CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125486Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: BLA 125486 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Hematology Products PDUFA Goal Date: December 20, 2013 Stamp Date: 4/22/2013

Proprietary Name: GAZYVA

Established/Generic Name: Obinutuzumab (GA101)

Dosage Form: Liquid single use vial

Applicant/Sponsor: Genentech, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Chronic Lymphocytic Leukemia (CLL)

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☒ dosing regimen; or ☒ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}
Beatrice Kallungal
Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

1.9.1 Request for Waiver of Pediatric Studies

REQUEST FOR WAIVER OF PEDIATRIC STUDIES

Indication(s): Chronic Lymphocytic Leukemia

1. What age ranges are included in your waiver request? 0 to < 18 years.
2. Reasons for waiving pediatric studies:
   - a. ☐ No meaningful therapeutic benefit over existing treatments and is unlikely to be used in a substantial number of pediatric patients
   - b. ☐ Studies are impossible or highly impractical because the number of patients is so small or geographically dispersed
   - c. ☐ The product would be ineffective or unsafe in all pediatric age groups
   - d. ☐ Attempts to develop a pediatric formulation for a specific age group have failed
   - e. ☒ Disease-specific waiver indicated for the treatment of the condition in adults (please check)

☐	Alzheimer's disease	☐	Age-related macular degeneration
☐	Prostate cancer	☐	Breast cancer
☐	Renal cell cancer	☐	Non-germ cell ovarian cancer
☐	Hairy cell cancer	☐	Pancreatic cancer, colorectal cancer
☐	Osteoarthritis	☐	Squamous cell cancers of the oropharynx
☐	Uterine cancer	☐	Basal cell and squamous cell cancer
☐	Endometrial cancer	☐	Small cell and non‑small cell lung cancer
☐	Parkinson's disease	☐	Amyotrophic lateral sclerosis
☐	Arteriosclerosis	☐	Symptoms of menopause
☐	Infertility	☒	Other (please state and justify)

3. Justification for waiver (not necessary if category 2(e) is checked):

   Orphan Drug Designation received for Chronic Lymphocytic Leukemia

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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
10/20/2013

1.3.3 Debarment Certification

Genentech, Inc. 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 for the investigation of product, obinutuzumab, in connection with this Biologic License Application at Genentech, Inc.

Signed by: _____ 04/22/2013

Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # **N/A** BLA # **125486**	NDA Supplement # **N/A** BLA Supplement # **N/A**	If NDA, Efficacy Supplement Type: **N/A**
Proprietary Name: **GAZYVA** Established/Proper Name: **Obinutuzumab** Dosage Form: **1000 mg/40 mL (25 mg/mL) liquid single use vials**		Applicant: **Genentech, Inc.** Agent for Applicant (if applicable): **N/A**
RPM: **Beatrice Kallungal**		Division: **Division of Hematology Products**

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is **December 21, 2013**	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☒ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS:
- ☐ MedGuide
- ☐ Communication Plan
- ☐ ETASU
- ☐ MedGuide w/o REMS
- ☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☒ Yes, dates **10/22/2013**
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☒ CDER Q&As ☒ Other **Information Advisory**

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

Reference ID: 3400136

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

Reference ID: 3400136

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	**11/01/2013**
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) **Approval 11/01/2013**
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	**10/29/2013**
• Original applicant-proposed labeling	**04/22/2013**
• Example of class labeling, if applicable	**N/A**

[4] Fill in blanks with dates of reviews, letters, etc.

Reference ID: 3400136

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	**N/A**
• Original applicant-proposed labeling	**N/A**
• Example of class labeling, if applicable	**N/A**
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	**10/18/2013**
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	**07/23/2013 (Acceptability)** **07/23/2013**
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM **06/24/2013** ☒ DMEPA **08/07/2013** ☐ DMPP/PLT (DRISK) ☐ OPDP (DDMAC) **10/23/2013** ☐ SEALD **N/A** ☐ CSS **N/A** ☐ Other reviews **N/A**
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	**06/24/2013 (RPM filing checklist);** ☐ Not a (b)(2) ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC **N/A** If PeRC review not necessary, explain: **Orphan drug designation** • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	**10/31/2013; 10/30/2013; 10/29/2013; 10/28/2013; 10/25/2013; 10/16/2013 (2); 10/10/2013; 10/09/2013 (3); 09/26/2013; 09/23/2013; 09/20/2013; 09/19/2013; 09/13/2013; 09/10/2013; 09/06/2013; 08/28/2013; 08/26/2013 (2); 08/23/2013; 08/20/2013; 08/16/2013; 08/15/2013; 08/14/2013; 08/12/2013 (2); 08/08/2013; 08/06/2013; 07/23/2013; 07/16/2013; 07/12/2013; 07/10/2013; 07/09/2013; 07/08/2013; 06/26/2013; 06/25/2013; 06/24/2013;06/21/2013; 06/19/2013; 06/18/2013; 06/17/2013 (2); 06/12/2013; 05/20/2013; 05/17/2013; 05/02/2013; 05/01/2013**
❖ Internal memoranda, telecons, etc.	**Telecon: 09/23/2013; 09/13/2013; 09/06/2013; 07/26/2013; 07/19/2013**
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg **03/05/2013 (CMC); 02/22/2013 (Pre-BLA); 06/08/2012 (Pre-BLA)**
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg **07/07/2009**
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	**09/24/2013 (Late-cycle meeting); 08/06/2013 (Mid-cycle communication); 09/19/2012 (CMC)**
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None **10/30/2013**
Division Director Summary Review *(indicate date for each review)*	☐ None **10/25/2013**
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None **10/22/2013**
PMR/PMC Development Templates *(indicate total number)*	☐ None **2**

Reference ID: 3400136

Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	**10/01/2013 Cosigned review dated 10/01/2013**
• Clinical review(s) *(indicate date for each review)*	**10/01/2013; 5/24/2013 – Filing checklist**
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	**See page 24, Clinical Review dated 10/01/2013**
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	**N/A** **N/A** ☐ None **09/19/2013**
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested **10/21/2013 – OSI Letter; 09/05/2013 – Review**
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None **08/30/2013 Cosigned Primary Review dated 08/29/13**
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None **08/29/2013 Cosigned Primary Review dated 08/29/13;**
Statistical Review(s) *(indicate date for each review)*	☐ None **08/29/2013; 05/28/2013 – Filing checklist**
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None **10/07/2013 Cosigned TL Review dated 10/07/2013**
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None **10/07/2013**
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None **09/25/2013 (primary); 06/03/2013 – Filing checklist**
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None

[6] Filing reviews should be filed with the discipline reviews.

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None **09/17/2013**
• Supervisory Review(s) *(indicate date for each review)*	☐ None **09/17/2013**
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None **09/17/2013; 05/24/2013 – Filing checklist**
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None **10/01/2013 Cosigned TL review dated 10/01/2013**
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None **10/01/2013**
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None **09/27/2013; Filing checklist - 06/13/2013**
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☒ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed **10/21/2013; 10/15/2013; 09/27/2013; 08/28/2013; Filing checklist - 06/20/2013**
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None **08/29/2013 (Statistical review)**
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	**See page 8 Product Quality review dated 09/27/2013**
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☒ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: **10/17/2013** ☒ Acceptable ☐ Withhold recommendation

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

Reference ID: 3400136

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

Reference ID: 3400136

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/s/

BEATRICE A KALLUNGAL
11/01/2013

From: Kallungal, Beatrice
To: Sarah Oliver
Cc: Kallungal, Beatrice
Subject: RE: BLA 125486, Obinutuzumab Labeling - Final version
Date: Wednesday, October 30, 2013 6:05:42 PM

Dear Sarah,
The edits proposed by your team in the most recent version of the USPI, as well as the minor edit noted below are acceptable to the Agency. Please accept these changes and submit via electronic gateway, the revised USPI to the BLA (final document and one in track changes) as soon as possible (if possible today).

Regards,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

From: Sarah Oliver [mailto:oliver.sarah@gene.com]
Sent: Wednesday, October 30, 2013 1:48 PM
To: Kallungal, Beatrice
Subject: Re: BLA 125486, Obinutuzumab Labeling - FDA's revisions dated 10/29/2013

Hi Beatrice -

My team just noted a minor error in the USPI we would like to flag for correction.

In the TOC regarding the PML boxed warning, the word 'LEUKOENCEPHALOPA**H**THY' is misspelled and should have the highlighted 'h' removed. Please feel free to correct this.

Thank you.

Sarah

On Wed, Oct 30, 2013 at 10:05 AM, Sarah Oliver <sarahef@gene.com> wrote:
Hi Beatrice -

Please see attached the USPI with our few editorial comments.

Let me know if you have any questions. I will give you a call tomorrow morning to touch base on any outstanding issues.

Sarah

On Tue, Oct 29, 2013 at 2:05 PM, Kallungal, Beatrice <Beatrice.Kallungal@fda.hhs.gov> wrote:

> Dear Sarah,
>
> Attached is the revised draft package insert (PI) for Obinutuzumab, BLA 125486.
>
> Please review the FDA's changes/comments and, using the same draft, do the following:
>
> - Where you agree with the labeling revisions, "accept" the tracked changes.
> - Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.
>
> In addition, please review the document for formatting.
>
> We request that you respond by **1 PM EDT, Wednesday October 30, 2013** via e-mail and officially submit to the BLA.
>
> If you have any questions, feel free to contact me.
>
> Kind regards,
>
> Beatrice
>
> Beatrice Kallungal
> Regulatory Project Manager
> Division of Hematology Products (DHP)
> FDA/CDER/OHOP
> WO22, Room 2354
> 10903 New Hampshire Avenue
> Silver Spring, MD 20993
> (301) 796-9304 (phone)
> (301) 796-9845 (fax)
> E-Mail: beatrice.kallungal@fda.hhs.gov

--
Sarah Oliver (formerly Fabes), Ph.D.
Associate Program Director - Regulatory
Genentech
1 DNA Way, South San Francisco, Ca 94080
(650) 467-3521
(650) 238-4978 (mobile)

This email and any and all attachments contain information that is confidential and may not be disclosed without prior written consent from Genentech/Roche.

--
Sarah Oliver (formerly Fabes), Ph.D.
Associate Program Director - Regulatory
Genentech
1 DNA Way, South San Francisco, Ca 94080
(650) 467-3521
(650) 238-4978 (mobile)

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/s/

BEATRICE A KALLUNGAL
10/30/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver (oliver.sarah@gene.com)
Cc:	Kallungal, Beatrice
Subject:	BLA 125486, Obinutuzumab Labeling - FDA"s revisions dated 10/29/2013
Date:	Tuesday, October 29, 2013 5:05:39 PM
Attachments:	BLA 125486 - draft label-v14 10-29-2013.doc

Dear Sarah,

Attached is the revised draft package insert (PI) for Obinutuzumab, BLA 125486.

Please review the FDA's changes/comments and, using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition, please review the document for formatting.

We request that you respond by **1 PM EDT, Wednesday October 30, 2013** via e-mail and officially submit to the BLA.

If you have any questions, feel free to contact me.

Kind regards,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
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E-Mail: beatrice.kallungal@fda.hhs.gov

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BEATRICE A KALLUNGAL
10/29/2013

From: Kallungal, Beatrice
To: Sarah Oliver (oliver.sarah@gene.com)
Cc: Kallungal, Beatrice
Subject: BLA 125486, Obinutuzumab - Post Marketing Studies (PMC #2)
Date: Monday, October 28, 2013 3:10:31 PM

Dear Sarah,

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by tcon if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

PMC #2 Description:

Submit a protocol for (b) (4) . The protocol should include bioburden and endotoxin limits to demonstrate continued microbial control (b) (4) . The protocol should be submitted as a CBE-30 by December 2013. Execute the approved protocol by August 2014. Provide the results in the first annual report following the approval of the CBE-30.

PMC Schedule Milestones: Final Protocol Submission: MM//YYYY
Study/Trial Completion: MM//YYYY
Final Report Submission: MM//YYYY

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR or PMC designation numbers will be assigned later

Some things you can do to expedite this process:

1. For labeling and PMRs or PMCs reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you

officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs or PMCs agreed upon. We ask the following:

a. Send the RPM an email courtesy copy of the draft versions, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.

b. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR or PMC NUMBER). This helps the document room and us code the submission properly.

Please provide your response by **1 PM** Tuesday **October 29, 2013**.

Regards,

Beatrice

Beatrice Kallungal

Regulatory Project Manager
Division of Hematology Products (DHP)

FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)

(301) 796-9845 (fax)

E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
10/28/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver (oliver.sarah@gene.com)
Cc:	Kallungal, Beatrice
Subject:	FW: BLA 125486, Obinutuzumab Labeling - FDA"s revisions dated 10/25/2013
Date:	Friday, October 25, 2013 1:09:43 PM
Attachments:	BLA 125486 - Draft label-v13_10-25-13.doc

Hi Sarah,

Please edit the Section 14 results table to clarify that Overall Response Rate [b] (ORR=CR+PR).

If you have any questions, please let me know.

Regards,

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

From: Kallungal, Beatrice
Sent: Friday, October 25, 2013 10:45 AM
To: Sarah Oliver (oliver.sarah@gene.com)
Cc: Kallungal, Beatrice (Beatrice.Kallungal@fda.hhs.gov)
Subject: BLA 125486, Obinutuzumab Labeling - FDA's revisions dated 10/25/2013

Dear Sarah,

Attached is the revised draft package insert (PI) for Obinutuzumab, BLA 125486.

Please review the FDA's changes/comments and, using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition, please review the document for formatting and add the month/year as appropriate in the final draft.

We request that you respond by **1 PM EDT, Monday October 28, 2013** via e-mail and officially submit to the BLA.

If you have any questions, feel free to contact me.

Kind regards,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
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BEATRICE A KALLUNGAL
10/25/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486, Obinutuzumab/GA101 - Information Request - Carton and Container labeling review - Additional edits
Date:	Wednesday, October 16, 2013 9:50:27 PM

Hi Sara,
Please find below additional comments on the carton and container labeling.

Container Label:

- Please decrease the prominence of the manufacturer name “Genentech” as this information competes for prominence with the most important information on the principle display panel such as proprietary and established name.

Carton Labeling:

- Please decrease the prominence of the manufacturer name “Genentech” as this information competes for prominence with the most important information on the principle display panel such as proprietary and established name.

Please respond to this information request and submit the revised carton and container labeling by **3 pm Friday, October 18, 2013**.
Regards,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
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E-Mail: beatrice.kallungal@fda.hhs.gov

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BEATRICE A KALLUNGAL
10/16/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver (oliver.sarah@gene.com)
Cc:	Kallungal, Beatrice
Subject:	BLA 125486, Obinutuzumab Labeling - FDA"s revisions dated 10/16/2013
Date:	Wednesday, October 16, 2013 5:09:17 PM
Attachments:	pop_pk_paramsCLL.PDF BLA 125486 - Draft_label-v11_10-16-13.doc

---

Dear Sarah,

Attached is the revised draft package insert (PI) for Obinutuzumab, BLA 125486. Also attached is the population PK parameters table, provided by our clinical pharmacology colleagues.

Please review the FDA's changes/comments and, using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition, please review the document for formatting.

We request that you respond by **3 PM EDT, Friday October 18, 2013** via e-mail and officially submit to the BLA.

Please confirm receipt of this e-mail. If you have any questions, feel free to contact me.

Kind regards,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
10/16/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver (oliver.sarah@gene.com)
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab/GA101 - Information Request - 10/09/2013
Date:	Wednesday, October 09, 2013 9:26:00 AM
Importance:	High

Dear Sarah,
Please provide the information requested below **ASAP or by 4 PM Today, October 9, 2013** via e-mail and officially submit to the BLA. However, if you need more time to respond, please let me know.

Please describe the methods for reconstitution of Dose #1 and 2 of obinutuzumab at the clinical trial sites. Specifically, were dose 1 and 2 prepared at the same time out of a single 1000mg vial? If so, what were the instructions to the sites as to the time frame for when dose 2 had to be administered?

OR Were doses 1 and 2 made from two different vials?

Thanks,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
10/09/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver (oliver.sarah@gene.com)
Cc:	Kallungal, Beatrice
Subject:	BLA 125486, Obinutuzumab Labeling - FDA"s revisions
Date:	Wednesday, October 09, 2013 5:02:32 PM
Attachments:	BLA 125486 - Draft label-v9_10-09-13.doc

Dear Sarah,

Attached is the revised draft package insert (PI) for Obinutuzumab, BLA 125486.

Please review the FDA's changes/comments and, using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition, please review the document for formatting.

We request that you respond by **3 PM EDT, Monday October 14, 2013** via e-mail and officially submit to the BLA.

Please confirm receipt of this e-mail. If you have any questions, feel free to contact me.

Kind regards,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
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E-Mail: beatrice.kallungal@fda.hhs.gov

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

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/s/

BEATRICE A KALLUNGAL
10/09/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver (oliver.sarah@gene.com)
Cc:	Kallungal, Beatrice
Subject:	BLA 125486, Obinutuzumab - Post Marketing Studies
Date:	Wednesday, October 09, 2013 5:26:43 PM

Dear Sarah,

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by tcon if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

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: MM//YYYY
Study/Trial Completion: MM//YYYY
Final Report Submission: MM//YYYY

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR or PMC designation numbers will be assigned later

Some things you can do to expedite this process:

1. For labeling and PMRs or PMCs reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs or PMCs agreed upon. We ask the following:

a. Send the RPM an email courtesy copy of the draft versions, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.

b. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR or PMC NUMBER). This helps the document room and us code the submission properly.

