

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125486Orig1s000

OTHER REVIEW(S)

**Therapeutic Biological Establishment Evaluation
Request (TB-EER) Form
Version 1.0**

Instructions:

The review team should email this form to the email account “CDER-TB-EER” to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing¹ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA date: October 22, 2013
BLA: 125486/0
Applicant: Genentech, Inc.
US License: 1048
Product: Obinutuzumab (GA101)
Dosage: Sterile solution for infusion, 1000mg/40mL (25 mg/mL)
Indication: For the treatment of patients with previously untreated chronic lymphocytic leukemia. in combination with chlorambucil is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL)

FACILITY INFORMATION

Manufacturing Location:

Firm Name: Roche Diagnostics GmbH
Address: Nonnenwald 2
D-82377 Penzberg
Germany

FEI: 3002806560

Short summary of manufacturing activities performed: Drug Substance manufacturing and release

¹ The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

This site was inspected by CDER-OMPQ from 8/7/2013 – 8/14/2013 and initially classified NAI. This was a PLI covering biotech drug substance manufacturing operations. The CBI profile was updated and has an initial acceptable classification. Although the inspection classification has not been finalized, DIDQ performed an expedited review of the EIR, and on the basis of that review, does not oppose the approval of this site for this BLA. The overall acceptability of this site is still pending.

Manufacturing Location:

Firm Name: Roche Diagnostics GmbH
Address: Sandhofer Straße 116
D-68305 Mannheim
Germany
FEI: 3002806559

Short summary of manufacturing activities performed: DS release bioassay; Drug product manufacturing and testing.

This site was inspected by ORAHQ from 4/18/2012 – 4/26/2012 and classified VAI. This was a routine GMP surveillance inspection covering biotech drug product manufacturing and drug substance testing operations. The SVS and TRP profiles were updated and are acceptable.

Manufacturing Location:

Firm Name:  (b) (4)
Address: 
FEI:

Short summary of manufacturing activities performed: Testing for adventitious viruses of the preharvest cell culture fluid

This site was inspected by IOG from  (b) (4) and classified VAI. This was a routine GMP surveillance inspection covering biotech drug substance testing operations. The CTX profile was updated and is acceptable.

Manufacturing Location:

Firm Name: F. Hoffmann-La Roche Ltd.
Address: Wurmisweg
CH-4303 Kaiseraugst Switzerland
FEI: 3003973536

Short summary of manufacturing activities performed: Drug product labeling and secondary packaging.

This site was inspected by CDER-OMPQ from 3/1/2012 – 3/9/2012 and classified NAI. This was a routine GMP surveillance inspection covering biotech drug product manufacturing

operations. The SVS profile was updated and is acceptable.

OVERALL RECOMMENDATIONS:

There are no pending or ongoing compliance actions that prevent approval of this application.

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/s/

CHRISTINA A CAPACCI-DANIEL
10/17/2013

- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The execution of this protocol is appropriate as a PMC because the production process is monitored at each critical step for bioburden and endotoxin to ensure that the product is not affected by microbial contamination. The execution of this protocol will provide additional assurances for microbial control.

2. Describe the particular review issue and the goal of the study.

The (b) (4) protocol should be executed (b) (4) in the production process to verify continued microbial control (b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process analysis
- Other

Describe the agreed-upon study:

The sponsor will execute the (b) (4) protocol on (b) (4) (b) (4) the commercial obinutuzumab manufacturing process and verify that pre-established bioburden and endotoxin limits are met. The results are intended to demonstrate the effectiveness of the (b) (4) procedures and the continued microbial control (b) (4)

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

R Kane _____
(signature line for BLAs only)

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/s/

ZHIHAO PETER QIU
10/31/2013

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # BLA 125486/0
Product Name: Gazyva, Obinutuzumab (GA101, RO5072759)

PMC #1 Description: Perform a formal verification study of the (b) (4) hold time for (b) (4). Submit the final study report to the Agency as a CBE-30 by February 28, 2014.

PMC Schedule Milestones:	Final Protocol Submission:	Not Applicable (study ongoing)
	Study/Trial Completion:	12/2013
	Final Report Submission:	2/28/2014

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Data were provided in the BLA to support a hold time for the (b) (4) for up to (b) (4). The most recent manufacturing campaign included hold times of up to (b) (4) and preliminary data were provided to support this. Genentech stated that the study would be completed in December 2013 and committed to providing the final study report to the Agency.

2. Describe the particular review issue and the goal of the study.

Data are required to support a hold time of up to (b) (4) for the (b) (4).

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
 Assay
 Sterility
 Potency
 Product delivery
 Drug substance characterization
 Intermediates characterization
 Impurity characterization
 Reformulation
 Manufacturing process issues
 Other

Describe the agreed-upon study:

The sponsor will provide the final study report after the current study is completed in December 2013.

5. To be completed by ONDQA/OBP Manager:
- Does the study meet criteria for PMCs?
 Are the objectives clear from the description of the PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

R Kane
(signature line for BLAs only)

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/s/

MATE TOLNAY
10/29/2013

MARJORIE A SHAPIRO
10/29/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 23, 2013

To: Beatrice Kallungal – Regulatory Project Manager
Division of Hematology Products (DHP)

From: Richard Lyght, Pharm.D. – Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Karen Rulli, Ph.D, Team Leader, OPDP

Subject: OPDP comments on draft Prescribing Information (PI) for GAZYVA (obinutuzumab) injection for intravenous infusion

This consult is in response to DHP’s May 2, 2013 request for OPDP review of the draft Gazyva Prescribing Information. OPDP comments are based on the proposed draft marked-up labeling revised by the review division and received by OPDP on October 16, 2013

OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Richard Lyght at 301-796-2874 or at richard.lyght@fda.hhs.gov.

