnay (Traditional Elements Reviewer)
Chikako Torigoe (Quality by Design Reviewer)**

Division of Monoclonal Antibodies; HFD-123

Teleconference #5	September 23, 2013
Information Request #7	September 26, 2013

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

Submission	Date Received	Review Completed (Yes/No)
STN 125486/0 (Original Submission)	April 22, 2013	
STN 125486/0.9 (response to IR #1)	July 18, 2013	Yes
STN 125486/0.12 (response to IR #2)	July 25, 2013	Yes
STN 125486/0.14 (response to IR #2)	July 31, 2013	Yes
STN 125486/0.20 (response to IR #3)	August 19, 2013	Yes
STN 125486/0.25 (response to IR #4)	September 3, 2013	Yes
STN 125486/0.29 (reference to tcon #3)	September 13, 2013	Yes
STN 125486/0.30 (response to IR #5)	September 17, 2013	Yes
STN 125486/0.31 (response to IR #5)	September 18, 2013	Yes
STN 125486/0.33 (response to IR #6)	September 23, 2013	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**

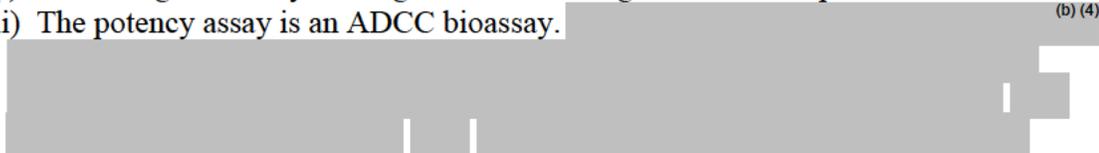
- a. Proprietary Name: GAZYVA
- b. Trade Name: Gazyva
- c. Non-Proprietary/USAN: Obinutuzumab
- d. CAS Registry Number: 949142-50-1
- e. Common name: Monoclonal anti-CD20
- f. INN Name: Obinutuzumab
- g. Compendial Name:
- h. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P11836 (CD20_HUMAN) [RO5072759]
- i. Other Names: RO5072759; huMAb < CD20 >; GA101

8. **PHARMACOLOGICAL CATEGORY:** Therapeutic recombinant monoclonal antibody to the human CD20

9. **DOSAGE FORM:** Concentrate for solution

10. **STRENGTH/POTENCY:**

- (i) The strength of Gazyva Drug Product is 25 mg/mL in 40 mL presentation.
- (ii) The potency assay is an ADCC bioassay.



11. **ROUTE OF ADMINISTRATION:** Intravenous

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)

(b) (4)	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA.
	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA.
	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA.

13. **INSPECTIONAL ACTIVITIES:** The pre-license inspection of the drug substance manufacturing site at Roche Diagnostics GmbH, Penzberg, Germany was conducted on August 7-14, 2013 by Donald C. Obenhuber, BMAB and Kurt Brorson, Mate Tolnay and Chikako Torigoe, DMA. The inspection covered the manufacturing of drug substance at the (b) (4). The inspection was system-based and covered Quality, Production, Laboratory Control, and Facilities and Equipment Systems. In addition, the inspection included extensive coverage of the QbD aspects of the manufacturing process. No Form FDA483 was issued. It was recommended that the inspection be classified as no action indicated. The pre-license inspection of the drug product manufacturing site was waived.

14. **CONSULTS REQUESTED BY OBP:** Biostatistics consult, provided by Xiaoyu Dong. The consult identified multiple issues regarding the assessment of the equivalence of the scale-down models to the manufacturing scale process.