Please provide your response by **4 PM Wednesday October 16, 2013**.

Regards,

Beatrice

Beatrice Kallungal

Regulatory Project Manager
Division of Hematology Products (DHP)

FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)

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E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
10/09/2013

MEMORANDUM OF TELECONFERENCE

Teleconference Date: September 13, 2013 at 9-10 A.M. Eastern Standard Time (EST)

Application Number: 125486
Product Name: Obinutuzumab
Sponsor/Applicant Name: Genentech, Inc.

Subject: Follow-up of IRs sent

FDA Participants:

Marjorie Shapiro, Ph.D.	Lab Chief, DMA
Laurie Graham, M.S.	Team Lead, DMA
Chikako Torigoe, Ph.D.	Product Quality Reviewer, DMA
Mate Tolnay, Ph.D.	Product Quality Reviewer, DMA
Lyndsay Hennessey	Regulatory Project Manager, OBP

Sponsor/Applicant Participants:

Process Development Drug Substance:	Annika Kleinjans, Christian Hakemeyer, Frank Zettl, Wolfgang Kuhne
Drug Product Manufacturing:	Thorsten Herkert
Analytical Development:	Nadja Alt, Felix Kepert, Gerald Gellermann, Hans Koll
Supply Clinical Trials:	Rolf Schiffmann
Technical Regulatory:	Elisabeth Kirchisner, Stephane Avella, Holger Raviol, Ines Krämer
Project Management:	Jacques Bourquin, Batu Berkok
Analytical Development:	Christof Finkler, Niklas Engler

1.0 BACKGROUND:

The following Agenda item was provided to the sponsor:

1. September 6th Information Request Responses

2.0 DISCUSSION:

(b) (4)

(b) (4)

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/s/

LYNDSAY J HENNESSEY
10/08/2013

MEMORANDUM OF TELECONFERENCE

Teleconference Date: September 23, 2013 at 9-10 A.M. Eastern Standard Time (EST)

Application Number: 125486
Product Name: Obinutuzumab
Sponsor/Applicant Name: Genentech, Inc.

Subject: Follow-up of IRs sent

FDA Participants:

Marjorie Shapiro, Ph.D.	Lab Chief, DMA
Laurie Graham, M.S.	Team Lead, DMA
Chikako Torigoe, Ph.D.	Product Quality Reviewer, DMA
Mate Tolnay, Ph.D.	Product Quality Reviewer, DMA
Lyndsay Hennessey	Regulatory Project Manager, OBP

Sponsor/Applicant Participants:

Process Development Drug Substance:	Annika Kleinjans, Christian Hakemeyer, Frank Zettl, Wolfgang Kuhne
Drug Substance Manufacturing:	Marion Hueckel
Analytical Development:	Nadja Alt, Felix Kepert, Gerald Gellermann, Niklas Engler, Christof Finkler, Klaus Leonhard
Technical Regulatory:	Elisabeth Kirchisner, Stephane Avella, Holger Raviol, Ines Krämer, Mathias Usteri, Rainer Lang
Project Management:	Jacques Bourquin
IMP Quality:	Ettore Ohage

1.0 BACKGROUND:

The meeting was held to discuss the Information Request sent September 19, 2013. The responses for the following questions were found acceptable and therefore no discussion was held: Questions 3, 6-8, 11-13, and 19.

2.0 DISCUSSION:

Question 4 Discussion:
The sponsor agreed to set committed to rejection limits for [redacted] (b) (4) *in drug substance in-process testing. However, the rejection limits were higher than the established acceptance criteria for these attributes. The sponsor was able to provide sufficient justification, including data from a clinical lot with* [redacted] (b) (4)*. The sponsor will continue to use tighter ranges as action limits. The Agency stated this appeared to be reasonable.*

Question 5 Discussion:
The Agency stated that the main concern was that the CQA-AC for [redacted] (b) (4) *appear to be too wide to provide assurance of manufacturing consistency.* (b) (4) [redacted] *The sponsor agreed to update the PALM plan with preliminary trend limits.*

Question 18 Discussion:
The sponsor was asked to limit the hold time of the [redacted] (b) (4) *in the BLA. The sponsor indicated that three batches manufactured for commercial launch used a hold time of* (b) (4) *The sponsor provided preliminary release data for these lots and indicated that a verification study to support the* (b) (4) *hold time was being conducted. The sponsor indicated that the verification study would be completed by December 2013. The sponsor agreed that the verification study would be a post-marketing commitment (PMC).*

Question 1 Discussion:
The Agency stated that the answers appeared sufficient; however, the reviewer will look further at the data that went through (b) (4) *freeze/thaw cycles. The Agency asked if the sponsor had tables with the actual breakdown of the hold times. The sponsor replied yes but there was only one hold time.*

Question 2 Discussion:
Sponsor stated that the [redacted] (b) (4) *would be removed from the BLA.*

Question 9 Discussion:

(b) (4)

The Agency found this acceptable. The sponsor indicated that the PALM plan would be updated.

Question 10 Discussion:

With regard to changes in process parameter ranges, the sponsor proposed (b) (4) *The proposal from the sponsor was found acceptable by the Agency. The sponsor indicated that the PALM plan would be updated.*

In a later communication with the Agency, the sponsor indicated (b) (4)

Question 15 Discussion:

As there are currently only single sites used for DS and DP manufacturing, pooling is not an issue. However, the sponsor agreed to update the PALM plan to indicate that pooling is not allowed.

Question 17 Discussion:

The Agency asked the sponsor to clarify when stability testing would be considered for changes within the design space. The sponsor indicated that this is not currently part of the PALM plan, but agreed to update the PALM plan (b) (4) .

Question 20 Discussion:

The Agency asked the sponsor to confirm that (b) (4) *The sponsor confirmed they were not.*

Action Items:

- *The sponsor will provide a table listing out all changes to the BLA from comments made in the Information Requests letters.*
- *The sponsor will provide the actual language for the PALM plan*
- *The sponsor will update the BLA in 1-2 weeks*

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/s/

LYNDSAY J HENNESSEY
10/08/2013

From:	Kirchisner, Elisabeth
To:	Hennessey, Lyndsay
Cc:	Stephane Avella; Kallungal, Beatrice
Subject:	Re: Obinutuzumab (GA101) - Teleconference call on Friday, Sept 27?
Date:	Thursday, September 26, 2013 12:38:51 PM

Dear Lyndsay,

thank you for this information.
I think the concerns listed are misunderstandings. We also did not want to propose these aspects. I will make sure that the PALM plan is adapted to reflect this in more clarity.
The document will be submitted tomorrow as agreed before.

Kind regards,
Elisabeth.

Roche Diagnostics GmbH
Werk Penzberg; Nonnenwald 2; D-82377 Penzberg; Telefon +49-8856-60-0; Telefax +49-8856-60-3896
Sitz der Gesellschaft: Mannheim - Registergericht: AG Mannheim HRB 3962 - Geschäftsführung:
Thomas Schmid, Sprecher; Edgar Vieth - Aufsichtsratsvorsitzender: Dr. Severin Schwan

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On Thu, Sep 26, 2013 at 6:25 PM, Hennessey, Lyndsay <Lyndsay.Hennessey@fda.hhs.gov> wrote:

> Hello Elisabeth,
>
> The following concerns have been identified with regard to the proposed changes in the post-approval lifecycle management (PALM) plan received on September 23, 2013.
>
> (b) (4)
> [redacted]

(b) (4)

[redacted]

Please let me know if your group has any questions.

Kind regards,

Lyndsay

From: Kirchisner, Elisabeth [mailto:elisabeth.kirchisner@roche.com]
Sent: Thursday, September 26, 2013 8:41 AM

To: Hennessey, Lyndsay
Cc: Stephane Avella; Kallungal, Beatrice
Subject: Re: Obinutuzumab (GA101) - Teleconference call on Friday, Sept 27?

Dear Lyndsay,

thank you very much for this confirmation.

Please contact me any time in case a new meeting needs to be set up.

Kind regards,

Elisabeth.

Roche Diagnostics GmbH
Werk Penzberg; Nonnenwald 2; D-82377 Penzberg; Telefon +49-8856-60-0; Telefax +49-8856-60-3896
Sitz der Gesellschaft: Mannheim - Registergericht: AG Mannheim HRB 3962 - Geschäftsführung:
Thomas Schmid, Sprecher; Edgar Vieth - Aufsichtsratsvorsitzender: Dr. Severin Schwan

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On Thu, Sep 26, 2013 at 1:43 PM, Hennessey, Lyndsay <Lyndsay.Hennessey@fda.hhs.gov> wrote:

Hello Elisabeth,

Yes, all TCs will be cancelled. If the reviewers would like to have another one, I will contact you to set it up.

Thank you,

Lyndsay

From: Kirchisner, Elisabeth [mailto:elisabeth.kirchisner@roche.com]
Sent: Wednesday, September 25, 2013 12:37 PM
To: Hennessey, Lyndsay
Cc: Stephane Avella; Kallungal, Beatrice
Subject: Obinutuzumab (GA101) - Teleconference call on Friday, Sept 27?

Dear Lyndsay,

my understanding from the teleconference call last Monday (Sept 23) is, that for this upcoming Friday, Sept 27, we do not plan to have an additional teleconference call to discuss CMC topics.

May I kindly ask you to confirm that the TC for Sept 27 is cancelled (and potentially also for the other upcoming Fridays)?

This question is just related to planning purposes. In case any discussion topics come up, we are happy to plan for additional/ new meetings.

Thank you and kind regards,

Elisabeth.

Roche Diagnostics GmbH
Werk Penzberg; Nonnenwald 2; D-82377 Penzberg; Telefon +49-8856-60-0; Telefax +49-8856-60-3896
Sitz der Gesellschaft: Mannheim - Registergericht: AG Mannheim HRB 3962 - Geschäftsführung:
Thomas Schmid, Sprecher; Edgar Vieth - Aufsichtsratsvorsitzender: Dr. Severin Schwan

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/s/

LYNDSAY J HENNESSEY
09/26/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	RE: BLA 125486, Obinutuzumab/GA101 - Information Request - Carton and Container labeling review - 9/23/2013
Date:	Monday, September 23, 2013 2:34:21 PM

Hi Sarah,
Thank you for your response to the information request regarding the carton and container labeling. Please find below the follow-up comment/additional request.

1.The Agency is in agreement with your rationale for keeping the statement “Single Use Vial. Discard Unused Portion”.
2. Delete (b) (4) from the carton labeling because it distracts the user's attention from more important information like the proprietary name, establish name, and statement of strength.

Please submit the revised carton labeling by **3 pm Wednesday, September 25, 2013**.

Regards,

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
09/24/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your biologics license application (BLA) dated April 22, 2013, received April 22, 2013, submitted under section 351 of the Public Health Service Act for Obinutuzumab (GA101, RO5072759).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application:

1. Please establish a maximum hold time for final container drug product testing by the [redacted] (b) (4). The hold time should be supported by the endotoxin LER study data.

2. Please address the following comments regarding crimping validation:
   a. Provide the English translation of the crimping validation report.
   b. Describe preparation of the positive controls for the container closure integrity tests [redacted] (b) (4) performed during crimping validation.

3. Regarding stopper sterilization validation, the data for [redacted] (b) (4) are provided for the maximum load configuration (Table 27) but not for the minimum load configuration (Table 26). Please provide this data or explain why the [redacted] (b) (4) were not used for the minimum load qualification runs.

4. [redacted] (b) (4)

5. Please provide the English translation of the rabbit pyrogen test validation report.

6. Please respond to the following comments regarding the helium leak test method for container closure integrity.
    a. Describe the positive controls that will be used during routine testing in terms of the defect size (20 micron, etc.).
    b. Summary data from the study comparing microbial ingress and the helium leak test is provided for groups of 15 vials, with a positive result shown if at least one vial in the group was positive. Indicate the number of positive vials that were obtained from each group of vials.

We request a prompt written response to the items enumerated above in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of the other sections of your application is continuing.

If you have any questions, please contact the Quality Regulatory Project Manager, Lyndsay Hennessey, at (240) 402-3746.

Sincerely,

{See appended electronic signature page}

Marlene Schultz-DePalo, M.S., M.A., RAC
Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MARLENE T SCHULTZ-DEPALO
09/20/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your biologics license application (BLA) dated April 22, 2013, received April 22, 2013, submitted under section 351 of the Public Health Service Act for Obinutuzumab (GA101, RO5072759).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application:

1. Regarding the [redacted] (b) (4) of obinutuzumab drug substance [redacted] (b) (4) [redacted] (b) (4)
2. Regarding the [redacted] (b) (4) verify whether the method is compendial or not. If it is not compendial, provide a method description.
3. It is recommended that the non-reduced CE-SDS assay for fragments be included in comparability for stability testing of both drug substance (DS) and drug product (DP) as well as in continual monitoring of DP.

4. With regard to the DS testing strategy, it is recommended that (b) (4) have committed reject limits.
5. Based upon manufacturing experience, the CQA-AC for (b) (4) are too high. Provided updated CQA-AC.
6. For DP (b) (4) the acceptance criteria using this approach appear to be too broad compared to manufacturing and clinical experience.
7. (b) (4) Update the PALM accordingly.
8. For Table 1 in the PALM plan, provide clarification as to why (b) (4) Update the Table 2 in the PALM plan accordingly.
9. Update the PALM plan to indicate how changes in the (b) (4) will be reported.
10. Update the PALM plan to indicate how the (b) (4) will be reported,
11. Update the PALM plan to indicate (b) (4)
12. Update the PALM plan with the list of (b) (4)
13. Update Table 1 of the PALM plan to distinguish between (b) (4)
14. Update the PALM plan to include (b) (4).
15. With regard to life-cycle management of attributes that are periodically or continuously monitored, clarify whether results from multiple sites can be pooled. Provide any pooling criteria that will be used.
16. Provide clarification on how changes to process parameters that are not included in the design space will be managed (i.e. those parameters that were dismissed from the design space by the FMEA or PC/PV studies).
17. Clarification is needed on how stability is assessed with changes within the design space. For example, in cases where a change within the design space result in a CQA value outside of what has been studied on stability, will stability be assessed?
18. Update 3.2.S.2.2 to limit the (b) (4) hold time to (b) (4).
19. Update 3.2.S.2.2 to limit the (b) (4) in the PC/PV studies (b) (4)

20. Provide clarification on the conditions under which site specific parameters were not considered for inclusion in the design space. For example, was the FMEA conducted without consideration for whether attributes were site specific or site independent? Were site specific parameters identified in the FMEA as pCPPS included in the design space?

We request a written response to the items enumerated above by September 23, 2013 in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of the other sections of your application is continuing.

If you have any questions, please contact me at (240) 402-3746.

Sincerely,

{See appended electronic signature page}

Lyndsay Hennessey
Quality Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Lyndsay.Hennessey@fda.hhs.gov

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/s/

LYNDSAY J HENNESSEY
09/19/2013

From: Kallungal, Beatrice
To: Sarah Oliver
Cc: Kallungal, Beatrice
Subject: RE: BLA 125486 - Feedback from the Agency on Proposal for (b) (4)
Date: Wednesday, August 28, 2013 2:24:34 PM

Hi Sarah,
(b) (4)

Regards,

Beatrice

From: Sarah Oliver [mailto:oliver.sarah@gene.com]
Sent: Wednesday, August 28, 2013 2:09 PM
To: Kallungal, Beatrice
Subject: Re: BLA 125486 - Feedback from the Agency on Proposal for (b) (4)

Thank you Beatrice - very helpful information. (b) (4)

As a follow up question, can you clarify what the Agency means (b) (4)"? Is this regrading (b) (4)

Thank you again for the information.

Kind regards,

Sarah

On Wed, Aug 28, 2013 at 7:48 AM, Kallungal, Beatrice <Beatrice.Kallungal@fda.hhs.gov> wrote:
Hi Sarah,
Upon review of the proposal you submitted regarding the (b) (4)

Regards,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue

Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

From: Sarah Oliver [mailto:oliver.sarah@gene.com]
Sent: Monday, August 26, 2013 2:24 PM
To: Kallungal, Beatrice
Subject: BLA 125486 - Feedback from the Agency on Proposal for [redacted] (b) (4)

Hi Beatrice -

I wanted to follow up with you and your review team to see if the Agency had any comments back on the proposal we submitted regarding [redacted] (b) (4). Based on the discussion at the Mid-Cycle meeting on this topic, we submitted a proposal on Aug 12, 2013 (Seq # 0018 to the BLA). We are currently working on developing the documents/data for submission to the Agency and wanted to ensure we had taken into account any feedback.

Thank you.

Kind regards,

Sarah

--
Sarah Oliver (formerly Fabes), Ph.D.
Associate Program Director - Regulatory
Genentech
1 DNA Way, South San Francisco, Ca 94080
(650) 467-3521
[redacted] (b) (6) (mobile)

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--
Sarah Oliver (formerly Fabes), Ph.D.
Associate Program Director - Regulatory
Genentech
1 DNA Way, South San Francisco, Ca 94080
(650) 467-3521
[redacted] (b) (6) (mobile)

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BEATRICE A KALLUNGAL
09/19/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver (oliver.sarah@gene.com)
Cc:	Kallungal, Beatrice
Subject:	BLA 125486, Obinutuzumab/GA101 - Information Request - Carton and Container labeling review - 09/13/2013
Date:	Friday, September 13, 2013 4:14:54 PM

Dear Sarah,
We have reviewed the proposed carton and container labeling for Obinutuzumab BLA 125486. Please revise as follows:

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)
For Intravenous Infusion after Dilution

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

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

6. Revise [redacted] (b) (4) 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. Carton Labeling

7. Ensure the carton labeling complies with recommendations A1 through A6.

C. Vial Cap and Ferrule

8. 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, 2013. We refer you to the following address:

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

Please respond to this information request and submit the revised carton and container labeling to the BLA by **3 PM Friday, September 20, 2013**.