Section	Statement from draft	Comment
General		Tradename "Gazyva" (b) (4) This is not consistent with other labels (b) (4)
Highlights—Boxed Warning	<ul style="list-style-type: none"> Hepatitis B Virus (HBV) reactivation (b) (4) in some cases resulting in fulminant hepatitis, hepatic failure, and death. 	fulminant hepatitis, hepatic failure, and death, (b) (4) Also consider including in the (b) (4)

		Highlights BW that patients should be screened for HBV before initiating treatment, and that Gazyva should be discontinued in the event of HBV reactivation.
Highlights—Indication	<ul style="list-style-type: none"> GAZYVA (obinutuzumab) is a CD20-directed cytolytic antibody 	To ensure consistency between the Highlights and FPI, consider revising Indication statement in the FPI so that it mentions the fact that Gazyva is a CD20 directed cytolytic antibody
Highlights--Dosing and Administration		Consider including the concepts "monitor blood counts", "administer by healthcare professional" and "premedication for anti-microbial prophylaxis" in the Dosing and Administration section of the Highlights to increase consistency with this section of the FPI
Highlights--Warnings & Precautions		In the Highlights, under "thrombocytopenia," consider adding "monitor platelet counts" to increase consistency with section 5.7 of the FPI
Highlights--Warnings & Precautions		We note that the "Infection" (section 5.5) is omitted from the Highlights. Consider including this Warning and Precaution.
Highlights--Warnings & Precautions	<ul style="list-style-type: none"> Tumor Lysis Syndrome: Anticipate tumor lysis syndrome; premedicate with anti-hyperuricemics and adequate hydration especially for patients with high tumor burden. 	In the Highlights, under "Tumor Lysis Syndrome," consider adding "Patients with high tumor burden and/or high circulating lymphocyte count " to be consistent with section 5.4 of the FPI.

Highlights--Warnings & Precautions		In the Highlights, under "Infusion Reactions," consider adding "Hypotension may occur as part of the GAZYVA infusion reaction. Consider withholding antihypertensive treatments for 12 hours prior to, during each GAZYVA infusion" to be consistent with section (b) (4) of the FPI
Highlights--Warnings & Precautions		In the Warnings and Precautions section of the Highlights, consider adding "Immunization" title to the last Warning and Precaution about vaccinations.
Highlights --Adverse Reactions		Consider adding "cough" in the Adverse Reactions section as it is included in Table 4 of the FPI.
FPI—Adverse Reactions (6.1)		Consider adding "musculoskeletal pains" to Table 4 to be consistent with the most common adverse reactions listed in the Highlights
Dosage and Administration (2.2)	<ul style="list-style-type: none"> (b) (4) 	Consider adding in "Patients with high tumor burden" to be consistent with the language in section 5.4 regarding tumor lysis syndrome
Description (11)	<ul style="list-style-type: none"> GAZYVA (obinutuzumab) is a humanized anti-CD20 monoclonal 	Terms like "humanized" suggests clinical relevance i.e. safer because it is humanized. Consider deleting this descriptor.
Mechanism of Action (12.1)	<ul style="list-style-type: none"> Obinutuzumab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre B- and mature B-lymphocytes 	Terms like "target" can suggest that Gazyva is specific for cancer cells and does not attack normal cells. Consider replacing "target" with "binds to".

<p>Mechanism of Action (12.1)</p>	<ul style="list-style-type: none"> • “Upon binding to CD20, obinutuzumab mediates B-cell lysis through (1) engagement of immune effector cells, (2) by directly activating intracellular death signaling pathways and/or (3) activation of the complement cascade. The immune effector cell mechanisms include antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis. 	<p>Is the exact MOA known? If not, consider reverting back to the original language from the Clinical Review, which includes the following statements :</p> <p>“The mechanism of direct cell death is under investigation but data provided suggests...”,</p> <p>“Possible mechanisms of cell lysis include...”</p> <p>“These postulated mechanisms of action may translate to enhanced B cell depletion and anti-tumor efficacy in nonclinical animal models.”</p>
<p>Clinical Studies (14.1)</p>		<p>Consider including definitions of the clinical endpoints PFS and ORR before presenting the results. For example, the Clinical Review (p.44) contains language such as the following:</p> <p>“PFS was defined as the time from randomization to the first occurrence of progression, relapse or death from any cause as assessed by the investigator.”</p> <p>“Response was assessed by the investigator according to standard NCI/International Workshop on CLL (IWCLL) guidelines which was considered primary for all endpoints. An independent review committee (IRC) composed of at least three CLL experts (two reviewers and one adjudicator) also assessed response and progression based on peripheral blood counts, bone marrow biopsy results, reports of physical examination, and radiology</p>