15. **QUALITY BY DESIGN ELEMENTS**

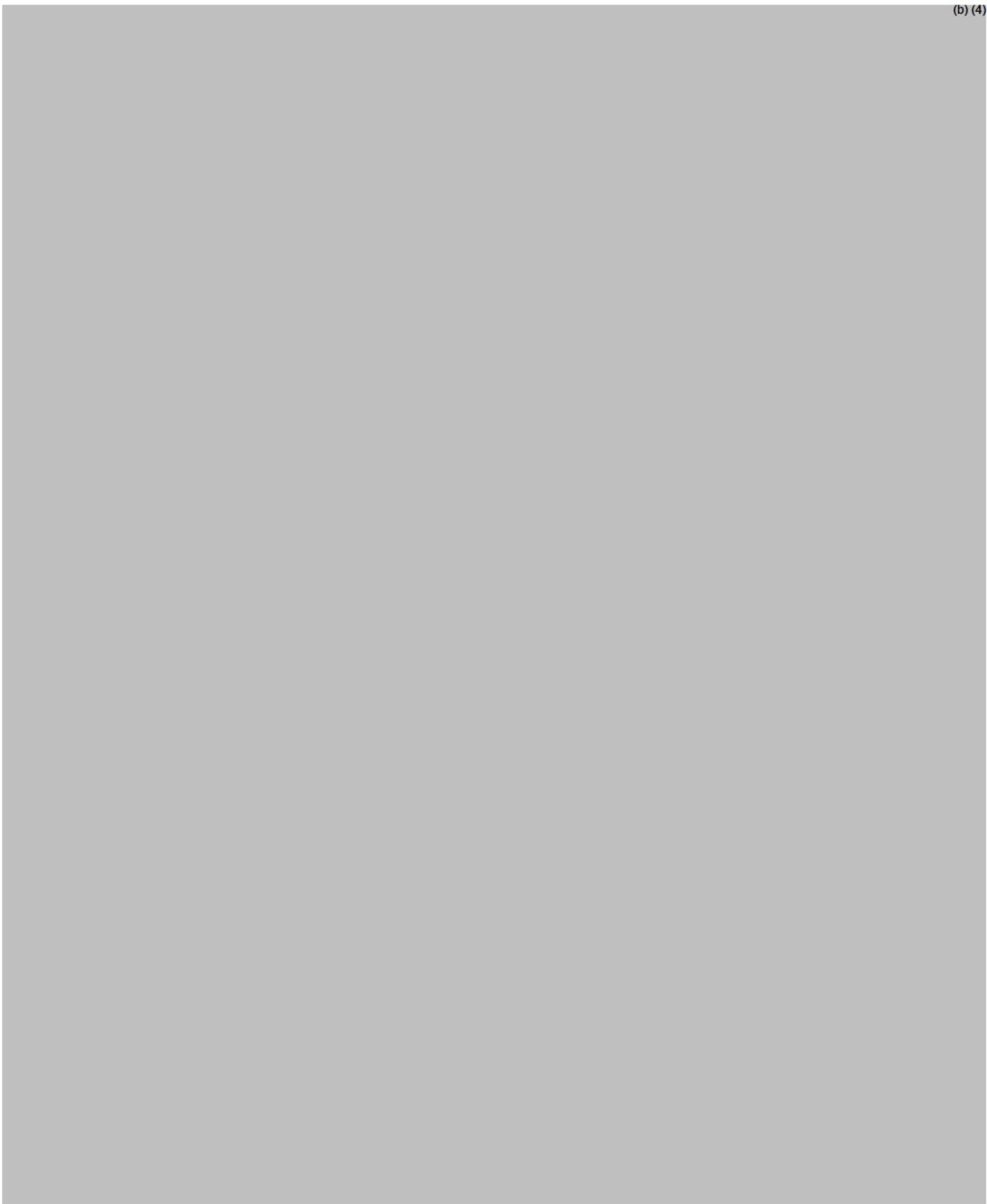
The following was submitted in the identification of QbD elements (check all that apply):

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

Summary of QbD Elements

- 1) Critical quality attributes (CQAs) of obinutuzumab include product and process related impurities; obligatory CQAs; and raw materials.

(b) (4)



- 5) A post-approval lifecycle management (PALM) plan is proposed as an agreement between the sponsor and the Agency with regard to the assurance of the product quality throughout the product lifecycle. The PALM plan describes how the sponsor will

monitor the process and product, manage changes within the design space, and update the control system.

16. PRECEDENTS

1. This will be the first OBP BLA with an approved design space.

2.  (b) (4). If the final action to approve the BLA occurs significantly earlier than the PDUFA deadline of December 22, 2013,  (b) (4)



 (b) (4)

A major difference is in the long term storage condition for drug substance, which was changed from  (b) (4). While  (b) (4) is considered a worst case storage condition, stability data for two batches support stability out to  (b) (4) when stored at  (b) (4). In addition, lot G015.03E was placed on stability and data through  (b) (4) support its stability.

Data at the recommended storage temperature of 2-8°C support stability of drug product up to 36 months when manufactured from drug substance batches stored at -  (b) (4). Data for drug product lot H0013 support its stability to date through 6 months at 2-8°C.