Thanks,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
09/13/2013

MEMORANDUM OF TELECONFERENCE

Teleconference Date: September 6, 2013 at 9-10A.M. Eastern Standard Time (EST)

Application Number: 125486
Product Name: Obinutuzumab
Sponsor/Applicant Name: Genentech, Inc.

Subject: Follow-up of IRs sent

FDA Participants:

Marjorie Shapiro, Ph.D.	Lab Chief, DMA
Laurie Graham, M.S.	Team Lead, DMA
Chikako Torigoe, Ph.D.	Product Quality Reviewer, DMA
Mate Tolnay, Ph.D.	Product Quality Reviewer, DMA
Lyndsay Hennessey	Regulatory Project Manager, OBP

Sponsor/Applicant Participants:

Process Development Drug Substance:	Annika Kleinjans, Christian Hakemeyer, Frank Zettl, Wolfgang Kuhne
Drug Product Manufacturing:	Thorsten Herkert
Analytical Development:	Nadja Alt, Felix Kepert, Gerald Gellermann, Hans Koll
Supply Clinical Trials:	Rolf Schiffmann
Technical Regulatory:	Elisabeth Kirchisner, Stephane Avella, Holger Raviol, Ines Krämer
Project Management:	Jacques Bourquin, Batu Berkok
Analytical Development:	Christof Finkler, Niklas Engler

1.0 BACKGROUND:

The following Agenda items were provided to the sponsor:

1. August 26, 2013 IR: Questions 1a and 2
2. Hold-times studies: additional information (CQAs data in addition to [redacted] (b) (4)) was provided after the 7/26 meeting – Agency requests further discussion on the appropriateness [redacted] (b) (4)
3. Status update on the outstanding microbiology data referenced in communication "FEEDBACK ON ADDITIONAL FDA COMMENTS ON MICROBIOLOGICAL ASPECTS WHICH WERE RECEIVED DURING THE OBINUTUZUMAB PRE-BLA MEETING (05 MARCH 2013)"

The sponsor stated that "concerning topic No. 3 (microbiological aspects) we will not be able to provide details, but only a high-level overview. Unfortunately, our microbiological experts will not be able to join today but we might be able to discuss more details next week or the week after". The Agency decided to wait until the following meeting to discuss the microbiology data status update.

2.0 DISCUSSION:

August 26, 2013 IR Question 1a Discussion:

The Agency acknowledged that the CD20 Biacore assay is not critical to have. The Agency asked the sponsor three questions relating to this assay: (1) what is the concentration of obinutuzumab (2) what is the signal being measured and (3) why are there [redacted] (b) (4) *different flow rates for injection? The sponsor stated they would follow up with their expert and provide a response.*

The Agency further questioned the significance of the low level obinutuzumab binding to the CD20 peptide. The sponsor said their intent was to have the surface saturated with antigen so that the antibody could bind and measure the mass concentration at different flow rates. The sponsor wanted to clarify with the Agency if what they wanted was to have an understanding and justification for the use of the assay.

August 26, 2013 IR Question 2 Discussion:

The Agency stated they were concerned with the exact variances on PK. They were not confident that the impact assessment was reliable in comprehending the effects on PK, especially since the FcRn assay was not validated. The Agency recommended looking at the limitations of PK in the overall strategy to ensure risk is addressed. The Agency wanted to clarify that they were not discouraging the use of a novel assay.

Hold-times studies Discussion:

The Agency asked the sponsor their rationale for (b) (4)

Additional Comments:

The Agency asked the sponsor to clarify that (b) (4) *The sponsor offered to have a discussion regarding this at the late cycle meeting. The Agency will follow-up. In addition, the Agency notified the sponsor that several Information Request letters may be provided in September.*

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/s/

LYNDSAY J HENNESSEY
09/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your biologics license application (BLA) dated April 22, 2013, received April 22, 2013, submitted under section 351 of the Public Health Service Act for Obinutuzumab (GA101, RO5072759).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application:

[Drug Substance]

PC/PV studies (General)

(b) (4)

1 Page has been Withheld in Full as b4(CCI/TS) immediately following this page

(b) (4)

CQA Assessment

The limit of leachables is (b) (4). During the pre-licensure inspection, you stated that the level was determined based on potential geno-toxicity. Provide the literature that supports this limit.

Design Space

1. Clarify how the number of (b) (4) is accounted for in the design space.

(b) (4)

[Drug Product]

For the drug product manufacturing process development

(b) (4)

For the formulation robustness assessment ("Drug Product" in 3.2.P.2)

a) Provide the confidence limit and the numerical criteria used to evaluate the significance of the regression coefficients.

b) Provide the *p*-values to evaluate the regression models (Table 9).

We request a written response to the items enumerated above by September 11, 2013 in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of the other sections of your application is continuing.

If you have any questions, please contact me at (240) 402-3746.

Sincerely,

{See appended electronic signature page}

Lyndsay Hennessey
Quality Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Lyndsay.Hennessey@fda.hhs.gov

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/s/

LYNDSAY J HENNESSEY
09/06/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your biologics license application (BLA) dated April 22, 2013, received April 22, 2013, submitted under section 351 of the Public Health Service Act for Obinutuzumab (GA101, RO5072759).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application:

1. Regarding the characterization of obinutuzumab:
    a. Provide a more detailed description of the Biacore assay used to monitor binding to CD20 antigen, together with representative data. Was the affinity determined using a full kinetic analysis?

    b. We note a [redacted] (b) (4) on the non-reduced SDS-PAGE gel that is unidentified [redacted] (b) (4) in Figure 40, Section 3.2.S.3.1.5.1.12). Provide a risk assessment for this [redacted] (b) (4)

2. For [redacted] (b) (4), we recommend that you reconsider the impact and uncertainty risk scores for PK. We note that the [redacted] (b) (4), and the reference included in your letter of July 24 has limited relevance.

3. Regarding obinutuzumab Reference Standards:

    a. Clarify the statement regarding the retesting of the secondary reference standard (SRS), "Retesting is performed through trend analysis of data (e.g. historical reference standard data generated during product release and/or stability testing) or by real-time testing (using a retesting protocol) of stability indicating analytical

procedures." It is not clear what is meant by "real-time testing". We understand that the trend analysis will be performed on results obtained from the reference standard used for release and stability testing.

b. Clarify your proposal for the qualification of future primary reference standards (PRS) and SRS. We note Table 5 proposes acceptance criteria for test methods that are part of release and stability testing; however, we're not sure we understand footnote "a". Does this indicate that results for a new PRS or SRS from methods such as CE-SDS and (b) (4) don't need to be comparable to results from the old reference standards? Also, justify the limited extended characterization methods for qualification of new PRS (Table 6). Wouldn't a more thorough characterization of the PRS be required for future comparability studies?

4. Please indicate whether inter-day precision and inter-analyst precision of the second generation immunogenicity assay were evaluated, and if yes, provide an assessment.

We request a written response by September 3, 2013 to the items enumerated above in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of the other sections of your application is continuing.

If you have any questions, please contact me at (240) 402-3746.

Sincerely,

{See appended electronic signature page}

Lyndsay Hennessey
Quality Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Lyndsay.Hennessey@fda.hhs.gov

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/s/

LYNDSAY J HENNESSEY
08/26/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab/GA101 - Information Request - Microbiology - 08/26/2013
Date:	Monday, August 26, 2013 2:24:43 PM

Dear Sarah,
Please provide the information requested below by **3 PM Tuesday, September 10, 2013** via e-mail and officially submit to the BLA.

The proposed labeling indicates that the prepared infusion solution may be stored for up to 24 hours at 2-8°C. Please submit microbiological studies in support of the 24 hour post-dilution storage time at 2-8°C. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, and use the label-recommended diluent. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of this data, the product labeling should recommend that the post-dilution storage period is not more than 4 hours at 2-8°C.

Thanks,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
08/26/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	RE: BLA 125486 - Obinutuzumab/GA101 - Information Request follow-up - Clinical Pharmacology - 08/23/2013
Date:	Friday, August 23, 2013 11:39:58 AM

Dear Sarah,
Thank you for your prompt response to our information request. Please provide the additional information requested below by **Noon, Wednesday, August 28, 2013** via e-mail and officially submit to the BLA.

Since your long term stability data is not available for review, please provide a table by submitted trial and then storage temperature indicating the mean +/- SD and median (range) sample storage time prior to analysis.

Thanks,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

From: Sarah Oliver [mailto:oliver.sarah@gene.com]
Sent: Wednesday, August 21, 2013 1:54 PM
To: Kallungal, Beatrice
Subject: Re: BLA 125486 - Obinutuzumab/GAZYVA - Information Request - Clinical Pharmacology - 08/15/2013

Hi Beatrice -

In response to the Agency's request for the addendum to the validation reports for report #1048588, given the stability still looked appropriate, the long-term frozen matrix stability testing was (b) (4) (b) (4) The expected end of the study (b) (4) No interim report in available at this time and will be generated at a later date to include the (b) (4) data.

Please let me know if you have any questions. I will submit this response, along with the other responses provided this week to the BLA shortly.

Kind regards,

Sarah

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/s/

BEATRICE A KALLUNGAL
08/23/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

GENERAL ADVICE

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your Biologics License Application (BLA) dated April 22, 2013 submitted under section 351 of the Public Health Service Act for obinutuzumab (GA101, RO5072759).

We also refer to the mid-cycle communication document issued on August 16, 2013, containing the record of the teleconference between your firm and the FDA on August 06, 2013.

This general advice letter is an addendum to the mid-cycle communication to document Genentech's presentation of the survival analysis data, as summarized below.

Additional Meeting Discussion:
Genentech announced that they had conducted a survival analysis from Stage 1A, and that the results demonstrated a survival advantage for obinutuzumab. (b) (4)

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, M.S., RN, ACNP-BC
Lead Clinical Analyst, Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

VIRGINIA E KWITKOWSKI
08/20/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab - Information Request - Clinical Pharmacology - 08/16/2013
Date:	Friday, August 16, 2013 4:50:51 PM

Dear Sarah,
Please find below an information request for BLA 125486.

Please amend your pop-PK dataset (poppk.xpt) to include a column that identifies the lab where the PK samples were assayed (i.e., Roche (b) (4) *for each subject. Please submit this revised dataset. If the assay lab can be identified by trial then the sponsor may submit a simple table identifying the trial # and lab where the samples were assayed for that entire trial, rather than update the dataset.*

Please submit your response to this request by 3 pm Wednesday August 21, 2013 via e-mail and officially submit to the BLA.

Thanks,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
08/16/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

MID-CYCLE COMMUNICATION

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Obinutuzumab (GA101, RO5072759).

We also refer to the teleconference between representatives of your firm and the FDA on August 06, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

MID-CYCLE COMMUNICATION

Meeting Date and Time: August 06, 2013 11:00 AM – 12:00 PM EDT

Application Number: BLA 125486
Product Name: Obinutuzumab (GA101, RO5072759)
Indication: For the treatment of patients with previously untreated chronic lymphocytic leukemia
Applicant Name: Genentech

Meeting Chair: Virginia Kwitkowski, M.S., RN, ACNP-BC
Meeting Recorder: Beatrice Kallungal, B.S.

FDA ATTENDEES

CDER Participants:
Office of Hematology and Oncology Products (OHOP)
Tamy Kim, Pharm.D., Associate Director of Regulatory Affairs

Division of Hematology Products
Ann Farrell, M.D., Division Director
Edvardas Kaminskas, M.D., Deputy Division Director
Robert Kane, M.D., Ph.D., Deputy Director Safety
Virginia Kwitkowski, M.S., RN, ACNP-BC, Lead Clinical Analyst, Clinical Team Leader
Hyon-Zu Lee, Pharm.D., Clinical Reviewer
Barry Miller, M.S., CRNP, Clinical Reviewer
Qin Ryan, M.D., Ph.D., Safety Medical Officer
Diane Leaman, B.S., Safety Regulatory Project Manager
Ebla Ali Ibrahim, M.S., Lead Regulatory Health Project Manager
Theresa Carioti, MPH, Acting Team Leader, Regulatory Project Manager
Beatrice Kallungal, B.S., Regulatory Project Manager

Office of Biostatistics
Chia-Wen Ko, Ph.D., Reviewer

Division of Hematology Oncology Toxicology
Haleh Saber, Ph.D., Supervisory Pharmacologist
Stacy Ricci, Ph.D., Reviewer
Pedro DelValle, Ph.D., Reviewer

Reference ID: 3358946

Office of Clinical Pharmacology
Julie Bullock, Pharm.D., Team Leader
Joseph Grillo, Pharm.D., Reviewer

Office of Scientific Investigations, Division of Good Clinical Practice Compliance
Anthony Orencia, M.D., F.A.C.P., Medical Officer

Office of Pharmacovigilance and Epidemiology, Division of Pharmacovigiliance
Peter Waldron, M.D., Medical Officer
Tracy Salaam, Pharm.D., Safety Evaluator Team Leader

Office of Planning and Informatics (OPI)
Kimberly Taylor, Operations Research Analyst

Office of Manufacturing and Product Quality (OMPQ)
Patricia Hughes, Ph.D., Microbiology, Team Leader
Marjorie Shapiro, Ph.D. Lab Chief, DMA
Laurie Graham, M.S. Team Lead, DMA
Colleen Thomas, Ph.D. Product Quality Microbiology Reviewer, BMAB
Kalavati Suvarna, Ph.D. Product Quality Microbiology Reviewer, BMAB
Lyndsay Hennessey Regulatory Project Manager, OBP

Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management (OMEPRM), Division of Medication Error Prevention and Analysis (DMEPA)
Kevin Wright, Pharm.D., Safety Evaluator

Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK)
Cynthia LaCivita, Pharm.D., Risk Management Analyst, Team Leader

EASTERN RESEARCH GROUP ATTENDEES
Patrick Zhou, Independent Assessor
Chris Sese, independent Assessor

APPLICANT ATTENDEES
Elina Asikanius, Biometrics
Stephane Avella Regulatory Program Manager
Christina Baladi, Regulatory Affairs Associate
Jacques Bourquin, Technical Team Lead
Michael Brewster, Clinical Pharmacology
Thomas Buechele, M.D., Global Lifecycle Leader
Guenter Fingerle-Rowson, M.D. Associate PD Medical Director
Kathryn Humphrey, Clinical Science
Elisabeth Husar Ph.D., Toxicology Lead
Ines Kraemer, CMC Regulatory Team Leader
Nafsika Kronidou Horst, Ph.D., Global Regulatory Leader

Reference ID: 3358946

Hanna Piper-Lepoutre, Safety Scientist Lead
Joerg Maurer, Biometrics Project Lead
Jeffrey Miller , Regulatory Team Leader-Hematology
Sarah Oliver, Ph.D., US Regulatory Lead
Nancy Valente, M.D., Vice President Head Global Hematology Development
Elisabeth Kirchisner, CMC Regulatory Affairs

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Clinical
No issues identified to date.

Product Quality Microbiology
Because the microbial retention capability of the [redacted] (b) (4) As discussed during the July 26, 2013 CMC teleconference, the study should be repeated as [redacted] (b) (4) We acknowledge receipt of your post-meeting comments from the July 26, 2013 CMC teleconference, which indicate that the microbial retention study data and report will be available the week of October 7, 2013. Please submit this information to the BLA as soon as it is available.

3.0 INFORMATION REQUESTS

Product Quality Microbiology
The information provided in the July 24, 2013 amendment is under review and additional information requests will be sent.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT
At this time, there are no major safety concerns identified and currently, there is no need for a Risk Evaluation and Mitigation Strategy (REMS).

5.0 ADVISORY COMMITTEE MEETING
At this time, there are no plans for an Advisory Committee meeting.

Reference ID: 3358946

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The late-cycle meeting is scheduled for September 16, 2013 at 3:00 PM EDT. We plan to communicate proposed labeling and, if necessary, any post-marketing requirement/commitment requests by October 25, 2013. As communicated earlier, the user fee goal date for BLA 125486 is December 20, 2013.

7.0 ATTACHMENTS AND HANDOUTS

The sponsor also shared with the Agency the following PowerPoint presentation (b) (4)

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Reference ID: 3358946

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/s/

ANN T FARRELL
08/16/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab/GAZYVA - Information Request - Clinical Pharmacology - 08/15/2013
Date:	Thursday, August 15, 2013 3:39:41 PM

Dear Sarah,
Please find below an information request for BLA 125486.

We note your assay validation report #1048588 [redacted] (b) (4) *states "Long-term frozen matrix stability will be determined at three time points (3, 6, 12 months) at both −20°C and −80°C under a separate project code. The results of these analyses will be reported as an addendum(s) to the validation report." We cannot locate this addendum in your submission. Please identify the location or submit this information.*

Please submit your response to this request by 3 pm Wednesday August 21, 2013 via e-mail and officially submit to the BLA.