		reports.”
Clinical Studies (14.1)	<ul style="list-style-type: none"> • (b) (4) 	<p>Th (b) (4)</p> <p>(b) (4) is promotional in nature. Consider deleting (b) (4) and just presenting the data.</p>
Clinical Studies (14.1)	<ul style="list-style-type: none"> • (b) (4) 	<p>Consider including Partial Response (PR) rates when in conjunction to CR and ORR efficacy data. The majority of responses were partial responses and by omitting this information, Gazyva may seem more efficacious than it is.</p>
Patient Counseling Information (17)	<ul style="list-style-type: none"> • Signs and symptoms of infusion reactions including dizziness, nausea, chills, fever, vomiting, diarrhea, breathing problems, or chest pain [see <i>Warnings and Precautions (5.3) and Adverse Reactions</i> (b) (4) . • Symptoms of tumor lysis syndrome such as nausea, vomiting, diarrhea and lethargy [see <i>Warnings and Precautions</i> (b) (4) and <i>Adverse Reactions</i> (b) (4) . • Signs of infections 	<p>Please check the references to the Warnings and Precautions and Adverse Reactions sections of the FPI, as many of them seem incorrect. .</p>

including fever and cough [see *Warnings and Precautions (5.5) and Adverse Reactions*

(b) (4).

Advise patients of the need for:

- Periodic monitoring of blood counts [see *Warnings and Precautions (5.6, and 5.7) and Adverse Reactions* (b) (4)].

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/s/

RICHARD A LYGHT
10/23/2013



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products

FINAL CARTON AND CONTAINER REVIEW

Date: September 26, 2013

Reviewer: Mate Tolnay, Ph.D.
Division of Monoclonal Antibodies

Through: Marjorie Shapiro, Ph.D.
Division of Monoclonal Antibodies

Application: BLA 125486.0

Product: Gazyva (obinutuzumab)

Applicant: Genentech, Inc.

Submission Date(s): April 22, 2013

Executive Summary

The carton and container labels for Gazyva (obinutuzumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 5/1/13-12/31/13, USP 36/NF 31. Labeling deficiencies were identified. Comments are listed in the conclusions section. The carton and container labels submitted on September 20, 2013 are acceptable.

Background and Summary Description

Gazyva (obintuzumab) is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia. The product is supplied as sterile solution containing 1000 mg /40 mL (25 mg/mL) in single-dose vials.

Materials Reviewed:

[Link to submission:](#)

<http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea6812000a4>

Sequence: 0033

Start of Sponsor Material



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]. **Conforms**

(2) The name, address, and license number of manufacturer; **Conforms**

(3) The lot number or other lot identification; **Conforms**

(4) The expiration date; **Conforms**

(5) The recommended individual dose, for multiple dose containers. **Not applicable.** Single-dose vial.

(6) The statement: “Rx only” for prescription biologicals. **Conforms**

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is

too small, the required statement may be placed on the package label. **Not applicable**

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. **Not applicable**

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. **Not applicable**

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. **Not applicable**

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – This conforms to the regulation per CMC visual inspection. **Conforms**

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; **Conforms**

C. 21 CFR 201.5 Drugs; adequate directions for use; **Conforms**

D. 21 CFR 201.6 Drugs; misleading statements; **Conforms**

E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence] **Conforms**

F. 21 CFR 201.15 Drugs; prominence of required label statements; **Conforms**

G. 21 CFR 201.17 Drugs; location of expiration date; **Conforms**

H. 21 CFR 201.25 Bar code; **Conforms**

I. 21 CFR 201.50 Statement of identity; **Conforms**

J. 21 CFR 201.51 Declaration of net quantity of contents; **Conforms.**

K. 21 CFR 201.55 Statement of dosage; **Conforms**

L. 21 CFR 201.100 Prescription drugs for human use; **Conforms**

Start of Sponsor Material

(b) (4)



End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label

a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] **Conforms**

- b) The name, addresses, and license number of manufacturer; **Conforms**
- c) The lot number or other lot identification; **Conforms**
- d) The expiration date; **Conforms**
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative”. **Conforms**
- f) The number of containers, if more than one; **Not applicable**
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; **Conforms**
- h) The recommended storage temperature; **Conforms**
- i) The words “Do not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product; **Conforms**
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; **Not applicable**
- k) The route of administration recommended, or reference to such directions in and enclosed circular; **Conforms**
- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; **Not applicable**. See prescribing information.
- m) The type and calculated amount of antibiotics added during manufacture; **Not applicable**
- n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; **Conforms**
- o) The adjuvant, if present; **Not applicable**
- p) The source of the product when a factor in safe administration; **Conforms**. **Information provided in prescribing information**

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; **Not applicable**

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency”; **Conforms**

s) The statement “Rx only” for prescription biologicals; **Conforms**

B. 21 CFR 610.62 Proper name; package label; legible type [*Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of “specified” biological products listed in 21 CFR 601.2(a)*]

a) Position. The proper name of the product on the package label shall be placed above any trademark or trade name identifying the product and symmetrically arranged with respect to other printing on the label. **Not applicable. Exempt biologic**

b) Prominence. The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name. **Not applicable. Exempt biologic**

c) Legible type. All items required to be on the container label and package label shall be in legible type. “Legible type” is type of a size and character which can be read with ease when held in a good light and with normal vision. **Not applicable. Exempt biologic**