 (b) (4)

 (b) (4)

 (b) (4)

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Marjorie A. Shapiro, PhD., Chief Laboratory of Molecular and Developmental Immunology Laurie Graham, MS, Team Leader RSPB4 Division of Monoclonal Antibodies	
Mate Tolnay, Ph.D., LMDI Chikako Torigoe, Ph.D., RSPB4 Division of Monoclonal Antibodies	

B. CC Block

Recipient	Date
Beatrice Kallungal, RPM, Division of Hematology Products, OHOP	
Division of Monoclonal Antibodies File/BLA STN 125486/0	

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/s/

MATE TOLNAY
09/27/2013

CHIKAKO TORIGOE
09/27/2013

LAURIE J GRAHAM
09/27/2013

MARJORIE A SHAPIRO
09/27/2013

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

BLA/NDA Number: 125486 Applicant: Genentech Stamp Date: 22-Apr-2013

Established/Proper Name: BLA/NDA Type: Priority BLA
Gazyva

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	Y	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling:	Y N	
<input type="checkbox"/> PI –non-annotated	Y N	
<input type="checkbox"/> PI –annotated	Y N	
<input type="checkbox"/> PI (electronic)	Y N	
<input type="checkbox"/> Medication Guide	Y N	
<input type="checkbox"/> Patient Insert	Y N	
<input type="checkbox"/> package and container	Y N	
<input type="checkbox"/> diluent	Y N	
<input type="checkbox"/> other components	Y N	
<input type="checkbox"/> established name (e.g. USAN)	Y N	
<input type="checkbox"/> proprietary name (for review)	Y N	

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

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

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

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
<input type="checkbox"/> Drug Substance	Y N	
<input type="checkbox"/> Drug Product	Y	
<input type="checkbox"/> Facilities and Equipment	Y	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y N	TBD by OBP.
<input type="checkbox"/> Novel Excipients	Y N	TBD by OBP.
<input type="checkbox"/> Executed Batch Records	Y N	TBD by OBP.
<input type="checkbox"/> Method Validation Package	Y	Micro-reviewed tests mentioned briefly; validation in Module 3.
<input type="checkbox"/> Comparability Protocols	Y N	Not applicable.

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	Y	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	
<input type="checkbox"/> description of manufacturing process and process control	Y	
<input type="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> cell culture and harvest		
<input type="checkbox"/> purification		
<input type="checkbox"/> filling, storage and shipping		
<input type="checkbox"/> control of materials	Y	
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		

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

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> ○ cell banking system, characterization, and testing <input type="checkbox"/> control of critical steps and intermediates <ul style="list-style-type: none"> ○ justification of specifications ○ stability <input type="checkbox"/> process validation (prospective plan, results, analysis, and conclusions) <input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> ○ specifications <ul style="list-style-type: none"> ○ justification of specs. ○ analytical procedures ○ analytical method validation ○ batch analyses <input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> ○ protocol ○ results ○ method validation 	<p>Y</p>	<p>Additional data will be requested.</p> <p>Additional data will be requested.</p>
<p>Drug Product [3.2.P] [Dosage Form]</p> <ul style="list-style-type: none"> <input type="checkbox"/> description and composition <input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> ○ preservative effectiveness ○ container-closure integrity <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) <input type="checkbox"/> batch formula <input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at 	<p>Y</p> <p>Y</p> <p>Y</p> <p>Y</p> <p>Y</p> <p>Y</p> <p>Y</p> <p>Y</p>	<p>N</p> <p>Not applicable (no preservative). Provided in 3.2.P.8.3</p> <p>Only the packaging and labeling steps are not described (will request).</p>

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

CTD Module 3 Contents	Present?	If not, justification, action & status
outside [e.g., contract] facilities)	Y	
<input type="checkbox"/> controls of critical steps and intermediates		
<input type="checkbox"/> process validation including aseptic processing & sterility assurance:	Y	
<input type="checkbox"/> Filter validation		
<input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation	Y	
<input type="checkbox"/> Validation of aseptic processing (media simulations)	Y	N
<input type="checkbox"/> Environmental Monitoring Program	Y	Provided in facilities and equipment appendix.
<input type="checkbox"/> Lyophilizer validation	Y	N
<input type="checkbox"/> Other needed validation data (hold times)		Not applicable (liquid product). Additional hold time validation data (for microbial control) may be needed. TBD by OBP.
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	
<input type="checkbox"/> control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	N
<input type="checkbox"/> reference standards or materials		TBD by OBP.
<input type="checkbox"/> container closure system [3.2.P.7]		Product quality microbiology review for this BLA will not require review of container closure component DMFs.
<input type="checkbox"/> specifications (vial, elastomer, drawings)	Y	
<input type="checkbox"/> availability of DMF & LOAs		
<input type="checkbox"/> administration device(s)		
<input type="checkbox"/> stability		
<input type="checkbox"/> summary		
<input type="checkbox"/> post-approval protocol and commitment		
<input type="checkbox"/> pre-approval		
<input type="checkbox"/> protocol		
<input type="checkbox"/> results		
<input type="checkbox"/> method validation		
Diluent (vials or filled syringes) [3.2P']		
<input type="checkbox"/> description and composition of diluent	Y	N
<input type="checkbox"/> pharmaceutical development	Y	N
<input type="checkbox"/> preservative	Y	N

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

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

**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 N	
Includes data demonstrating consistency of manufacture	Y N	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	TBD by OBP.
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	TBD by OBP.
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	TBD by OBP
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	TBD by OBP
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	N Y N Y N	Rabbit pyrogen test data not provided (will request). TBD by OBP. Not applicable – sterility test performed.
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	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same	Y	General information provided, but other products made in the same area of the DP site are not identified (will request).