Thanks,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
08/15/2013

From: Kallungal, Beatrice
To: Sarah Oliver
Cc: Kallungal, Beatrice
Subject: BLA 125486 - Obinutuzumab/GAZYVA - Information Request - Clinical Pharmacology - 08/14/2013
Date: Wednesday, August 14, 2013 12:41:33 PM

Dear Sarah,
Please find below an information request for BLA 125486.

We note your validation report for the ELISA developed by (b) (4) *and used to detect obinutuzumab concentrations in your clinical trials reports* (b) (4) *Unfortunately we cannot find similar "Goodness of fit" information for your Roche assay that was also used to detect obinutuzumab concentrations in your clinical trials.*

Please submit your response to this request by 3 pm Tuesday August 20, 2013 via e-mail and officially submit to the BLA.

Thanks,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
08/14/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your biologics license application (BLA) dated April 22, 2013, received April 22, 2013, submitted under section 351 of the Public Health Service Act for Obinutuzumab (GA101, RO5072759).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application.

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

1. Please provide the acceptance criterion used for the internal control to ensure consistent [redacted] (b) (4). Information on the impact of spiked sample storage on [redacted] (b) (4) should be provided.

2. Please clarify which of the assay validation activities used more than one analyst.

3. Please clarify how false positive Cps are assessed.

4. Please explain how cycle threshold was determined for the Leptospira PCR assay.

5. Please commit to evaluate the matrix interference and sensitivity of the Leptospira assay if used to test samples of obinutuzumab [redacted] (b) (4) where the [redacted] (b) (4) [redacted].

We request a written response by August 22, 2013 to the items enumerated above in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of the other sections of your application is continuing.

If you have any questions, please contact me at (240) 402-3746.

Sincerely,

{See appended electronic signature page}

Lyndsay Hennessey
Quality Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Lyndsay.Hennessey@fda.hhs.gov

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/s/

LYNDSAY J HENNESSEY
08/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your biologics license application (BLA) dated April 22, 2013, received April 22, 2013, submitted under section 351 of the Public Health Service Act for Obinutuzumab (GA101, RO5072759).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application:

We acknowledge that [redacted] (b) (4) Please address the following comments and questions related to the [redacted] (b) (4)

1. [redacted] (b) (4)
2. [redacted] (b) (4)

[redacted] (b) (4)

(b) (4)

(b) (4)

We request a written response by August 31, 2013 to the items enumerated above in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of the other sections of your application is continuing.

If you have any questions, please contact me at (240) 402-3746.

Sincerely,

{See appended electronic signature page}

Lyndsay Hennessey
Quality Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Lyndsay.Hennessey@fda.hhs.gov

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/s/

LYNDSAY J HENNESSEY
08/12/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab/GAZYVA - Information Request - Non-clinical - 08/08/2013
Date:	Thursday, August 08, 2013 11:43:01 AM

Dear Sarah,
Please find below an information request for BLA 125486.

Please refer to your original BLA submission, Section 3.2.S.2.3 Control of Materials, Attachment 3.

1. Provide the references used for calculation of ADEs for the following compounds:

(b) (4)

2. Provide the safety factors used in your calculations, e.g. safety factors used for oral to intravenous extrapolation and for animal to human conversions if animal data were used.

Please submit your response to this request by 3 pm Thursday August 15, 2013 via e-mail and officially submit to the BLA.

Thanks,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
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/s/

BEATRICE A KALLUNGAL
08/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your biologics license application (BLA) dated April 22, 2013, received April 22, 2013, submitted under section 351 of the Public Health Service Act for Obinutuzumab (GA101, RO5072759).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application:

A response to the following comments (#1-10) should be submitted by August 14, 2013.

<u>Product Quality Microbiology (drug product)</u>

1. Please respond to the following comments regarding environmental and personnel monitoring for [redacted] (b) (4).
   a. Tables 11 and 12 in the process validation report (section P.3.5) do not include alert limits for environmental and personnel monitoring. Provide tables that show both action limits and alert limits.
   b. Provide the incubation conditions for environmental monitoring samples.

2. Please list the interventions typically performed during [redacted] (b) (4). Indicate other ways in which the [redacted] (b) (4) simulate worst-case conditions [redacted] (b) (4).

3. Please respond to the following comments regarding each of the [redacted] (b) (4).
   a. Describe the container closure system, fill volume, number of units filled, number of units incubated, and number of units filled but not incubated (briefly explain why these units were excluded).

b. Indicate the hold time after (b) (4) .

c. Provide the growth promotion test procedure and the growth promotion test results for incubated containers.

d. Provide the (b) (4) reports.

4. Please provide the (b) (4) for the 50 ml vial.

5. Please respond to the following comments regarding sterilization/depyrogenation of the 50 ml vial (b) (4)

(b) (4)

6. List the items (b) (4) for validation studies.

7. Please respond to the following comments regarding stopper sterilization validation.

(b) (4)

8. Please respond to the following comments regarding 20 mm stopper depyrogenation validation.

a. Provide the parameters for the stopper (b) (4).

b. State the number of endotoxin-spiked positive controls prepared for each validation load.

c. Briefly describe the endotoxin indicator and the methods used for spiking and recovery. Indicate whether the EU/item results were obtained from individual stoppers or from pooled samples. Explain how the EU/item results are reported (min, max, or average).

9. Please respond to the following comments regarding (b) (4).

(b) (4)

10. Please respond to the following comments regarding (b) (4)

(b) (4)

A response to the following comments (#11-16) should be submitted by August 19, 2013.

11. Regarding comparability of (b) (4) manufacturing processes,

(b) (4)

(b) (4)

12. For raw materials, it is unclear how estimated daily intake is calculated for complex proprietary materials containing multiple unknown chemicals, for which the manufacturer did not provide maximum concentration values. Please provide an explanation.

13. During characterization of the ADCC bioassay, (b) (4) Please clarify.

14. Regarding the assessment of color for drug substance and drug product, it is stated that the color of the solution may be determined using (b) (4) instead of the visual inspection method according to Ph. Eur. 2.2.2. Provide a description of the method incorporating (b) (4) and the validation of its use.

15. Regarding Drug Substance stability, (b) (4)

16. Regarding the immunogenicity assays,
    a. Provide the total number of inconclusive HAHA results obtained in assessing clinical samples.
    b. When testing samples using the (b) (4) HAHA assay, (b) (4) . Please indicate how long samples can be stored and the storage temperature. Also indicate whether a similar requirement is in place for the (b) (4) HAHA assay.

We request a prompt written response to the items enumerated above in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of the other sections of your application is continuing.

If you have any questions, please contact me at (240) 402-3746.

Sincerely,

{See appended electronic signature page}

Lyndsay Hennessey
Quality Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Lyndsay.Hennessey@fda.hhs.gov

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/s/

LYNDSAY J HENNESSEY
08/06/2013

MEMORANDUM OF TELECONFERENCE

Teleconference Date: July 26, 2013 at 9:00-10:00A.M. Eastern Standard Time (EST)

Application Number: 125486
Product Name: Obinutuzumab
Sponsor/Applicant Name: Genentech, Inc.

Subject: Follow-up of July 12, 2013 IR and Discussion of Sponsor's Response to July 23, 2013 IR

FDA Participants

Marjorie Shapiro, Ph.D.	Lab Chief, DMA
Laurie Graham, M.S.	Team Lead, DMA
Chikako Torigoe, Ph.D.	Product Quality Reviewer, DMA
Mate Tolnay, Ph.D.	Product Quality Reviewer, DMA
Patricia Hughes, Ph.D.	Team Lead, BMAB
Donald Obenhuber, Ph.D.	Product Quality Microbiology Reviewer, BMAB
Colleen Thomas, Ph.D.	Product Quality Microbiology Reviewer, BMAB
Kalavati Suvarna, Ph.D.	Product Quality Microbiology Reviewer, BMAB
Lyndsay Hennessey	Regulatory Project Manager, OBP

Sponsor/Applicant Participants

Process Development Drug Substance:	Annika Kleinjans, Christian Hakemeyer, Frank Zettl, Wolfgang Kuhne
Process Development Drug Product:	Christine Wurth, Alexander Streubel
Drug Product Manufacturing:	Tobias Vocke
Microbiology:	Ulf Gurok, Friedrich von Wintzingerode, Holger Kavermann, Wilfried Cyrol, Andreas Krug
FcRn assay:	Tilman Schlothauer
Analytical Development:	Nadja Alt, Felix Kepert, Gerald Gellermann, Christof Finkler, Niklas Engler
Commercial Analytics:	Klaus Leonhard
Technical Regulatory:	Elisabeth Kirchisner, Stephane Avella, Holger Raviol, Ines Krämer

1.0 BACKGROUND:

A Quality Information Request (IR) was sent to the sponsor on July 23, 2013 which the sponsor responded to July 24, 2013. This meeting was held to discuss the responses provided by the sponsor.

The sponsor stated that they were in agreement with the minutes provided from the July 19, 2013 meeting and no further discussion or clarification was needed.

2.0 DISCUSSION:

Information Request provided July 12, 2013

IR 11: Insufficient information was provided to support that the (b) (4) is sufficiently representative of the manufacturing scale data. Specifically,

(b) (4)

IR 11 Meeting Discussion:

In their IR response, the Sponsor provided data demonstrating a decrease in detectable levels (b) (4). The Agency asked for further clarification with regard to (b) (4). Specifically, the Agency wanted to know whether the differences observed in (b) (4) The Sponsor indicated that while the (b) (4)

(b) (4) the Agency asked whether there was manufacturing scale data from additional products that would demonstrate an increase in (b) (4) The sponsor responded (b) (4).

The Agency stated that, in general, there is a concern (b) (4)

(b) (4)

IR 12: Provide additional information on how worse case rates for hold times were calculated, including the criteria used to select the models for the calculation.

IR 12 Meeting Discussion: ***The Agency inquired how the sponsor decides whether a model was acceptable to be used. For example,*** (b) (4) ***In addition, the Agency asked about*** (b) (4) ***to the hold time studies, which appear to rely on*** (b) (4) ***The Agency asked how the sponsor was able to bridge the two studies when the effects seen were not linear. The sponsor indicated that they needed to consult with their experts and that the topics of model fit and linearity could be discussed at a future meeting.***

The Agency indicated that there was a lack of clarity (b) (4)

IR 14: Provide a justification for extrapolation of the (b) (4) hold time data to (b) (4) (b) (4)

IR 14 Meeting Discussion: ***The sponsor provided data for five manufacturing scale runs held for*** (b) (4) ***; however, they are asking for a hold time of*** (b) (4) ***The Agency stated that this will be a review issue, but there are concerns regarding the*** (b) (4) ***hold time data based only*** (b) (4)***.***

Information Request provided July 23, 2013

July 12th IR 1a Follow-up: Thank you for providing assay descriptions. Please clarify whether in the Biacore assay β2m is co-immobilized with FcRn, as shown in Figure 1 of Attachment 1.

July 12th IR 1c and d Follow-up: We acknowledge that the affinity chromatography method yielded results that correlated with clearance in human FcRn transgenic mice. However, the extent of this correlation is unclear due to the limited data set. In particular, it is unclear whether product variants that displayed altered binding in the Biacore assay, but not in the affinity chromatography assay, show altered PK properties or not. For such variants, assessment of clearance based on literature references is an option, as discussed during the July 19th meeting. Until further assessment is provided, it is uncertain which of the two FcRn assays better predict PK properties.

IR 1a, c and d Follow-up Meeting Discussion: ***The Agency confirmed that the references provided for the clearance of product variants looked reasonable to include in assessing the impact of each variant on FcRn mediated clearance. Based on the references, glycosylation variants appeared not to impact clearance. However, the Agency will have to look further into the clearance of charge variants, for which one reference using a rat model was provided.***

IR 1: Please provide the study report for the low endotoxin recovery (LER) study performed with the drug substance. Provide the endotoxin results for individual test and control samples, the % CV for duplicate samples, and the sample pH.

IR 1 Meeting Discussion: ***The sponsor stated that there is a full study report for the low endotoxin recovery in German, however the data provided in Attachment 1 of the IR response contains the data from this study. The Agency stated that Attachment 1 was sufficient. The Agency asked if additional studies were conducted with different concentrations of endotoxin in order to determine whether the endotoxin recovery rate declines more rapidly at lower concentrations. The sponsor did have studies of other products with a high concentration but did not observe the recovery of endotoxin. The Agency asked whether lower endotoxin concentrations were ever tested. The sponsor stated they will need to check but the concentration of (b) (4) is usually done. The sponsor stated that if you spike with a lower concentration, the test samples are too close to the detection limit of the assay. Therefore the concentration of (b) (4) provides a good detectability range.***

IR 8: Please address the following comments regarding the microbial retention study for the (b) (4)

a. Provide the microbial retention study report.
b. Provide the viability data for *B. diminuta* in the presence of the product.
c. (b) (4) . Indicate any other attempts to overcome the bactericidal effect, such as performing the study with a higher inoculum level, using a reduced exposure time, etc. If no additional studies were done, propose a strategy and timeframe for conducting these studies.

IR 8 Meeting Discussion: ***The Agency indicated that the parameters for the microbial retention study (pressure, batch size, etc.) appeared to be acceptable, but the study did not consider the effect of the drug product on the microbial suspension. The Agency pointed out that long exposure times were used for the viability study and asked whether the microbial retention study could be repeated with the challenge organism suspended in the drug product for a reduced exposure time during stage 2 of the test. The sponsor agreed, and stated that the microbial retention test did include a (b) (4) The sponsor will repeat the microbial retention study (b) (4)***

(b) (4). ***The sponsor is discussing the test schedule with the contract laboratory. The sponsor indicated that it should be feasible to provide the data by the end of November but that the target date would be the end of October. The Agency indicated that they would like to have the data as soon as possible in order to complete the review. The sponsor will follow up with a time frame.***

The Agency asked whether the (b) (4) ***The sponsor indicated that the time for*** (b) (4) ***during routine production is normally*** (b) (4) ***but the sponsor wants to qualify the process for*** (b) (4) ***to*** (b) (4)

(b) (4)

IR 16 Meeting Discussion: (b) (4)

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***Leptospira* PCR**

<u>Leptospira PCR Discussion:</u> The Agency asked the sponsor whether they observed any Leptospira contamination issues at the Pennsburg facility. The sponsor responded that there were no Leptospira contamination at the Pennsburg site and that implementation of Leptospira PCR was built into the control strategy for all sites and products due to contamination observed with another product at the Vacaville site in California. The Agency

also inquired if the PCR amplicons were sequenced by the vendor who supplied the primers. (b) (4) ***. The sponsor further explained that the internal control was a*** (b) (4) ***; therefore, non-specific amplicons were not expected to be present. The Agency stated they would like to see raw data and PCR graphs. The sponsor confirmed they would provide these.***

In addition, the Agency asked if acceptance criteria for (b) (4) ***should be set to*** (b) (4) ***rather than*** (b) (4) ***The sponsor clarified that homology of the primer for several Leptospira species shown in Table 1 of the validation report was determined. Based on this information, the sponsor stated that all pathogenic Leptospira species can be detected.***

Furthermore, the Agency inquired about the (b) (4) ***that was tested during the validation of the assay.*** (b) (4) ***The sponsor stated they have to review their validation study and would provide the data.***

3.0 ACTION ITEMS:

- Next teleconference will cover the hold time models in addition to any further questions regarding the July 23, 2013 IR
- Another IR will be provided the week of July 29th, 2013
- After the inspection, DMA will issue an IR with the final drug substance issues/requests

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/s/

LYNDSAY J HENNESSEY
07/31/2013

MEMORANDUM OF TELECONFERENCE

Teleconference Date: July 19, 2013 at 9:00-10:00A.M. Eastern Standard Time (EST)

Application Number: 125486
Product Name: Obinutuzumab
Sponsor/Applicant Name: Genentech, Inc.

Subject: Discussion of Sponsor's Response to July 12, 2013 IR

FDA Participants

Marjorie Shapiro, Ph.D.	Lab Chief, DMA
Laurie Graham, M.S.	Team Lead, DMA
Chikako Torigoe, Ph.D.	Product Quality Reviewer, DMA
Mate Tolnay, Ph.D.	Product Quality Reviewer, DMA
Donald Obenhuber, Ph.D.	Product Quality Microbiology Reviewer, BMAB
Colleen Thomas, Ph.D.	Product Quality Microbiology Reviewer, BMAB
Lyndsay Hennessey	Regulatory Project Manager, OBP
Beatrice Kallungal	Regulatory Project Manager, DHP

Sponsor/Applicant Participants

Markus Hammel	Cell Banking
Christian Hakemeyer	Cell Culture Development
Annika Kleinjans	DSP Development
Frank Zettl	DSP Development
Nadja Alt	Analytics
Gerald Gellermann	Analytics
Klaus Leonhard	Analytics
Michael Wiedmann	Analytics
Felix Kepert	Analytics
Til Schlothauer	FcRn
Ulf Gurok	Microbiology
Elisabeth Kirchisner	PTR
Stephane Avella	PTR
Ines Krämer	Management
Niklas Engler	Management
Wolfgang Kuhne	Management

1.0 BACKGROUND:

A Quality Information Request (IR) was sent to the sponsor on July 12, 2013 which the sponsor responded to July 18, 2013. This meeting was held to discuss the responses provided by the sponsor.

At the start of the meeting, Genentech stated that a few figures appeared to have been corrupted once publishing was applied and therefore they would resubmit the response indicating which figures were affected.