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; **Not applicable**

D. 21 CFR 610.64 Name and address of distributor

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: “Manufactured for _____”, “Distributed by _____”, “Manufactured by _____ for _____”, “Manufactured for _____ by _____”, “Distributor: _____”, or “Marketed by _____”. The qualifying phrases may be abbreviated. **Not applicable**

- E. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter; **Conforms**
- F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35] **Conforms**
- G. 21 CFR 201.5 Drugs; adequate directions for use; **Conforms**
- H. 21 CFR 201.6 Drugs; misleading statements; **Conforms**
- I. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and Prominence]. **Conforms**
- J. 21 CFR 201.15 Drugs; prominence of required label statements; **Conforms**
- K. 21 CFR 201.17 Drugs; location of expiration date; **Conforms**
- L. 21 CFR 201.25 Bar code label requirements; **Conforms**
- M. 21 CFR 201.50 Statement of identity; **Conforms**
- N. 21 CFR 201.51 Declaration of net quantity of contents; **Conforms**
- O. 21 CFR 201.55 Statement of dosage; **Conforms**
- P. 21 CFR 201.100 Prescription drugs for human use; **Conforms**

Conclusions

The labels submitted on September 20, 2013 meet regulatory requirements and are acceptable. However, there are CDER preferences that may be recommended by the Division of Medication Error and Prevention.

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/s/

MATE TOLNAY
09/27/2013

MARJORIE A SHAPIRO
09/27/2013

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: September 4, 2013

TO: Beatrice Kallungal Regulatory Project Manager
Virginia Kwitkowski, M.S., R.N., ANCP-BC, Team Leader
Hyon-Zu Lee, Pharm.D., Clinical Analyst
Barry Miller, M.S., CRNP, Clinical Analyst
Division of Hematology Products (DHP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125486

APPLICANT: Genentech, Inc.

DRUG: obinutuzumab

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Priority

INDICATION: Obinutuzumab in combination with chlorambucil in the treatment of previously untreated patients with chronic lymphocytic leukemia

CONSULTATION REQUEST DATE: May 15, 2013 (signed)
INSPECTION SUMMARY GOAL DATE: November 22, 2013 (original)
DIVISION ACTION GOAL DATE: December 20, 2013 (original)
PDUFA DATE: December 20, 2013 (original)

I. BACKGROUND:

Chronic lymphocytic leukemia (CLL) is an indolent lymphoproliferative disorder with a median age at diagnosis of 72 years. Approximately 95% of CLL is of B-cell origin with a characteristic immunophenotype (CD5+, D23+, weak surface expression of CD19, CD20, CD79b and IgM or IgD) and blood smear morphology (i.e., mature looking lymphocytes or Gumprecht's shadows). Advanced disease stages are characterized by the appearance of lymphadenopathy, hepatomegaly or splenomegaly, and bone marrow failure.

As there is no survival benefit associated with early intervention, asymptomatic patients with early stage CLL (Binet stage A and B) are usually not treated but are followed on a 'watch and wait' principle. Treatment is usually initiated when the patient becomes symptomatic or progresses to late stage CLL (Binet stage C). During its disease evolution, 50% of CLL patients ultimately require therapy. Obinutuzumab and rituximab share the same target (i.e., CD20, a cell surface marker for B-cells). While the exact mechanism of action for obinutuzumab is not completely known, drug treatment leads to extensive CD20+ cell depletion.

A single adequate clinical study was submitted in support of the sponsor's BLA. Inspections of two foreign clinical sites and the sponsor were planned. The inspections of the two clinical sites were cancelled at the request of the CDER review division.

Study Protocol CLL11 (BO21004)

CLL11 (BO21004) was a Phase 3, open-label, multi-center, three-arm randomized, parallel group comparative study. Patients received up to 6 months of study treatment. Patients who crossed-over treatment arms received an additional 6 months of study treatment. The primary objective of Study BO21004 was to demonstrate clinically relevant statistical superiority in progression-free survival (PFS) with obinutuzumab with chlorambucil [GC1b] compared to rituximab in combination with chlorambucil [RC1b] and chlorambucil alone [C1b], and rituximab in combination with chlorambucil [RC1b] compared to chlorambucil [C1b] in previously untreated CLL patients with co morbidities. The primary efficacy endpoint was progression free survival (PFS).

II. RESULTS:

Name of CI City, State	Protocol/Study Site/Number of Subjects Enrolled (n)	Inspection Date	Final Classification*
Genentech, Inc. South San Francisco, CA	Sponsor	July 29-August 2, 2013	Pending Preliminary: NAI

*Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/Critical findings may affect data integrity.

Preliminary= The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed out, the preliminary designation is converted to a final regulatory classification.

SPONSOR

1. Genetech, Inc.

1 DNA Way MS242
South San Francisco, CA

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.810, from July 29 to August 2, 2013.

The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:

The ORA field investigator reviewed, the sponsor monitoring activities for 53 subjects (approximately 9% of all involved subjects in the clinical trial). Serious adverse events (SAEs) were adequately reported to the sponsor via a centralized process to a safety group located in (b) (4)

Many of the clinical sites enrolled only one to two subjects during the entire clinical trial. The following clinical sites were reviewed and found adequate, in regards to sponsor's oversight and monitoring of the clinical trial: (1) Site 164871 (Dr. Olga Samoylova, Russia, 20 subjects); (2) Site 164866 (Dr. Alexey Kuzmin, Russia, 7 subjects); (3) Site 166013 (Dr. Lothar Mueller, Germany, 5 subjects); (4) Site 164841 (Dr. Eulogio Conde, Spain, 5 subjects); (5) Site 164764 (Dr. Marco Montillo, Italy, 4 subjects); (6) Site 194932 (Dr. Heinz Ludwig, Austria, 6 subjects) and (7) Site 166942 (Dr. Philippe Solal-Celigny, France, 6 subjects).