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

Examples of Filing Issues	Yes?	If not, justification, action & status
manufacturing areas and equipment		

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.

Rabbit pyrogen test data as required in 21CFR610.13(b) was not provided for obinutuzumab drug product. The rabbit pyrogen test should be performed at least once to demonstrate that the drug product does not contain pyrogenic substances other than bacterial endotoxin.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONALD C OBENHUBER
06/20/2013

PATRICIA F HUGHES TROOST
06/20/2013

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

BLA/NDA Number: STN 1254860 **Applicant:** Genentech, Inc. **Stamp Date:** April 22, 2013
Established/Proper Name: Obinutuzumab **BLA/NDA Type:** Priority

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	(Y) N	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	(Y) N	
Comprehensive Table of Contents	Y (N)	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	(Y) N	
Labeling:	(Y) N	
<input type="checkbox"/> PI –non-annotated	(Y) N	
<input type="checkbox"/> PI –annotated	(Y) N	
<input type="checkbox"/> PI (electronic)	(Y) N	
<input type="checkbox"/> Medication Guide	Y (N)	Not applicable.
<input type="checkbox"/> Patient Insert	Y (N)	Not applicable.
<input type="checkbox"/> package and container	(Y) N	
<input type="checkbox"/> diluent	Y (N)	Not applicable.
<input type="checkbox"/> other components	Y (N)	Not applicable.
<input type="checkbox"/> established name (e.g. USAN)	(Y) N	
<input type="checkbox"/> proprietary name (for review)	(Y) N	

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

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

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

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y <input checked="" type="radio"/> N	
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="radio"/> nomenclature		
<input type="radio"/> structure (e.g. sequence, glycosylation sites)		
<input type="radio"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> description of manufacturing process and process control	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="radio"/> batch numbering and pooling scheme		
<input type="radio"/> cell culture and harvest		
<input type="radio"/> purification		
<input type="radio"/> filling, storage and shipping		
<input type="checkbox"/> control of materials	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="radio"/> raw materials and reagents		
<input type="radio"/> biological source and starting materials		
<input type="radio"/> cell substrate: source, history, and generation		
<input type="radio"/> cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and intermediates	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="radio"/> justification of specifications		
<input type="radio"/> stability		

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

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

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

CTD Module 3 Contents	Present?	If not, justification, action & status
finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	
<input type="checkbox"/> controls of critical steps and intermediates	Y N	
<input type="checkbox"/> process validation including aseptic processing & sterility assurance: <ul style="list-style-type: none"> <input type="checkbox"/> Filter validation <input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation <input type="checkbox"/> Validation of aseptic processing (media simulations) <input type="checkbox"/> Environmental Monitoring Program <input type="checkbox"/> Lyophilizer sterilization validation <input type="checkbox"/> Other needed validation data (hold times) 	Y N	
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
<input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
<input type="checkbox"/> reference standards	Y N	
<input type="checkbox"/> container closure system <ul style="list-style-type: none"> <input type="checkbox"/> specifications (vial, elastomer, drawings) <input type="checkbox"/> availability of DMF & LOAs 	Y N	
<input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results 		
Other components to be marketed (full description and supporting data, as listed above):		
<input type="checkbox"/> other devices	Y <input checked="" type="radio"/> N	Not applicable.
<input type="checkbox"/> other marketed chemicals (e.g. part	Y <input checked="" type="radio"/> N	Not applicable.

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

Examples of Filing Issues	Yes?	If not, justification, action & status
trial to commercial production lots		
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 <input checked="" type="radio"/> N	Not applicable.
Certification that all facilities are ready for inspection	Y N	BMAP will determine this.
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	<input checked="" type="radio"/> N	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	<input checked="" type="radio"/> N <input checked="" type="radio"/> N <input checked="" type="radio"/> N Y N	Not applicable (USP <71> is used).
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	<input checked="" type="radio"/> N	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	<input checked="" type="radio"/> N	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	<input checked="" type="radio"/> N	

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

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?

Yes **No**

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

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

No issue to be sent at this time.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATE TOLNAY
05/30/2013

MARJORIE A SHAPIRO
06/13/2013