2.0 DISCUSSION:

IR 1: Regarding the surface plasmon resonance and affinity chromatography assays used to assess FcRn binding, only brief descriptions are provided in 3.2.S.3.1.

a. Provide a detailed description of both the FcRn surface plasmon resonance and FcRn affinity chromatography assays, including assay qualifications and variability of the assays, if available.
b. The FcRn surface plasmon resonance assay appears to include a single injection of product, measuring the signal at the end of the association phase. Such measurement will not provide the on-rate of the interaction. Furthermore, because the molecular mass of the protein in solution directly impacts the signal, the assay appears particularly unsuitable to assess FcRn binding of product variants with molecular masses significantly different than that of the reference standard. To assess FcRn binding, we recommend performing a full kinetic analysis.
c. It is not clear if the FcRn affinity chromatography method is physiologically relevant. In addition, data included in the submission using the FcRn affinity chromatography assay indicated no more than 10% changes in column retention times for the assessed variants, and analysis was not provided as to what change was statistically significant. Provide data supporting sufficient sensitivity of this assay, as well as justification that the assay is a relevant surrogate for in vivo product half-life.
d. The two FcRn assays appear complementary, with the surface plasmon resonance assay reflecting the association phase of the interaction and the affinity chromatography assay reflecting the dissociation phase. The Biacore assay appears more sensitive than the affinity chromatography method, as it detected significant differences in the binding of differentially galactosylated variants, charge variants, and deglycosylated product. However, based on the negative results of the FcRn affinity chromatography assay for these variants, it was concluded that the modifications have no impact on FcRn binding. Provide clarification and justification for your overall approach. We note your reference to a human FcRn transgenic mouse model. Clarify if you have used this model to assess the in vivo product half-life and, if such data are available, if there is a correlation with data obtained using the in vitro assays.

IR 1 Meeting Discussion: ***The sponsor provided a response to this request in their July 18, 2013 submission in addition to a slide presentation attached to the end of this document.***

- ***(a) In regards to FcRn binding kinetics, Agency recommended immobilizing the IgG so that the FcRn molecule in solution is monovalent, allowing for the calculation of KD. There has been published literature regarding this process which the Agency stated they would provide to the sponsor. However, the methods in these references*** (b) (4) ***do not need to be implemented at this time.***
- ***(b) The Agency agreed that the design of the current Biacore assay was useful for its intended purpose; however, we stated that in case of analytes with different molecular masses, the signal is also affected by the mass of the molecule. The sponsor confirmed that the same molar concentration is used for each sample. The Agency replied that aggregates will have increased molecular mass. In addition, the Agency pointed out that for samples 1-3 shown on Fig. 2, equilibrium binding was not reached during the time of the analysis.***
- ***(c) The Agency agreed that the chromatography assay provided was useful for its intended purpose. However, the pH of 8.8 appears high at the end of pH gradient. There is concern that if IgG binds at a higher pH level, the product may not dissociate and show abnormal FcRn binding in vivo. The Agency stated that they will need to review this further.***
- ***(d) The Agency asked whether the sponsor assessed the clearance of IgG variants that had altered binding in the Biacore assay, but not the chromatography method, in human FcRn transgenic mice. The sponsor responded that such testing was not conducted. The Agency inquired whether there is further support that the chromatography assay was a better indicator of FcRn binding than the Biacore assay. The sponsor replied that there is supporting literature, which they will provide to the Agency.***

IR 2: Regarding the Master Cell Bank, it is unclear how (b) (4) was achieved and verified. Provide data that support (b) (4) of the Master Cell Bank. Note that (b) (4).

IR 2 Meeting Discussion: ***The sponsor provided a response to this request in their July 18, 2013 submission. The Agency stated that the*** (b) (4) ***analysis performed by the sponsor will need to be reviewed in more detail. It appears that a few assumptions were made by the sponsor. The Agency stated that they will need to review this further.***

IR 3: Regarding 3.2.S.2.5 Process Validation and/or Evaluation,

a. In Site-specific process validation, (b) (4)

b. In Process consistency, (b) (4) Provide a description of the assays that were used to measure removal of the (b) (4) If the methods were qualified or validated, provide a summary of these

studies. In addition, provide a justification for why the [redacted] (b) (4) is considered a suitable marker for the removal of these [redacted] (b) (4).

IR 3 Meeting Discussion: ***The sponsor provided a response to this request in their July 18, 2013 submission. The Agency stated the response for part A was clarified but will need to review the response for part B further.***

IR 4: In section S.3.3 Materials, Preparation of product variants: [redacted] (b) (4).

IR 4 Meeting Discussion: ***The sponsor provided a response to this request in their July 18, 2013 submission. The Agency stated that this was clarified.***

IR 5: Provide an update to the status of the microbiology data referenced in the most recent communication "FEEDBACK ON ADDITIONAL FDA COMMENTS ON MICROBIOLOGICAL ASPECTS WHICH WERE RECEIVED DURING THE OBINUTUZUMAB PRE-BLA MEETING (05 MARCH 2013), Table 1 Additional FDA Comments for Drug Substance" dated 7/5/2013.

IR 5 Meeting Discussion: ***The sponsor provided a response to this request in their July 18, 2013 submission. The Agency stated that the data provided from the completed low endotoxin recovery studies*** [redacted] (b) (4) ***appeared to be adequate (additional information may be requested). It appeared that LER may not be a problem with the control hold times. The Agency stated that this may be acceptable solution as long as the samples are not held past the hold time.***

The Agency inquired whether process validation for hold time was completed during manufacturing. The sponsor replied that samples were only taken [redacted] (b) (4) ***to test endotoxin and bioburden. The Agency also inquired whether they looked into extended hold times or a max hold time. The sponsor stated that the validation process was an ongoing topic and will remain open.***

IR 6: Provide [redacted] (b) (4) sanitization and storage validation data prior to the pre-approval inspection.

IR 6 Meeting Discussion: ***The sponsor provided a status update to this request in their July 18, 2013 submission. A full response will be provided to the Agency July 25, 2013.***

IR 7: There are concerns that PK was underestimated in the critical quality attribute (CQA) risk assessments. Specifically:

a. Insufficient information was provided to support the methods used to assess binding of obinutuzumab to FcRn. See question 1.
b. Only the Fc region of obinutuzumab was considered for an impact on FcRn binding, and it has been reported that the Fab domain of antibodies can affect FcRn binding and PK (Wang, W. et al. (2011) Drug Metab. Dispos. **39**, 1469-1477; Mathur, A. et al. (J. Immunol. Methods, **390**, 81-91). Provide additional information to support the CQA risk assessment strategy of excluding the Fab region for an impact on FcRn binding.

IR 7 Meeting Discussion: ***The sponsor provided a response to this request in their July 18, 2013 submission in addition to a slide presentation attached to the end of this document. The Agency inquired as to whether there were any data assessing Fab variants of obinutuzumab for binding to FcRn and, if not, whether this should have resulted in an increase in the uncertainty scores in the CQA risk assessments. The Sponsor indicated that charge variants of obinutuzumab have been tested for FcRn binding with differences seen with the Biacore, but not the chromatography, based method .The Agency indicated that a final conclusion will be based on evaluating the sponsor's overall approach to assessing PK. The Agency reiterated that one of the main concerns is classifying variants as having a low impact on PK when the Biacore FcRn binding assay demonstrates an impact but the chromatography FcRn assay does not.***

IR 8: Provide clarification on which process characterization/process validation (PV/PV) studies were used to determine whether a critical quality attribute target range (CQA-TR) is needed for a CQA.

IR 8 Meeting Discussion: ***The sponsor provided a response to this request in their July 18, 2013 submission. The Agency stated that they will need to review this further. However, the Agency asked for clarification on how the sponsor uses PC/PV studies to determine whether a CQA-TR is needed for a CQA when having CQA-TRs is a prerequisite for evaluating certain PC/PV studies and calculating impact factors. The sponsor indicated that they use available information to determine if a CQA is likely to meet the criteria for not needing a CQA-TR.***

(b) (4)

IR 9: With regard to the qualification of the scale down production bioreactor:
a. For a number of CQA and key process indicators (KPI), it appears there was increased variability with the manufacturing scale bioreactor compared to the reduced scale bioreactor. It is unclear, therefore, if the small scale bioreactor is sufficiently representative of the manufacturing scale process. For example, differences in the

(b) (4)

<u>IR 9 Meeting Discussion:</u> The sponsor provided a response to this request in their July 18, 2013 submission.

(a) The Agency indicated that there is an overall expectation that differences in the variability of CQAs and KPIs between the manufacturing scale process and the scale down models would be considered and discussed with regard to the qualification of the scale down models.

(b) (4)

(d) The Agency stated they did not have any questions regarding the sponsor's response.

<u>IR 10:</u> For the qualification of the chromatography models, provide dot plots as performed for the production bioreactor (Figures 3 and 4 of Process Validation and/or Evaluation: Qualification of Scale-Down Models).

<u>IR 10 Meeting Discussion:</u> The sponsor provided a response to this request in their July 18, 2013 submission. The Agency stated they will need to review this further.

IR 11: Insufficient information was provided to support that the scale down (b) (4) is sufficiently representative of the manufacturing scale data. Specifically,

(b) (4)

(b) (4)

IR 11 Meeting Discussion: ***The sponsor provided a response to this request in their July 18, 2013 submission. Only part A was discussed during the meeting. The sponsor indicated that*** (b) (4) ***is acceptable for the qualification of scale down models used for*** (b) (4) ***The Agency stated they will need to review this issue which can be discussed further, if needed.***

3.0 ACTION ITEMS:

- In regards to Question 1b, we agree that the current Biacore assay is likely suitable for its intended purpose of assessing the relative on-rates of product variants, as long as the variants have similar molecular masses. For variants with significantly different molecular masses, such as HMWS, the differences in mass should be considered during analysis.

  We refer you to a study published by your colleagues at Genentech (*Yeung et al., 2009, J. Immunol., 182:7663*) containing a Biacore protocol to measure FcRn binding affinities. The method includes the following elements. (1) IgG is immobilized, while FcRn is run in solution, ideal due to the 1-2 molar interaction of IgG-FcRn. (2) Equilibrium dissociation constants are estimated by steady-state analysis, preferred with heterologous analytes and rapid interactions. (3) Low immobilization level (~100 RU) and relatively long association phase. We note additional publications of Biacore protocols that incorporate immobilization of IgG and steady-state analysis (*Dall'Acqua et al., 2002, J. Immunol., 169:5171; Oganesyan et al., 2009, Mol. Immunol., 46:1750)*).

- The sponsor will provide the Agency with the literature reference used to support their chromatography data.

- Further discussion of Question 1 will be held at the next meeting July 26, 2013

- An additional Quality IR will be sent to the sponsor

4.0 ATTACHMENTS AND HANDOUTS:

- Attached is the slide presentation provided by the sponsor.

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/s/

LYNDSAY J HENNESSEY
07/24/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your biologics license application (BLA) dated April 22, 2013, received April 22, 2013, submitted under section 351 of the Public Health Service Act for Obinutuzumab (GA101, RO5072759).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application:

Drug Product Testing

1. Please provide the study report for the low endotoxin recovery (LER) study performed with the drug substance. Provide the endotoxin results for individual test and control samples, the % CV for duplicate samples, and the sample pH.

2. Please address the following comments regarding endotoxin testing and endotoxin test method qualification (USP <85>) for the drug product.
   a. Recalculate the MVD based on the (b) (4) specification for the drug product.
   b. Provide all of the acceptance criteria for the endotoxin assay. The detection limit acceptance criterion should be based on the (b) (4) specification for the drug product.
   c. Regarding the endotoxin method qualification study, provide the endotoxin results for individual test and control samples, the % CV for duplicate samples, and the sample pH.

3. Please provide summary data and the study report for rabbit pyrogen testing of the drug product.

Drug Product Manufacturing

4. Please address the following comments regarding drug substance thawing:
   [redacted] (b) (4)
   b. Indicate whether the drug substance may be exposed to the environment (due to open operations) during multiple freeze/thaw cycles.

5. Please describe the packaging and labeling steps of the drug product manufacturing process.

6. The "Critical Process Parameters and Manufacturing Ranges" table in section 3.2.P.3.3 indicates that [redacted] (b) (4) may be performed [redacted] (b) (4) Please list all of the circumstances under which repetition of the [redacted] (b) (4) would be permitted [redacted] (b) (4)

7. Please address the following comments regarding the [redacted] (b) (4)
   a. Provide summary data and the validation report for the [redacted] (b) (4).
   b. Provide the [redacted] (b) (4) for the process validation lots [redacted] (b) (4) There appear to be errors in Table 6 of the process validation report provided in section 3.2.P.3.5 [redacted] (b) (4)

8. Please address the following comments regarding the microbial retention study for the [redacted] (b) (4).
   a. Provide the microbial retention study report.
   b. Provide the viability data for *B. diminuta* in the presence of the product.
   c. [redacted] (b) (4). Indicate any other attempts to overcome the bactericidal effect, such as performing the study with a higher inoculum level, using a reduced exposure time, etc. If no additional studies were done, propose a strategy and timeframe for conducting these studies.

9. Please address the following comments regarding crimping/capping forces and container closure integrity.
   a. Provide the acceptance criteria for crimping/capping forces used for routine production of the obinutuzumab drug product.
   b. Provide summary data and reports demonstrating container closure integrity for vials sealed with minimum and maximum crimping/capping forces. Describe the

container closure integrity test used for the study, including positive control preparation.

***Leptospira* PCR**

10. Please provide the raw data obtained for the *Leptospira* PCR assay validation and calculations of Cp values.
11. Please clarify if the PCR products were sequenced.
12. Please provide the *Leptospira* assay results for all obinutuzumab (b) (4) lots tested.
13. Please explain your choice of internal control for the assay.
14. Please explain how you assessed matrix interference for the *Leptospira* PCR assay. The (b) (4) age used in the matrix interference studies should be specified.
15. Please explain how the (b) (4) instrument performance is assessed and the frequency of the assessment.

PSD

16. The practically significant differences (PSDs) used for qualification of the scale down models and to assess round 1 site and scale independent process characterization/process validation (PC/PV) studies are not consistently determined for the different critical quality attributes (CQAs) and key process indicators (KPIs). Specifically, the size of the PSD relative to the standard deviation (SD) of the manufacturing-scale data is significantly different for different CQAs. (b) (4) For those CQAs and KPIs in which the manufacturing scale data demonstrates greater variation than the small scale models, provide additional information to justify the size of the PSDs.

Follow up questions to July 12, 2013 Information Request

Question 1a. Thank you for providing assay descriptions. Please clarify whether in the Biacore assay β2m is co-immobilized with FcRn, as shown in Figure 1 of Attachment 1.

Question 1c and d. We acknowledge that the affinity chromatography method yielded results that correlated with clearance in human FcRn transgenic mice. However, the extent of this correlation is unclear due to the limited data set. In particular, it is unclear whether product variants that displayed altered binding in the Biacore assay, but not in the affinity chromatography assay, show altered PK properties or not. For such variants, assessment of clearance based on literature references is an option, as discussed during the July 19th meeting. Until further assessment is provided, it is uncertain which of the two FcRn assays better predict PK properties.

We request a written response by July 24, 2013 to the items enumerated above in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of the other sections of your application is continuing.

If you have any questions, please contact me at (240) 402-3746.

Sincerely,

{See appended electronic signature page}

Lyndsay Hennessey
Quality Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Lyndsay.Hennessey@fda.hhs.gov

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/s/

LYNDSAY J HENNESSEY
07/23/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125486

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Genentech, Inc.
1 DNA Way
San Francisco, CA 94080-4990

ATTENTION: Sarah Oliver, Ph.D.
Regulatory Program Management

Dear Dr. Oliver:

Please refer to your Biologics License Application (BLA) dated April 22, 2013, received April 22, 2013, submitted under section 351 of the Public Health Service Act, for Obinutuzuamab, 25 mg/mL.

We also refer to your April 25, 2013, correspondence, received April 25, 2013, requesting review of your proposed proprietary name, Gazyva. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Gazyva, will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 25, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Beatrice Kallungal at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/23/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab/GA101 - Information Request - 07/16/13
Date:	Tuesday, July 16, 2013 4:08:17 PM

Dear Sarah,
Please find below an information request for BLA 125486.

- *In BO21004, there are 9 patients in the Clb arm and 27 patients in the GClb arm who initiated treatment for other reasons. Please provide "the other reason" for initiating treatment in these patients.*

Please submit your response to this request by 3 pm Thursday July 18, 2013 via e-mail and officially submit to the BLA.

Thanks,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
07/16/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

INFORMATION REQUEST

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your biologics license application (BLA) dated April 22, 2013, received April 22, 2013, submitted under section 351 of the Public Health Service Act for Obinutuzumab (GA101, RO5072759).

We have reviewed the Quality section of your application and have determined that the following information is necessary to take a complete action on your application:

Questions 1- 6 pertain to the traditional sections of the BLA. Questions 7 – 14 pertain to QbD elements of the BLA.

1. Regarding the surface plasmon resonance and affinity chromatography assays used to assess FcRn binding, only brief descriptions are provided in 3.2.S.3.1.
   a. Provide a detailed description of both the FcRn surface plasmon resonance and FcRn affinity chromatography assays, including assay qualifications and variability of the assays, if available.
   b. The FcRn surface plasmon resonance assay appears to include a single injection of product, measuring the signal at the end of the association phase. Such measurement will not provide the on-rate of the interaction. Furthermore, because the molecular mass of the protein in solution directly impacts the signal, the assay appears particularly unsuitable to assess FcRn binding of product variants with molecular masses significantly different than that of the reference standard. To assess FcRn binding, we recommend performing a full kinetic analysis.
   c. It is not clear if the FcRn affinity chromatography method is physiologically relevant. In addition, data included in the submission using the FcRn affinity chromatography assay indicated no more than (b) (4) changes in column retention times for the assessed variants, and analysis was not provided as to what change was statistically significant.