The sponsor maintained adequate oversight of the clinical trial. Monitoring of clinical investigator sites appeared to be adequate. The sponsor took appropriate steps to bring noncompliant sites into compliance. At the conclusion of the inspection, no List of Inspectional Observations (Form FDA 483) was issued.

c. Assessment of data integrity:

The study appears to have been conducted adequately. Data submitted by this sponsor appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The sponsor was inspected in support of this BLA. The sponsor maintained adequate oversight of the clinical trial. No regulatory deficiencies were observed. The preliminary classification was No Action Indicated (NAI). The study data collected and submitted by the sponsor appear generally reliable in support of the requested indication.

Note: The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), and final review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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Janice Pohlman, M.D., M.P.H.
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/s/

ANTHONY J ORENCIA
09/05/2013

JANICE K POHLMAN
09/05/2013

KASSA AYALEW
09/05/2013



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products

FINAL CARTON AND CONTAINER REVIEW

Date: August 20, 2013

Reviewer: Kimberly Rains, Pharm.D.
Office of Biotechnology Products

Through: Mate Tolnay, Ph.D.
Division of Monoclonal Antibodies

Marjorie Shapiro, Ph.D.
Division of Monoclonal Antibodies

Application: BLA 125486

Product: Tradename (obinutuzumab)

Applicant: Genentech, Inc.

Submission Date(s): April 22, 2013

Executive Summary

The carton and container labels for Tradename (obinutuzumab) were reviewed and found not to comply with one or more of the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 5/1/13-12/31/13, USP 36/NF 31. Labeling deficiencies were identified. Comments are listed in the conclusions section. The carton and container labels submitted on April 22, 2013 are unacceptable.

Background and Summary Description

Tradename (obintuzumab) is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia. The product is supplied as sterile solution containing 1000 mg /40 mL (25 mg/mL) in single-dose vials.

Materials Reviewed:

[Link to submission:](#)

<http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea6812000a4>

Sequence: 0000

Start of Sponsor Material



End of Sponsor Material

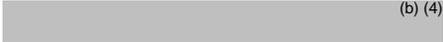
Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]. **Conforms**

(2) The name, address, and license number of manufacturer; **Does not conform.**  (b) (4)

(3) The lot number or other lot identification; **Conforms**

(4) The expiration date; **Conforms**

(5) The recommended individual dose, for multiple dose containers. **Not applicable.** Single-dose vial.

(6) The statement: ““Rx only”” for prescription biologicals. **Conforms**

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide

to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. **Not applicable**

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. **Not applicable**

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. **Not applicable**

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. **Not applicable**

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – This conforms to the regulation per CMC visual inspection. **Does not conform.**

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; **Conforms**

C. 21 CFR 201.5 Drugs; adequate directions for use; **Conforms**

D. 21 CFR 201.6 Drugs; misleading statements; **Conforms**

E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence] **Does not conform**

F. 21 CFR 201.15 Drugs; prominence of required label statements; **Conforms**

G. 21 CFR 201.17 Drugs; location of expiration date; **Conforms**

H. 21 CFR 201.25 Bar code; **Conforms**

I. 21 CFR 201.50 Statement of identity; **Conforms**

J. 21 CFR 201.51 Declaration of net quantity of contents; **Conforms.**
Recommend revising presentation

K. 21 CFR 201.55 Statement of dosage; **Conforms**

L. 21 CFR 201.100 Prescription drugs for human use; **Conforms**

Start of Sponsor Material



End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label

- a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] **Conforms**
- b) The name, addresses, and license number of manufacturer; **Does not conform.** (b) (4)
- c) The lot number or other lot identification; **Conforms**
- d) The expiration date; **Conforms**
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative”. **Conforms**
- f) The number of containers, if more than one; **Not applicable**
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; **Conforms**
- h) The recommended storage temperature; **Conforms**
- i) The words “Do not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product; **Conforms**
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; **Not applicable**
- k) The route of administration recommended, or reference to such directions in and enclosed circular; **Conforms**
- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; **Not applicable.** See prescribing information.
- m) The type and calculated amount of antibiotics added during manufacture; **Not applicable**
- n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; **Conforms**

- o) The adjuvant, if present; **Not applicable**
- p) The source of the product when a factor in safe administration; **Conforms**. Information provided in prescribing information
- q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; **Not applicable**
- r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency”; **Conforms**
- s) The statement “Rx only” for prescription biologicals; **Conforms**

B. 21 CFR 610.62 Proper name; package label; legible type [*Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of “specified” biological products listed in 21 CFR 601.2(a)*]