Provide data supporting sufficient sensitivity of this assay, as well as justification that the assay is a relevant surrogate for in vivo product half-life.

d. The two FcRn assays appear complementary, with the surface plasmon resonance assay reflecting the association phase of the interaction and the affinity chromatography assay reflecting the dissociation phase. The Biacore assay appears more sensitive than the affinity chromatography method, as it detected significant differences in the binding of differentially galactosylated variants, charge variants, and deglycosylated product. However, based on the negative results of the FcRn affinity chromatography assay for these variants, it was concluded that the modifications have no impact on FcRn binding. Provide clarification and justification for your overall approach. We note your reference to a human FcRn transgenic mouse model. Clarify if you have used this model to assess the in vivo product half-life and, if such data are available, if there is a correlation with data obtained using the in vitro assays.

2. Regarding the Master Cell Bank, it is unclear how [redacted] (b) (4) was achieved and verified. Provide data that support [redacted] (b) (4) of the Master Cell Bank. Note that [redacted] (b) (4) may not be sufficient to [redacted] (b) (4).

3. Regarding 3.2.S.2.5 Process Validation and/or Evaluation,
   a. In Site-specific process validation, [redacted] (b) (4).
   b. In Process consistency, [redacted] (b) (4) If the methods were qualified or validated, provide a summary of these studies. In addition, provide a justification for why the [redacted] (b) (4) is considered a suitable marker for the removal of these [redacted] (b) (4).

4. In section S.3.3 Materials, Preparation of product variants: [redacted] (b) (4)

5. Provide an update to the status of the microbiology data referenced in the most recent communication "FEEDBACK ON ADDITIONAL FDA COMMENTS ON MICROBIOLOGICAL ASPECTS WHICH WERE RECEIVED DURING THE OBINUTUZUMAB PRE-BLA MEETING (05 MARCH 2013), Table 1 Additional FDA Comments for Drug Substance" dated 7/5/2013.

6. Provide [redacted] (b) (4)

7. There are concerns that PK was underestimated in the critical quality attribute (CQA) risk assessments. Specifically:

a. Insufficient information was provided to support the methods used to assess binding of obinutuzumab to FcRn. See question 1.
b. Only the Fc region of obinutuzumab was considered for an impact on FcRn binding, and it has been reported that the Fab domain of antibodies can affect FcRn binding and PK (Wang, W. et al. (2011) Drug Metab. Dispos. **39**, 1469-1477; Mathur, A. et al. (J. Immunol. Methods, **390**, 81-91). Provide additional information to support the CQA risk assessment strategy of excluding the Fab region for an impact on FcRn binding.

8. Provide clarification on which process characterization/process validation (PV/PV) studies were used to determine whether a critical quality attribute target range (CQA-TR) is needed for a CQA.

9. With regard to the qualification of the scale down production bioreactor:
   a. For a number of CQA and key process indicators (KPI), it appears there was increased variability with the manufacturing scale bioreactor compared to the reduced scale bioreactor. It is unclear, therefore, if the small scale bioreactor is sufficiently representative of the manufacturing scale process. (b) (4)

(b) (4)

10. For the qualification of the chromatography models, provide dot plots as performed for the production bioreactor (Figures 3 and 4 of Process Validation and/or Evaluation: Qualification of Scale-Down Models).

11. Insufficient information was provided to support that the scale down (b) (4) is sufficiently representative of the manufacturing scale data. Specifically,

(b) (4)

[redacted] (b) (4)

12. Provide additional information on how worse case rates for hold times were calculated, including the criteria used to select the models for the calculation.

13. Provide clarification on how parameters shown to have an impact on attributes during hold times are controlled [redacted] (b) (4) Provide additional justification for excluding these conditions from the modeling.

14. Provide a justification for extrapolation of the [redacted] (b) (4) hold time data to [redacted] (b) (4).

We request a written response by July 18, 2013 to the items enumerated above in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of the other sections of your application is continuing.

If you have any questions, please contact me at (240) 402-3746.

Sincerely,

{See appended electronic signature page}

Lyndsay Hennessey
Quality Regulatory Project Manager
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Lyndsay.Hennessey@fda.hhs.gov

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/s/

LYNDSAY J HENNESSEY
07/12/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab/GA101 - Information Request - Statistical 07/10/13
Date:	Wednesday, July 10, 2013 1:41:01 PM

Dear Sarah,
Please find below an information request for BLA 125486.

- *For Study BO21004, please clarify how the primary endpoint PFS was determined in the presence of missing response assessments.*
- *Also please provide two additional analyses, for both investigator-assessed and IRC-assessed PFS, to evaluate the robustness of PFS results:*
  (1) censor death or progression after more than one missed assessment at the date of the last adequate assessment;
  (2) treat lost-to-follow-ups (missing at least one tumor assessment before data cut-off) as events in the GClb arm but as censored in the Clb arm.

Please submit your response to this request by 3 pm Monday July 15, 2013 via e-mail and officially submit to the BLA.

Thanks,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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BEATRICE A KALLUNGAL
07/10/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab/GA101 - Information Request - Safety
Date:	Tuesday, July 09, 2013 5:06:12 PM

Dear Sarah,
Please find below an information request for BLA 125486.

Please explain how you handled Adverse reactions that were coded as YES on either AEINFUS, AEINF24, or AETIREL. Were these events grouped and included to create an event of IRR? Or were they reported separately? We need to be able to replicate the AE tables in the proposed labeling, but are having difficulty with your numbers.

Please submit your response to this request by 3 pm Thursday July 11, 2013 via e-mail and officially submit to the BLA.

Thanks,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
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E-Mail: beatrice.kallungal@fda.hhs.gov

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BEATRICE A KALLUNGAL
07/09/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab/GA101 - Information Request - Statistical
Date:	Monday, July 08, 2013 4:14:52 PM

Dear Sarah,
Please find below an information request for BLA 125486.

For Study BO21004: (1) Please provide the event-specific follow-up time for progression-free survival and overall survival;
(2) There is about 10% difference between the investigator-assessed and IRC-assessed 1-year progression-free survival rate for the Clb arm. Please provide any possible explanations, if any, to this discrepancy.

Please submit your response to this request by 3 pm Friday July 12, 2013 via e-mail and officially submit to the BLA.

Thanks,

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
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(301) 796-9304 (phone)
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BEATRICE A KALLUNGAL
07/08/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab/GA101 - Information Request - Non-Clinical
Date:	Wednesday, June 26, 2013 2:56:05 PM

Dear Sarah,
Please find below an information request for BLA 125486.

- *In order to expedite the review of the animal toxicology studies submitted with BLA 125486, please provide tabulated summaries of histopathology results that display Intergroup Comparisons (columns shown for all groups and sexes in one table). Each table should include severity scores for each finding and the number of animals on study and evaluated per group.*

Please submit your response to this request by 3 pm Wednesday July 03, 2013 via e-mail and officially submit to the BLA.

Regards,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
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/s/

BEATRICE A KALLUNGAL
06/26/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab/GA101 - Information Request - 06/25/2013
Date:	Tuesday, June 25, 2013 5:31:06 PM

Dear Sarah,
Please find below additional request for information. Please provide the additional clarification as noted below by **COB Thursday (6/27)**.

- The reviewers were not able to verify the statement in the proposed label: (b) (4) [redacted] Please clarify.

Thanks,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
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/s/

BEATRICE A KALLUNGAL
06/25/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	RE: BLA 125486 - Obinutuzumab/GA101 - Information Request2 - 06/17/2013 - Additional information
Date:	Monday, June 24, 2013 6:09:46 PM

Hi Sarah,
Thank you for the response for this information request. Please provide the additional clarification as noted below by **COB Tuesday (6/25).**

- Provide the format $MT_HLGT used to generate the High Level Group Term from the EFEX.EFRSPQ2 variable (preferred term)

Thanks,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

From: Sarah Oliver [mailto:oliver.sarah@gene.com]
Sent: Thursday, June 20, 2013 10:33 AM
To: Kallungal, Beatrice
Cc: Sarah Oliver
Subject: Re: BLA 125486 - Obinutuzumab/GA101 - Information Request2 - 06/17/2013 - Additional information

Hi Beatrice -

I wanted to reply to the below Agency request received on July 18th:

Agency comment:

1. Please clarify the dataset and variables used to generate BO21004 clinical study report Figure 3 Disposition of Stage 1a Patients (ITT). Specifically, explain why there were more patients that reached the follow-up month 3 visit (Clb: 106, GClb: 212) than started the followup period (Clb: 84, GClb: 195).

Sponsor response:

Please note that the category "Follow up month 3 visit reached at time of cutoff" actually includes in the "YES" category the patients who are used in the denominator

for end of treatment response and MRD rates. End of treatment response is measured at follow up month 3 visit. At the time of the cutoff of this analysis, not all patients were that far in the study yet, i.e., had had their last dose less than 56 days before the cutoff or were still under treatment. Please see ST_DISP_SPECS.pdf and the reviewers guide for further details (PAGE 13, end of treatment response (ETR)).

Agency comment:

2. According to Table 6 in CSR, 39 patients in GClb withdrew from follow up. Explain how 26 patients completed the follow up period in Figure 3 (considering 195 patients started and 39 patients withdrew from follow up). Also explain the same for the Clb arm.

Sponsor response:

Table 6 (EX15Z_R) is based exclusively on data coming from the CRF pages on post treatment follow-up completion (page 101, page 103). In total there were 39 (out of 238) GClb and 48 (out of 118) Clb patients withdrawn (i.e. the tickbox 'Did patient complete the post treatment follow-up?' ticked 'NO').. However, not all these patients were considered as having started the follow up period because they did not have any follow up assessments. The CRF was set up so that if a patient e.g. withdrew from treatment due to toxicity and then immediately withdrew consent for any further follow up assessment, the latter is recorded on the follow up completion page. In Figure 3, this example patient is not considered as having started follow up (and thus cannot complete it either) because the patient never had any follow up assessments.

In Figure 3, patients are only considered as having completed follow up if the start and end dates of the follow up period are available (analysis dataset TRTDATES.TFUBEGDN, TRTDATES.TFUENDDN). The follow up end date is derived based on information in the CRF on post treatment completion and on the date of last available follow up assessment (raw datasets .AE, TUMOR, QOL, LABP, MEDO and EFEX).

Patients who withdrew during follow up are handled differently than those that completed follow according to the protocol. If the post-treatment completion page is filled in and the patient has completed follow up, the follow up end date is set to date of last available follow up assessment; if post-treatment CRF page is filled in and patient has not completed follow up, the follow up end date is set to the withdrawal date (raw data set EXIT.EX_WDC).

In case the CRF post treatment page is not filled in, the follow up end date would not be available (except for patients who died after follow up start; here follow up end date is set to death date). Consequently these patients would be displayed in category 'Not completed follow up' in Figure 3.

For details referring to derivation of analysis dataset TRTDATES. TFUENDDN, TFUBEGDN please see the define.pdf file for the analysis datasets.

As with the other submission, I will plan to submit this response to the BLA next week.

Please let me know if this is OK with you.

As usual, please let me know if you have any questions.

Sarah

On Tue, Jun 18, 2013 at 3:03 PM, Kallungal, Beatrice <Beatrice.Kallungal@fda.hhs.gov> wrote:
Hello,
As a follow-up to the following information request, also please provide the information listed below.

1. Please clarify the dataset and variables used to generate BO21004 clinical study report Figure 3 Disposition of Stage 1a Patients (ITT). Specifically, explain why there were more patients that reached the follow-up month 3 visit (Clb: 106, GClb: 212) than started the follow-up period (Clb: 84, GClb: 195).

2. According to Table 6 in CSR, 39 patients in GClb withdrew from follow up. Explain how 26 patients completed the follow up period in Figure 3 (considering 195 patients started and 39 patients withdrew from follow up). Also explain the same for the Clb arm.

Please submit the response to this information request together.

Thanks,

Beatrice

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/s/

BEATRICE A KALLUNGAL
06/24/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486

FILING COMMUNICATION

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:
Please refer to your Biologics License Application (BLA) dated April 22, 2013 submitted under section 351(a) of the Public Health Service Act for obinutuzumab (GA101, RO5072759).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority.** This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm . Therefore, the user fee goal date is December 20, 2013.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 25, 2013. In addition, the planned date for our internal mid-cycle review meeting is July 23, 2013. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Clinical

1. Provide the number of investigators (and their names/sites) in the BO21004/CLL11 trial who are sponsor employees (including both full-time and part-time employees).

Clinical Pharmacology

1. In your clinical pharmacology summary you state "NCA was used to analyze the obinutuzumab concentration data in serum samples in the following studies: BO20999, BO21003, BO21000 (only first-line follicular NHL [fNHL] patients) and JO21900; however we are unable to locate the electronic data set files for the PK parameters derived from this analysis. Please identify the location of these files or submit them within 10 business days with appropriate identification and demographic variables included. These file may be submitted in CDISK or SAS file transport (.xpt) format.
2. We note the November 29, 2011 type C meeting where you proposed to evaluate the effect of obinutuzumab on the QT/QTc interval in patients with previously untreated, low tumor-burden indolent NHL in a substudy of Study BO25454; however, we are unable to find your assessment of other available data (i.e., *in vitro* data and ECG data from submitted P1-P3 trials) relative to this issue. If such an analysis was submitted please identify the location or submit an addendum to your clinical pharmacology summary within 10 business days addressing this issue. In addition, please provide an update regarding the status and timeline for the conduct and submission of the QT/QTc substudy of Study BO25454.
3. While we note your hypothesis, in section 3.9 of your clinical pharmacology summary, that an interaction between chlorambucil and obinutuzumab is "highly unlikely," we are unable to locate any *in vitro* or clinical data in your submission that directly supports it. If such information was submitted please identify the location or submit additional supporting information and analyses, if they exist, as an addendum to your clinical pharmacology summary **within 10 business days**.

Product Quality

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

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form

with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
06/21/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	RE: BLA 125486 - Obinutuzumab/GA101 - IR - Response to sponsor"s request for clarification
Date:	Wednesday, June 19, 2013 8:49:59 AM

Hi Sarah,
Please find below the Agency's response to your request for clarification. Please let me know when you can provide the request information.

Regards

Beatrice

From: Sarah Oliver [mailto:oliver.sarah@gene.com]
Sent: Thursday, June 13, 2013 12:09 PM
To: Kallungal, Beatrice
Subject: Re: BLA 125486 - Obinutuzumab/GA101 - Information Request

HI Beatrice -

As discussed on the phone today, we could use a bit more information on what the Agency is interested in regarding the pharmacovigilance plan.

Response: *FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with obinutuzumab following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the plan is available, please include it in the BLA application in the appropriate module so it can be reviewed accordingly.*

Are you interested in the company process about pharmacovigilance? The plans for this molecule?
Response: *Yes. We want to see your thought process about safety risks for this product.*
Is there a specific concern?

Response: *No*

We haven't gotten this type of request in the past and want to ensure we are providing the information you are looking for. Is this something the Agency in general is interested in receiving for molecules in the future?

Response: *Yes*

As for the Agency's requests on the patients listed in Table 31 of the BO21004/CLL11 CSR, I will have something for you by tomorrow.

Response: *Thank you.*

Thanks.

sarah

On Wed, Jun 12, 2013 at 3:05 PM, Sarah Oliver <sarahef@gene.com> wrote:
Hi Beatrice -

Thank you for the email - I can confirm receipt. I will let you know if we have any questions.

It was good to see you earlier this week. Talk to you soon.

sarah

On Wed, Jun 12, 2013 at 2:00 PM, Kallungal, Beatrice <Beatrice.Kallungal@fda.hhs.gov> wrote:
Dear Dr. Oliver:
Please find below an information request for BLA 125486.

- *If you have a proposed pharmacovigilance plan as part of your global pharmacovigilance activities, please submit your plan to the FDA.*

- *According to Table 31 CSR for study BO21004, on page 126, there were 95 patients in the Clb arm and 224 in the GClb arm, who experienced at least one AE (total 319). In our analyses of the dataset AEX for study BO21004 Randomized patients, we identified 322 patients who received study drug and are identified by variable POP_SAF as being included in the study safety population. Please clarify this discrepancy.*

Please submit your response to this request by 3 pm Friday June 14, 2013 via e-mail and officially submit to the BLA.

Regards,

Beatrice

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

FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

--

Sarah Oliver (formerly Fabes), Ph.D.
Associate Program Director - Regulatory
Genentech
1 DNA Way, South San Francisco, Ca 94080
(650) 467-3521
(b) (6) (mobile)

This email and any and all attachments contain information that is confidential and may not be disclosed without prior written consent from Genentech/Roche.

--

Sarah Oliver (formerly Fabes), Ph.D.
Associate Program Director - Regulatory
Genentech
1 DNA Way, South San Francisco, Ca 94080
(650) 467-3521
(b) (6) (mobile)

This email and any and all attachments contain information that is confidential and may not be disclosed without prior written consent from Genentech/Roche.

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/s/

BEATRICE A KALLUNGAL
06/19/2013

From: Kallungal, Beatrice
To: Sarah Oliver
Cc: Kallungal, Beatrice
Subject: RE: BLA 125486 - Obinutuzumab/GA101 - Information Request2 - 06/17/2013 - Additional information
Date: Tuesday, June 18, 2013 6:03:37 PM

Hello,
As a follow-up to the following information request, also please provide the information listed below.

1. Please clarify the dataset and variables used to generate BO21004 clinical study report Figure 3 Disposition of Stage 1a Patients (ITT). Specifically, explain why there were more patients that reached the follow-up month 3 visit (Clb: 106, GClb: 212) than started the follow-up period (Clb: 84, GClb: 195).

2. According to Table 6 in CSR, 39 patients in GClb withdrew from follow up. Explain how 26 patients completed the follow up period in Figure 3 (considering 195 patients started and 39 patients withdrew from follow up). Also explain the same for the Clb arm.

Please submit the response to this information request together.

Thanks,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

From: Kallungal, Beatrice
Sent: Monday, June 17, 2013 4:16 PM
To: Sarah Oliver
Cc: Kallungal, Beatrice
Subject: BLA 125486 - Obinutuzumab/GA101 - Information Request2 - 06/17/2013

Dear Dr. Oliver:
Please refer to your BLA 125486 submission for obinutuzumab. Under study protocol BO21004 (CLL11), submit the following information to the BLA.

The reviewers were not able to verify BO21004 clinical study report Table 18 on comorbidities at baseline. Please clarify the used dataset and variables, and provide the SAS program code responsible for generating that table.

Please submit requested information by 4 pm Wednesday, **June 19, 2013**. If you have further questions, Please let me know.

Thank you.

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
06/18/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab/GA101 - Information Request2 - 06/17/2013
Date:	Monday, June 17, 2013 4:16:19 PM

Dear Dr. Oliver:
Please refer to your BLA 125486 submission for obinutuzumab. Under study protocol BO21004 (CLL11), submit the following information to the BLA.

The reviewers were not able to verify BO21004 clinical study report Table 18 on comorbidities at baseline. Please clarify the used dataset and variables, and provide the SAS program code responsible for generating that table.

Please submit requested information by 4 pm Wednesday, **June 19, 2013**. If you have further questions, Please let me know.

Thank you.

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
06/17/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab/GA101 - Information Request - 06/17/2013
Date:	Monday, June 17, 2013 9:59:11 AM

Dear Dr. Oliver:
Please refer to your BLA 125486 submission for obinutuzumab. Under study protocol BO21004 (CLL11), submit the following information to the BLA.

Provide patient data listings to the BLA for (a) Site 164932. Heinz Ludwig, M.D. in Vienna, Austria and (b) Site 166942. Katell LeDu, M.D. in Le Man, France. The study subject data listings should capture the following:
(1) patients enrolled per cohort.
(2) subject discontinuation (site subject number, screening visit date, informed consent date, assent date, date of first dose/last dose, date of discontinuation, reason for discontinuation).
(3) concomitant medications (non-study medications): (site subject number, type (prior and/or concomitant meds), medication (preferred term), indication/reason taken, date started, date stopped.
(4) prohibited medications (non-study medications): as above with concomitant medications
(5) adverse events, (MEDRA preferred term/investigator entry, detailed drug name, date start/stopped, severity/resolution, SAE (yes, no), death (yes/no))
(6) protocol deviation/s: site subject number, per treatment group, date of occurrence, describe deviation e.g., informed consent obtained after baseline examination; serious adverse event not reported by site in timely manner
(7) primary efficacy endpoints: (If applicable, provide all components of efficacy response listed under each patient, categorized BY CLINICAL SITE (Identify if centrally adjudicated, if not, by whom (e.g., committee/CRO, etc.).

Please submit requested information on 4 pm Thursday, **June 20, 2013**. If you have further questions, Please let me know.

Thank you.

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
06/17/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab/GA101 - Information Request
Date:	Wednesday, June 12, 2013 5:00:35 PM

Dear Dr. Oliver:
Please find below an information request for BLA 125486.

- *If you have a proposed pharmacovigilance plan as part of your global pharmacovigilance activities, please submit your plan to the FDA.*

- *According to Table 31 CSR for study BO21004, on page 126, there were 95 patients in the Clb arm and 224 in the GClb arm, who experienced at least one AE (total 319). In our analyses of the dataset AEX for study BO21004 Randomized patients, we identified 322 patients who received study drug and are identified by variable POP_SAF as being included in the study safety population. Please clarify this discrepancy.*

Please submit your response to this request by 3 pm Friday June 14, 2013 via e-mail and officially submit to the BLA.

Regards,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
06/12/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab/GA101 - Information Request
Date:	Monday, May 20, 2013 4:49:00 PM

Dear Dr. Oliver:
Please refer to your BLA 125486 submission for obinutuzumab. Under study protocol BO21004 (CLL11), submit the following information to the BLA. This information is needed as part of the complete review of your application.

Part 1: Submit a sample case report form (CRF)/electronic case report form (eCRF) blank template printout.

Part 2: Provide the following patient data listings to the BLA as applicable, categorized by clinical site. Specifically, provide study subject data listings BY clinical site in the Russian Federation (Please identify the corresponding site number and clinical investigator name for this adequate study). The Russian study subject data listings should capture the following:
(1) patients enrolled per cohort (by cohort or treatment arm, as applicable)
(2) subject discontinuation (site subject number, screening visit date, informed consent date, assent date, date of first dose/last dose, date of discontinuation, reason for discontinuation).
(3) concomitant medications (non-study medications): (site subject number, type (prior and/or concomitant meds), medication (preferred term), indication/reason taken, date started, date stopped.
(4) prohibited medications (non-study medications): as above with concomitant medications
(5) adverse events, (MEDRA preferred term/investigator entry, detailed drug name, date start/stopped, severity/resolution, SAE (yes, no), death (yes/no))
(6) protocol deviation/s: site subject number, per treatment group, date of occurrence, describe deviation e.g., informed consent obtained after baseline examination; serious adverse event not reported by site in timely manner
(7) primary efficacy endpoints: (If applicable, provide all components of efficacy response listed under each patient, categorized BY CLINICAL SITE (Identify if centrally adjudicated, if not, by whom (e.g., committee/CRO, etc.).

Submit requested information on **COB Friday, May 24, 2013**. If you have further questions, feel free to contact me.

Thank you.

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP

WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
05/20/2013

From:	Kallungal, Beatrice
To:	Sarah Oliver
Cc:	Kallungal, Beatrice
Subject:	BLA 125486 - Obinutuzumab/GA101 - Information Request
Date:	Friday, May 17, 2013 5:28:46 PM

Dear Dr. Oliver:
Please find below an information request for BLA 125486.

- *In your clinical pharmacology summary you state "NCA was used to analyze the obinutuzumab concentration data in serum samples in the following studies: BO20999, BO21003, BO21000 (only first-line follicular NHL [fNHL] patients) and JO21900; however we are unable to locate the electronic data set files for the PK parameters derived from this analysis. Please identify the location of these files or submit them within 10 business days with appropriate identification and demographic variables included. These file may be submitted in CDISK or SAS file transport (.xpt) format.*
- *We note the November 29, 2011 type C meeting where you proposed to evaluate the effect of obinutuzumab on the QT/QTc interval in patients with previously untreated, low tumor-burden indolent NHL in a substudy of Study BO25454; however, we are unable to find your assessment of other available data (i.e., in vitro data and ECG data from submitted P1-P3 trials) relative to this issue. If such an analysis was submitted please identify the location or submit an addendum to your clinical pharmacology summary within 10 business days addressing this issue. In addition, please provide an update regarding the status and timeline for the conduct and submission of the QT/QTc substudy of Study BO25454.*
- *While we note your hypothesis, in section 3.9 of your clinical pharmacology summary, that an interaction between chlorambucil and obinutuzumab is "highly unlikely," we are unable to locate any in vitro or clinical data in your submission that directly supports it. If such information was submitted please identify the location or submit additional supporting information and analyses, if they exist, as an addendum to your clinical pharmacology summary within 10 business days.*

Please submit your response to this request by 3 pm May 31, 2013 via e-mail and officially submit to the BLA.

Regards,

Beatrice

Beatrice Kallungal
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993

(301) 796-9304 (phone)
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E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
05/17/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486

BLA ACKNOWLEDGEMENT

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: obinutuzumab

Date of Application: April 22, 2013

Date of Receipt: April 22, 2013

Our Secondary Tracking Number (STN): BLA 125486

Proposed Use: For the treatment of patients with previously untreated chronic lymphocytic leukemia

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3907.

Sincerely,

{See appended electronic signature page}

Tyree Newman
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

TYREE L NEWMAN
05/02/2013

Newman, Tyree

From: Newman, Tyree
Sent: Wednesday, May 01, 2013 2:22 PM
To: 'Sarah Oliver'
Subject: BLA 125486 - Information request

Hello Dr. Oliver, we are currently reviewing your submission regarding BLA 125486 and would like you to respond to the following information request as soon as possible, but no later than **May 15, 2013**:

Please submit amended raw AE datasets that include all of the following MedDRA terms in addition to the variables that are already included:

HLT
HLGT
SOC

Please submit the requested information to your BLA.

Kind regards,

Tyree

Tyree Newman
Regulatory Health Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

Reference ID: 3302312

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/s/

TYREE L NEWMAN
05/01/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104405

MEETING MINUTES

Genentech, Inc.
Attention: Dr. Elisabeth Kirchisner
Senior Manager, Pharma Technical Regulatory
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Kirchisner:

Please refer to your Investigational New Drug Application (IND) 104405 submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RO5072759 (obinutuzumab).

We also refer to the meeting between representatives of your firm and the FDA on March 5, 2013. The purpose of the meeting was to discuss the proposed CMC strategy and content for obinutuzumab.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact me.

Sincerely,

{See appended electronic signature page}

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Andrew.Shiber@fda.hhs.gov

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: CMC Only

Meeting Date and Time: March 5, 2013 at 11AM Eastern
Meeting Location: FDA White Oak Building 21
Conference Room 1537
10903 New Hampshire Ave.
Silver Spring, MD 20993

Application Number: 104405
Product Name: obinutuzumab
Indication: chronic lymphocytic leukemia (CLL) (b) (4)
lymphoma, (b) (4)
Sponsor/Applicant Name: Genentech, Inc.

Meeting Chair: Patrick Swann, Ph.D.
Meeting Recorders: Andrew Shiber, Pharm.D.
Marlene Schultz-Depalo, M.S.
Lyndsay Hennessey

FDA ATTENDEES:

Patrick Swann, Ph.D.	Deputy Division Director, Division of Monoclonal Antibodies (DMA)
Marjorie Shapiro, Ph.D.	Lab Chief, DMA
Laurie Graham, M.S.	Team Leader, DMA
Mate Tolnay, Ph.D.	Product Quality Reviewer, DMA
Andrew Shiber, Pharm.D.	Project Manager, Office of Biotechnology Products (OBP)
Marlene Schultz-Depalo, M.S.	Project Manager, OBP
Lyndsay Hennessey	Project Manager, OBP

Office of Compliance/Biotech Manufacturing Assessment Branch (BMAB)

Patricia Hughes, Ph.D.	Team Leader, BMAB
Colleen Thomas, Ph.D.	Microbiologist, BMAB
Lakshmi Narasimhan, Ph.D.	Microbiologist, BMAB

Office of Translational Sciences/Office of Biostatistics

Meiyu Shen, Ph.D.	Biostatistician

Office of New Drugs/Division of Hematology Products

Tyree Newman	Project Manager, DHP
Hyon-Zu Lee, M.D.	Clinical Review

SPONSOR ATTENDEES

Stephane Avella, M.S.	Senior Regulatory Associate, Pharma Technical Regulatory
Jacques Bourquin, Ph.D.	Technical Development Team Lead
Sven Deutschmann, Ph.D.	Director, Quality Control, Micro and Cell biology

Reference ID: 3296697

Niklas Engler, Ph.D.	Head of Development Analytics Europe
Gerald Gellermann, Ph.D.	Manager, Development Analytics
Jochen Felix Kepert, Ph.D.	Manager, Development Analytics
Elisabeth Kirchisner, Ph.D.	Senior Manager, Pharma Technical Regulatory
Lynne Krummen, Ph.D.	Head of Pharma Technical Regulatory Biologics
Wolfgang Kuhne, Ph.D.	Head of Bioprocess Development Purification Europe
Ettore Ohage, Ph.D.	Senior Manager, Quality Assurance
Rolf Schäfer, Ph.D.	Director, API Team Lead
Roland Schmidt, Ph.D.	Senior Manager, Drug Product Process and Formulation Development
Alexander Streubel, Ph.D.	Manager, Drug Product Process and Formulation Development
Frank Zettl, Ph.D.	Manager, Development Purification
Christof Finkler, Ph.D.	Director, Analytical Development

Teleconference participants:

Christian Hakemeyer, Ph.D.	Manager, Development Cell Culture
Robert Puskeiler, Ph.D.	Technical Development Lead
Sarah Oliver	

1.0 BACKGROUND

1. **Purpose:** The purpose of the meeting was to discuss the proposed CMC strategy and content for obinutuzumab.
2. **Objective:** The sponsor is preparing for a BLA submission and would like to discuss the suitability of scale-down models, post approval lifecycle management, inspection readiness and strategy for establishing shelf-life of drug substance and drug product.
3. **History:** This is a Pre-BLA meeting with CMC only content which will include the scale down model qualifications for Drug Substance, the post approval lifecycle management approach for obinutuzumab as well as the Drug Substance and Drug Product control system and the strategy for establishing shelf-life for obinutuzumab Drug Substance and Drug Product.

2.0 DISCUSSION

1. Question 1: According to the feedback from the Biometrics group (provided as Post Meeting Note within the meeting minutes for the Type C meeting for obinutuzumab, held on Sept 19, 2012) it appears that a scale-down model is only regarded as valid if an equivalent result is obtained. (b) (4)

(b) (4)

Reference ID: 3296697

FDA Response:
Historically, bioreactor scale down models have been an important part of process development and deemed suitable for that general purpose. Our ability to conclude that the scale down models as you describe are "suitable" depends upon their intended use. For [redacted] (b) (4) **Whether or not the** (b) (4) **(which by definition requires demonstration to "…provide assurance of quality") will be a review issue.**

We have the following recommendations for additional information to be provided in the BLA:

a) **Information will be needed to support practically significant differences. From statistical point of view, equivalence margin for each parameter used for equivalence tests is not yet justified by the sponsor. In addition, information will be needed to support that results for attributes that are different from equivalent would not indicate that the scale down models are not sufficiently representative of the full scale process or, alternately, how the risk of using the models is reduced. The acceptability of the models will depend upon the level of residual risk, which will include evaluations of not only available independent data set verifications, but also the overall QbD strategy.**

b) **Provide additional information on how inclusion of attributes in the testing strategy is used to mitigate the risk of the small scale models. For example,** [redacted] (b) (4)

c) [redacted] (b) (4)

d)

e)

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(b) (4)

Meeting Discussion: (b) (4)

(b) (4)

(b) (4)

Reference ID: 3296697

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Meeting Discussion: Sponsor provided the following information related to Drug Product Manufacturing

1) Drug Product Manufacturing is performed at the Roche facility in Mannheim, Germany [redacted] (b) (4)
2) Filling of obinutuzumab 1,000 mg vials at [redacted] (b) (4) is currently planned for [redacted] (b) (4)
3) [redacted] (b) (4)
4) [redacted]

The FDA requested that 3 hypothetical examples be used to illustrate change management of process parameters within the design space which would include the type of changes and the action to be taken.

The Agency asked how will unexpected changes in output values be identified and addressed. [redacted] (b) (4) [redacted] (b) (4) The Post-approval lifecycle management (PALM) plan should provide an overview of the procedures.

[redacted] (b) (4) according to the PALM plan based on available dataset.

5. Question 5: Does the Agency agree with the Sponsor's proposal to use real-time stability data [redacted] (b) (4) (b) (4) (b) (4)

FDA Response:
The data from the two representative clinical batches stored at [redacted] (b) (4) may support a shelf life [redacted] (b) (4) but this will be a review issue. We agree that existing stability data support the proposed Drug Substance shelf life of [redacted] (b) (4)

6. Question 6: Does the Agency agree with the Sponsor's proposed shelf life of 36 months for Drug Product that is based on 36 months real-time stability data from representative Drug Product material (Phase III material, Roche Mannheim) and 12 months real- time stability data from the Drug Product registration material (filled at Roche Mannheim)?

FDA Response: The data from the three representative clinical batches and the one toxicology batch stored may support a shelf life beyond 12 months, but this will be a review issue.

Reference ID: 3296697

Administrative Questions

1. Obinutuzumab Drug Substance is manufactured at the Roche facility in Penzberg, Germany, Drug Product at Roche Mannheim, Germany. Does the Agency foresee a product-specific PAI for obinutuzumab at the Penzberg and Mannheim facilities? If this [redacted] (b) (4)

FDA Response:
The need for a drug product PLI will be determined during the BLA review cycle. [redacted] (b) (4)

2. Does the Agency agree with the Sponsor's proposal for how QbD content will be documented in [redacted] (b) (4) of the obinutuzumab BLA?

FDA Response:
No. [redacted] (b) (4) (b) (4)

In addition, please provide a QbD strategy overview be part of the Quality overall summary (2.3).

<u>Additional FDA comments:</u>
Please clarify whether drug substance filling includes a [redacted] (b) (4) and whether the bioburden release test sample [redacted] (b) (4)

Please indicate whether low endotoxin recovery (LER) is an issue for the drug substance, drug product, or any of the in-process intermediates.