- a) Position. The proper name of the product on the package label shall be placed above any trademark or trade name identifying the product and symmetrically arranged with respect to other printing on the label. **Not applicable**. Exempt biologic
- b) Prominence. The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name. **Not applicable**. Exempt biologic
- c) Legible type. All items required to be on the container label and package label shall be in legible type. “Legible type” is type of a size and character which can be read with ease when held in a good light and with normal vision. **Not applicable**. Exempt biologic

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; **Not applicable**

D. 21 CFR 610.64 Name and address of distributor

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the

manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: “Manufactured for _____”. “Distributed by _____”, “Manufactured by _____ for _____”, “Manufactured for _____ by _____”, “Distributor: _____”, or “Marketed by _____”. The qualifying phrases may be abbreviated. **Not applicable**

- E. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter; **Conforms**
- F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35] **Conforms**
- G. 21 CFR 201.5 Drugs; adequate directions for use; **Conforms**
- H. 21 CFR 201.6 Drugs; misleading statements; **Conforms**
- I. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and Prominence]. **Does not conform. Tradename not provided. Prominence cannot be determined.**
- J. 21 CFR 201.15 Drugs; prominence of required label statements; **Conforms**
- K. 21 CFR 201.17 Drugs; location of expiration date; **Conforms**
- L. 21 CFR 201.25 Bar code label requirements; **Conforms**
- M. 21 CFR 201.50 Statement of identity; **Conforms**
- N. 21 CFR 201.51 Declaration of net quantity of contents; **Conforms**
- O. 21 CFR 201.55 Statement of dosage; **Conforms**
- P. 21 CFR 201.100 Prescription drugs for human use; **Conforms**

Conclusions

- I. Carton and Container
 - a. Revise “Distributed by:” to “Manufactured by:” on all labels to comply with the definition of a manufacturer [21 CFR 600.3(t), 21 CFR 610.60 and 21 CFR 610.61.]
 - b. Revise the strength presentation to reflect the total concentration followed by the per mL concentration on the next line. *See recommended format

- c. Revise all labels to include the tradename in title case for increased readability and determination of applicable prominence per 21 CFR 201.10.

II. Container

- a. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

III. Vial Cap and Ferrule

- a. Please comment on if there is any text on the ferrule and cap overseal. A revised USP standard will go into effect on December 1, 2010. We refer you to the following address:

http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf

*Recommended format

Tradename

(obinutuzumab)

Injection

1,000 mg/40 mL

(25 mg/ mL)

For Intravenous Infusion after Dilution

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/s/

KIMBERLY M RAINS
08/22/2013

MARJORIE A SHAPIRO
08/23/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: August 6, 2013

Reviewer: Kevin Wright, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Gazyva
Obinutuzumab
Injection
1,000 mg per 40 mL (25 mg/mL)

Application Type/Number: BLA 125486

Applicant/sponsor: Genentech USA, Inc.

OSE RCM #: 2013-1009

*** This document contains proprietary and confidential information that should not be released to the public.***

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2.1	Labels and Labeling	1
3	CONCLUSIONS.....	2
4	RECOMMENDATIONS.....	2
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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Gazyva BLA 125486 for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the April 22, 2013 BLA submission.

- Intended pronunciation: ga zyé vah
- Active Ingredient: Obinutuzumab
- Indication of Use: is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) in combination with chloroambucil.
- Route of Administration: Intravenous
- Dosage Form: Liquid Concentrate
- Strength: 1000 mg per 40 mL (25 mg per mL)
- Dose and Frequency: 100 mg on day 1 of Cycle 1, 900 mg on day 2 of Cycle 1 and 1000 mg on days 8, and 15 of Cycle 1 followed by 1000 mg on day 1 of Cycle 2 to 6
- How Supplied: 50 mL single dose glass vial; colorless to slightly brownish liquid
- Storage: Store under refrigeration at 2°C to 8°C; protect from light, store in carton
- Container and Closure Systems: colorless glass vial with flip off cap

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted April 22, 2013 (Appendix A)
- Carton Labeling submitted April 22, 2013 (Appendix B)
- Insert Labeling submitted April 22, 2013 (no image)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 CONCLUSIONS

DMEPA concludes that the proposed container label and carton labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4 RECOMMENDATIONS

We are providing the following comments for consideration by the review Division prior to the approval of this BLA.

A. Insert Labeling

1. Section 2: Dosage and Administration

a. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert.² As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations as follows:

- Revise the '>' symbol appearing in the body of the text of Section 2.2 (Recommended Premedication), to read "greater than".
2. Revise Table 1 in the Section 2.1 (Recommended Dosage Regimen) to clearly delineate Cycle 1 from Cycles 2 to 6. Ensure all dosing information is displayed for Cycles 2 to 6 (i.e. day, dose, and rate of infusion).
 3. We recommend incorporating the route of administrations for the pre-medications (e.g. Acetaminophen and anti-histamine) in Table 2: (Premedication to be Administered Before Gazyva Infusion to Reduce Infusion Reactions) of Section 2.2 Recommended Premedication.
 4. We recommend using two bullet points in the sentence, "Administer as an intravenous infusion only. Do not administer as an intravenous push or bolus" of Section 2.5 Preparation and Administration under the subheading Administration. The addition of second bullet will help to differentiate the correct process versus the incorrect process (see example below):
 - Administer as an intravenous infusion only.
 - Do not administer as an intravenous push or bolus.

² <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 10/28/2009.

5. We recommend deleting the statement, [REDACTED] (b) (4) [REDACTED]” appearing in Section 2.5 (Preparing and Administration) under the subheading Preparation.

Based on this review, DMEPA recommends the following be implemented prior to approval of this BLA:

A. Container Label

1. Ensure the proper name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the proper name should have a prominence commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10(g)(2).
2. Revise the proprietary name to appear in title case (i.e. Gazyva), this will help to optimize the readability of the proprietary name.
3. Revise the statement of strength to appear in a stacked format (see example below)

Gazyva
Obinutuzumab
Injection
1,000 mg/40 mL
(25 mg/mL)

4. Revise the statement, “Single Use Vial. Discard Unused Portion” to read, “Single Dose Vial. Discard Unused Portion”.

B. Carton Labeling

1. Ensure the carton labeling complies with recommendations A1 through A4.

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KEVIN WRIGHT
08/06/2013

YELENA L MASLOV
08/06/2013

SCOTT M DALLAS
08/07/2013

Division of Hematology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: BLA 125486

Name of Drug: GAZYVA (Obinutuzumab) 1000 mg/40 mL (25 mg/mL) Liquid Single use vial

Applicant: Genentech

Labeling Reviewed

Submission Date: April 22, 2013

Receipt Date: April 22, 2013

Background and Summary Description: Obinutuzumab is a novel type II glycoengineered, humanized anti-CD20 monoclonal antibody of the IgG1 subclass. Obinutuzumab is being developed for the treatment of (b) (4) CLL (b) (4)

Genentech submitted a new Biologics License Application (BLA 125486) for Obinutuzumab with a proposed indication to use obinutuzumab (GA101, RO5072759) in combination with chlorambucil as first-line treatment for patients with previously untreated chronic lymphocytic leukemia (CLL). As part of this BLA submission, the applicant also submitted the proposed package insert (PI) in Microsoft Word.

Review

The applicant’s proposed PI was reviewed in accordance with the labeling format requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” checklist (see the Appendix). There were minor SRPI format deficiencies identified.

Recommendations

The deficiencies identified during this review will be conveyed to the applicant during the labeling negotiations.

Beatrice Kallungal, B.S.

6/21/2013

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is

the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **“HIGHLIGHTS OF PRESCRIBING INFORMATION”**.

Comment:

Highlights Limitation Statement

NO

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: **“These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).”**

Comment: *The name of the drug product is not in UPPER CASE (i.e., GAZYVA)*

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

- N/A** 12. All text must be **bolded**.

Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) -- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “To report **SUSPECTED ADVERSE REACTIONS**, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “See 17 for **PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling.”
- “See 17 for **PATIENT COUNSELING INFORMATION** and Medication Guide.”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “Revised: MM/YYYY or Month Year”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.
Comment:
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.
Comment:
- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment: *The subsection title and numbering for sections 2 and 3 are different in TOC and FPI. Also Section 9 is not listed in the TOC, but it is included in FPI.*
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:
-

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:

YES

38. The **boxed** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [see *Warnings and Precautions (5.2)*].
- Comment:** *Minor corrections are needed in section 4, 5.8, 8.1, 8.6, and 17 (see attached label with tracked changes)*

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.
- Comment:**

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.
- Comment:**
- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
- Comment:**
- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the **Boxed Warning**.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

N/A

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

BEATRICE A KALLUNGAL
06/24/2013

EBLA ALI IBRAHIM
06/24/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 125486	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: GAZYVA Established/Proper Name: Obinutuzumab Dosage Form: Liquid single use vial Strengths: 1000 mg/40 mL (25 mg/mL)		
Applicant: Genentech, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: April 22, 2013 Date of Receipt: April 22, 2013 Date clock started after UN: N/A		
PDUFA Goal Date: December 20, 2013	Action Goal Date (if different): November 22, 2013	
Filing Date: June 21, 2013	Date of Filing Meeting: May 23, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indication(s)/Proposed change(s): Chronic Lymphocytic Leukemia (CLL)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>): N/A				
List referenced IND Number(s): IND 104405				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			Proprietary name can be added to the application tracking system, after the issue of the proprietary name approval notification.
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].				X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?				X	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?				X	
<i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i>			X		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>			X	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?			X	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #		X		
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			X	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	X			
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the</i>	X			

<i>supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>		X		

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>		X		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
<u>BPCA (NDAs/NDA efficacy supplements only):</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			Under the IND
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): July 07, 2009	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): February 22, 2013 & March 5, 2013 (CMC)	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 20, 2013

BLA/NDA/Supp #: 125486

PROPRIETARY NAME: GAZYVA

ESTABLISHED/PROPER NAME: Obinutuzumab

DOSAGE FORM/STRENGTH: Single 1000 mg dose of colorless to slightly brownish liquid concentrate with a strength of 25 mg/mL

APPLICANT: Genentech, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Obinutuzumab in combination with chlorambucil, for the treatment of patients with chronic lymphocytic leukemia

BACKGROUND: Obinutuzumab is a novel type II glycoengineered, humanized anti-CD20 monoclonal antibody of the IgG1 subclass. Obinutuzumab is being developed for the treatment of (b) (4) CLL (b) (4)

Genentech submitted a Biologics License Application (BLA 125486) for Obinutuzumab with a proposed indication to use obinutuzumab (GA101, RO5072759) in combination with chlorambucil as first-line treatment for patients with previously untreated chronic lymphocytic leukemia (CLL).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Beatrice Kallungal	Y
	CPMS/TL:	Lara Akinsanya	Y
Cross-Discipline Team Leader (CDTL)	Virginia Kwitkowski		Y
Clinical	Reviewer:	Hyon-Zu Lee; Barry Miller	N
	TL:	Virginia Kwitkowski	Y
Social Scientist Review (for OTC products)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (for OTC products)	Reviewer:	N/A	
	TL:	N/A	

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Joseph Grillo	Y
	TL:	Julie Bullock	Y
Biostatistics	Reviewer:	Chia-Wen Ko	Y
	TL:	Mark Rothmann	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Stacy Ricci; Pedro Del Valle	Y
	TL:	Haleh Saber	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Mate Tolnay	Y
	TL:	Marjorie Shapiro	Y
Product Quality Microbiology (<i>QbD</i>)	Reviewer:	Chikako Torigoe	Y
	TL:	Laurie Graham	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Colleen Thomas	Y
	TL:	Patricia Hughes	Y
CMC Labeling Review	Reviewer:	Don Obenhuber	Y
	TL:	Patricia Hughes	Y
Facility Review/Inspection	Reviewer:	Anthony Orenca	Y
	TL:	Janice Pohlman	N
OSE/DMEPA (proprietary name)	Reviewer:	Kevin Wright	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Bob Pratt	Y

	TL:	Cynthia LaCivita	N
OSE/DPV II	Reviewer:	Afrouz Nayornama	Y
	TL:	N/A	
Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca	Y
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
OCP, Div. of Pharmacometrics	Jeffrey Florian		Y
Office Director	Richard Pazdur		Y
Division Director	Ann Farrell		Y
Deputy Director	Edvardas Kaminskas		Y
Deputy Director of Safety	Robert Kane		Y
OHOP ADRA	Tamy Kim		Y
OSE RPM	Sue Kang		Y
DHP RPM	Theresa Carioti		Y
	Michael Wissing		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
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<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p>	<input checked="" type="checkbox"/> Not Applicable

Comments:	<input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIOSTATISTICS	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
<u>Environmental Assessment</u>	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
If no , was a complete EA submitted?	<input type="checkbox"/> YES <input type="checkbox"/> NO
If EA submitted , consulted to EA officer (OPS)?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

Comments:	
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Ann Farrell, M.D., Division Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): July 23, 2013

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>

ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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

/s/

BEATRICE A KALLUNGAL
06/24/2013

EBLA ALI IBRAHIM
06/24/2013

DGCPC/OSI CONSULT: Request for Clinical Inspections

Date: 5/29/2013

To: Ann Meeker-O'Connell, Acting Division Director, DGCPC
Susan Thompson, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
CDEROCDSIPMOs@fda.hhs.gov
Anthony Orenca, M.D.
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Hyon-Zu Lee, Pharm.D., Clinical Analyst
Division of Hematology Products
and
Virginia Kwitkowski, MS, RN, ACNP-BC, Clinical Team Leader
and
Ann Farrell, M.D., Director

From: Beatrice Kallungal, Division of Hematology Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: BLA 125486
IND#: 104405
Applicant: Genentech
Phone: (650) 225-1558
Regulatory Point of Contact: Sarah Oliver
Regulatory Point of Contact Phone: (650) 467-3521
Regulatory Point of Contact Email: oliver.sarah@gene.com

Drug Proprietary Name: Gazyva
Generic Drug Name: Obinutuzumab (GA101, RO5072759)
NME or Original BLA (Yes/No): Yes
Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication: For use in combination with chlorambucil as first-line treatment for patients with chronic lymphocytic leukemia (CLL)

DGCPC/OSI Consult
version: 09/28/2011

PDUFA: November 22, 2013

Action Goal Date: November 22, 2013

Inspection Summary Goal Date: October 22, 2013

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
164932 Heinz Ludwig Address: Montleartstrasse 37 Wien, 1160 Austria Email: heinzludwig@wienkav.at Phone #: 51209 Fax #: 51217	BO21004	6	In combination with chlorambucil for the treatment of patients with previously untreated CLL.
166942 Katell LeDu Address: 194 Avenue Rubillard Pavillon Le Mans, 72037 France Email: katell.ledu@free.fr Phone #: 33 2 43434360 Fax #: 33 3 81668215	BO21004	6	In combination with chlorambucil for the treatment of patients with previously untreated CLL.

III. Site Selection/Rationale

Site selection was based on the numbers of patient enrollment.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):

- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other: Enrollment of large numbers of study subjects.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DGCPC.

IV. Tables of Specific Data to be Verified (if applicable)

None.

Should you require any additional information, please contact
Virginia Kwitkowski, MS, RN, ACNP-BC at 301-796-2318 or *Hyon-Zu Lee, Pharm.D.* at 301-796-2192.

Concurrence: (as needed)

Virginia Kwitkowski, MS, RN, ACNP-BC Medical Team Leader
Hyon-Zu Lee, Pharm.D. Medical Reviewer
Ann Farrell, M.D. Division Director (for foreign inspection requests or requests for 5 or more sites only)

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

/s/

BEATRICE A KALLUNGAL
05/29/2013

EDVARDAS KAMINSKAS
05/30/2013