The CMC Drug Substance section of your BLA (Section 3.2.S) should include the following product quality microbiology information:

a) **Monitoring of bioburden and endotoxin levels at critical manufacturing steps using qualified bioburden and endotoxin tests. Pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).**
b) **Three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowable hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).**

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c) [redacted] (b) (4) **validation data and information (3.2.S.2.5)**
d) **Bioburden and endotoxin data obtained during manufacture of the three conformance lots (3.2.S.2.5)**
e) **Data summaries of shipping validation studies (3.2.S.2.5)**
f) **Drug substance bioburden and endotoxin release specifications. The bioburden limit should be** [redacted] (b) (4) **CFU/10 mL for bulk materials allowed to be stored for extended periods of time at refrigerated temperatures (3.2.S.4).**
g) **Qualification data for bioburden and endotoxin test methods performed for in-process intermediates and the drug substance (3.2.S.4)**
h) **Please clarify whether drug substance filling includes** [redacted] (b) (4) **and whether the bioburden release test sample** [redacted] (b) (4)

Meeting Discussion: The sponsor noted that Low endotoxin recovery (LER) is not an issue for obinutuzumab. The Agency requested that both the CMC drug substance and drug product sections of the BLA include a statement on whether low endotoxin recovery is an issue for drug substance, drug product or any in-process intermediates. LER studies should be included in the BLA submission.

The CMC Drug Product section of your BLA (Section 3.2.P) should include validation data summaries supporting the [redacted] (b) (4) **sterility assurance. For guidance on the types of data and information that should be submitted, refer to the 1994 "FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products".**

1. **The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:**
   a) **Bacterial retention study for** [redacted] (b) (4)
   b) **Sterilization and depyrogenation of equipment and components that contact the sterile drug product. The equipment requalification program should be described.**
   c) **In-process microbial controls and hold times. Hold times should be validated at manufacturing scale.**
   d) [redacted] (b) (4) **if applicable.**
   e) **Three successful consecutive** [redacted] (b) (4) **runs, including summary environmental monitoring data obtained during the runs.** [redacted] (b) (4) **environmental monitoring procedures should be described.**
   f) **Shipping validation studies.**
2. **The following method validation information should be provided:**
   a) **Container closure integrity testing (3.2.P.2.5). Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. We recommend that container closure integrity testing be performed in lieu of sterility testing for stability samples at initial time point and every 12 months (annually) until expiry (3.2.P.8.2).**

b) **Qualification data for bioburden, sterility and endotoxin test methods performed for in-process intermediates (if applicable) and the drug product, as appropriate (3.2.P.5).**

Additional FDA Comments

Microbiological Controls (1)

- No Low Endotoxin Recovery (LER) effect was observed
- Requested information will be provided
- All measures regarding microbial control strategy are either already implemented or will be implemented with the upcoming obinutuzumab launch campaign
  - Product (b) (4) hold time validation at manufacturing scale
  - Qualification of bioburden and bacterial endotoxin test for the additional samples (b) (4)
  - Qualification of the bioburden test due to the revision of the test method (b) (4) (b) (4)
- (b) (4) is included in Drug Substance filling
  - (b) (4)
  -
- Given as the bulk material (b) (4) (b) (4)
- The requested Drug Product data will be included in Section 3.2.P.3.5
- Shipping validation Drug Product: information will be provided from (b) (4)

Additional FDA comments from CMC statistical team of Office of Biostatistics:

(b) (4)

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/s/

PATRICK G SWANN
04/22/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

¶
¶
IND 104405

MEETING MINUTES

Genentech, Inc.
Attention: Sarah Oliver, Ph.D.
Associate Program Director, Regulatory
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Oliver:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RO5072759 (obinutuzumab).

We also refer to the meeting between representatives of your firm and the FDA on February 22, 2013. The purpose of the meeting was to discuss and reach agreement on the acceptability of the clinical trial results from the Stage 1a (GClb against Clb) of the pivotal Phase 3 trial, BO21004/CLL11, to form the basis of a biological license application (BLA) for obinutuzumab for the proposed indication of " '*Tradename*' in combination with Chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia".

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Tyree Newman, Regulatory Project Manager at (301) 796-3907.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C.
Lead Clinical Analyst, Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: February 22, 2013 11:00 AM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 104405
Product Name: RO5072759 (obinutuzumab)
Indication: untreated patients with B-cell Chronic Lymphocytic Leukemia
Sponsor Name: Genentech, Inc.

Meeting Chair: Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C.
Meeting Recorder: Tyree Newman

FDA ATTENDEES

Division of Hematology Products

Ann Farrell, M.D., Director
Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C., Lead Clinical Analyst, Clinical Team Leader
Hyon-Zu Lee, Pharm.D., Clinical Reviewer
Barry Miller, M.S., C.R.N.P., Clinical Reviewer
Robert Kane, M.D., Deputy Director Safety
Diane Leaman, B.S., Safety Regulatory Project Manager
Tyree Newman, B.S., Regulatory Health Project Manager

Office of Hematology and Oncology Products

Richard Pazdur, M.D., Director
Tamy Kim, Pharm.D., Associate Director for Regulatory Affairs

Office of Clinical Pharmacology

Rachelle Lubin, Pharm.D., Clinical Pharmacology Reviewer
Julie Bullock, Pharm.D., Clinical Pharmacology Reviewer Team Leader

Division of Monoclonal Antibodies

Mate Tolnay, Ph.D., Product Quality Reviewer *(via phone)*
Marjorie A. Shapiro, Ph.D., Chief, Laboratory of Molecular and Developmental Immunology *(via phone)*

Division of Biometrics V

Chia-Wen Ko, Ph.D., Biostatistics Reviewer
Mark Rothmann, Ph.D., Biostatistics Team Leader
Rajeshwari Sridhara, Ph.D., Director

Office of Business Informatics

Douglas Warfield, Ph.D., Interdisciplinary Scientist - Technical Lead

Office of Surveillance & Epidemiology

Tzu-Yun McDowell Ph.D., Epidemiologist
Kevin Wright, Pharm.D., Safety Evaluator *(via phone)*
LT Zachary Oleszczuk, Pharm.D., Team Leader *(via phone)*

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou, Independent Assessor

SPONSOR ATTENDEES

Elina Asikanius, Biometrics
Christina Baladi, Regulatory Affairs Associate
Thomas Buechele, M.D., Global Lifecycle Leader
David Carlile, Ph.D., Lead Clinical Pharmacologist
Nafsika Kronidou Horst, Ph.D., Global Regulatory Leader
Kathryn Humphrey, Clinical Science
Bea Lavery, Global Regulatory Hematology Franchise Lead
Joerg Maurer, Biometrics Project Lead
Sarah Oliver, Ph.D., US Regulatory Lead
Michael Wenger, M.D., Global Development Lead and Clinical Science Lead
Somnath Sarkar, Ph.D., Global Head, Oncology Biostatistics
Nancy Valente, M.D., Vice President Head Global Hematology Development
Elisabeth Kirchisner, Regulatory Affairs – CMC *(via phone)*

Reference ID: 3268958

1.0 BACKGROUND

On December 26, 2012, the Agency received a Type B meeting request from Genentech. The Agency granted the meeting request on January 3, 2013.

Genentech plans to submit a Biologics License Application (BLA) for obinutuzumab for the treatment of CLL in late April 2013. The BLA will be based on the analysis of efficacy and safety data from a single trial BO21004/CLL11 entitled "An open-label, multi-center, three arm randomized, phase III study to compare the efficacy and safety of RO5072759 + Chlorambucil (GClb), rituximab + Chlorambucil (RClb) or Chlorambucil (Clb) alone in previously untreated CLL patients with comorbidities." The analysis will be supported by nonclinical data and clinical pharmacology, efficacy, and safety data from four Phase 1 and Phase 2 trials (BO21000, BO20999, BO21003, and JO21900) in patients with CD20-positive malignant disease, including patients with CLL and NHL who have relapsed or whose disease is refractory to treatment, as well as for the first-line treatment of patients with indolent NHL.

The meeting package was received on January 25, 2013. On February 14, 2013, the Division emailed Genentech the preliminary responses to the questions contained in the meeting information package dated January 21, 2013.

2.0 DISCUSSION

2.1. Questions

Question 1: Does the Agency agree that the results from the pivotal trial (BO21004/CLL11) and supporting studies proposed to be included in this BLA provide sufficient clinical evidence to characterize the benefits and risks of obinutuzumab in the CLL patient population studied?

FDA Response: Your proposal appears to be acceptable at this time. However, whether these data will be sufficient to support the proposed indication will be a review issue.

Discussion: No discussion occurred.

Question 2: Based on the BO21004/CLL11 study the Sponsor proposes the following indication:

"Tradename" in combination with chlorambucil is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia (see Section 14.1)

This indication statement will be supported by a detailed description of the patient population in the Clinical Trials section of the label (Section 14.1). Does the Agency agree with this proposal?

FDA Response: The indication that will be granted and the patient population description in the Clinical Trials section of the labeling will be determined after review of the data that is submitted to the BLA. Also, see response to Question #1.

Discussion: No discussion occurred.

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Question 3: *Does the Agency agree with the updated proposal (previously presented in the PMP submitted October 1, 2012 Serial No. 0550 to support the Type B meeting to discuss the content and format of the proposed BLA) regarding the population PK analysis based on a combined CLL and NHL patient dataset to identify the main sources of variability in PK which would include disease type as a covariate?*

FDA Response: Your proposed population PK analysis plan appears to be reasonable. Your population PK submission should include model files (txt format), analysis data set (SAS transport format), and the population PK report.

Discussion: No discussion occurred.

Question 4: *Given that the final Stage 1b (RClb vs. Clb) results are already available and to ensure complete transparency, the Sponsor plans to include an abbreviated report in the dossier which will contain a high level summary of safety and efficacy results from Stage 1b. This will not be submitted to support a labeling claim for RClb. Does the Agency agree with the proposed content and format of the report to be provided related to Stage1b?*

FDA Response: Your proposal is acceptable as long as no data or claims from Stage 1b are proposed in the draft labeling.

Discussion: No discussion occurred.

Question 5: *Given the magnitude of the treatment effect observed for the combination regimen of obinutuzumab plus Clb over Clb alone in study BO21004/CLL11, does the Agency agree that this represents a sufficient advancement in the treatment of 1st line CLL in the patient population studied to qualify the proposed BLA for Priority Review?*

FDA Response: The review priority will be decided at the time of filing. You should submit your justification for priority review with the BLA submission.

Also, at this meeting, please plan to discuss your plans for requesting breakthrough designation. This should include a specific plan for the timing of the planned components of a rolling BLA submission. Also plan to discuss any manufacturing issues that could impact an expedited review of the application.

Discussion: The Agency reiterated that Genentech should work to ensure that GA-101 product development (CMC) would be prepared for launch at the time of expedited action. Genentech stated that based upon information available at this time, (b) (4) (b) (4) Genentech will submit a request for breakthrough therapy designation as soon as possible.

The Agency also encouraged Genentech to submit an expanded access program for GA-101 in CLL as soon as possible to bridge the time to availability of drug, should the action be taken early. For combination with other chemotherapies than Chlorambucil, justification

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for the safety of such a combination would need to be provided. Any disease outside CLL would need to be handled by Single Patient INDs.

Discussion occurred regarding the availability of rolling submission should a breakthrough therapy designation be granted. Genentech stated that they will be submitting a complete BLA application in late April 2013.

Genentech will submit the safety update 90 days after submission of the BLA.

Question 6: In light of the results from study BO21004/CLL11, does the Agency agree with the proposal not to submit a REMS or a Medication Guide for the use of obinutuzumab in the proposed indication?

FDA Response: At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Discussion: No discussion occurred.

Question 7: Does the Agency agree that a pediatric requirement is not required for the proposed BLA given that orphan designation has been granted for the CLL indication?

FDA Response: Because obinutuzumab has an orphan drug designation for the CLL indication, it is exempt from the Pediatric Research Equity Act (PREA) requirement.

Discussion: No discussion occurred.

Question 8: Does the Agency foresee that the proposed BLA will be reviewed by the Oncologic Drugs Advisory Committee (ODAC)?

FDA Response: We will notify you of any plans for ODAC discussion as early as possible.

Discussion: The Agency stated that an ODAC will be unlikely, but reserved the right to request an ODAC review should an unexpected issue arise.

Question 9: Would the Agency like to have an orientation meeting with the Sponsor after the submission of the BLA to outline the major components of the BLA?

FDA Response: Yes.

Discussion: The Agency expects the timing of the application orientation meeting to be approximately 30-60 days after the BLA submission. Genentech should plan for a 60 minute presentation to the OHOP group followed by a 30-minute data technical walk-through with just the review team members.

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Additional Comments:

- **Please note that the proposed Phase 3 trial is an open-label design trial. Patient reported outcomes (listed as secondary objective) are not interpretable from a regulatory or labeling standpoint for open-label trials. Please refer to the Guidance for Industry, "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims."**

- **In your forthcoming BLA, please include a brief summary of the number of the number of cases of Hepatitis B reactivation that have been reported throughout the entire drug development program. Also, please discuss a "root cause analysis" that was done in response to any of these reports.**

  Discussion: Genentech confirmed there were no Hepatitis B cases in the GA-101 arm of the CLL program. The Agency requested that Genentech submit all available information on Hepatitis B inclusion criteria and events in the drug development program. All patients were screened for Hepatitis B at the time of enrollment. Genentech confirmed they will provide narrative information on any cases.

- **We noted in your briefing package the CDER Data Standards Check-list (Vol2. pg 537) was not current. Research study designs should define the protocol for data collection. The Agency's methodology and submission structure supports research study design, as indicated in the *Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* and the *Study Data Specifications*. The Agency's methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. The Agency prefers implementation of analyses datasets to tabulations datasets traceability. In addition, the Agency prefers each study submitted to be complete and evaluated on its own merits.**

  The Agency prefers sponsors submit datasets based on the Study Data Specifications version published at the time of submission (currently 2.0). However, in general, the Agency accepts datasets, which comply, within a reasonable timeframe, with previous versions of the Study Data Specifications and other related guidance; based on the timing of protocol design, protocol initiation, and data collection.

  The Agency expects sponsors to evaluate the risk involved converting study data collected to standardized data, if applicable. The Agency prefers sponsors to submit study data conversion explanation and rationale. The study data conversion rationale and explanation should address either scenario; decision rationale for not converting or decision rationale for converting. The Agency expects the sponsor's evaluation and rationale includes study data scientifically relevant to the

Reference ID: 3268958

application's safety and efficacy representation. As such, the evaluation and explanation may include rationale based on the pooling/integrating of data from multiple studies.

The Agency also prefers studies be maintained independently in the SEND datasets, SDTM datasets, and that analyses (ADaM) datasets provide traceability to the study's SDTM, including analyses that combine multiple studies (e.g. Safety and/or Efficacy analyses) (See *SEND*, *SDTM* and *ADaM* as referenced in *Study Data Specifications*).

In addition, please reference the *CDER Common Data Standards Issues Document* for further information on data standardization in submissions.

If you have any further questions, please feel free to send an email to cder-edata@fda.hhs.gov.

Additional Links:

Electronic Regulatory Submissions and Review Helpful Links
Electronic Common Technical Document (eCTD)
Study Data Standards Resources

Discussion: Genentech stated that datasets will not be provided in SDTM format. The data will be study data specification compliant. The Agency agreed.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
The Agency will provide Genentech with the request for clinical trial site inspection information from OSI.	FDA	With meeting minutes
The Agency will provide Genentech with a list of required documentation needed to request breakthrough therapy designation.	FDA	With meeting minutes

Reference ID: 3268958

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts given during the meeting.

Reference ID: 3268958

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/s/

VIRGINIA E KWITKOWSKI
02/28/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104405

MEETING MINUTES

Genentech, Inc.
Attention: Mary B. Sliwkowski, Ph.D.
Vice President, Pharma Technical Regulatory
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Sliwkowski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RO5072759 (obinutuzumab).

We also refer to the meeting between representatives of your firm and the FDA on September 19, 2012. The purpose of that meeting was to discuss the quality-by-design strategy for obinutuzumab.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Joel Welch, Regulatory Project Manager at (301) 796-2017.

Sincerely,

{See appended electronic signature page}

Marjorie Shapiro, Ph.D.
CMC Team Leader
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	CMC
Meeting Date and Time:	September 19, 2012; 8:30 a.m.
Meeting Location:	NIH Campus, Bld 29B, Conf Room C
IND Number:	104405
Product Name:	Obinutuzumab
Sponsor Name:	Genentech, Inc.
Meeting Requestor:	Elisabeth Kirchisner
Meeting Chair:	Marjorie Shapiro
Meeting Recorder:	Joel Welch

FDA Participants:
Office of Pharmaceutical Science
Office of Biotechnology Products
Division of Monoclonal Antibodies

Jeffrey Baker, Ph.D.	Deputy Office Director
Sean Fitzsimmons, Ph.D.	Product Quality Reviewer
Laurie Graham, M.S.	Product Quality Reviewer
Patrick Swann, Ph.D.	Deputy Division Director
Mate Tolnay, Ph.D.	Product Quality Reviewer
Joel Welch, Ph.D.	Regulatory Health Project Manager

Genentech, Inc.

Nadja Alt, Ph.D.	Manager, Development Characterization
Jacques Bourquin, Ph.D.	Technical Development Team Lead
Niklas Engler, Ph.D	Head of Development Analytics Europe
Christof Finkler, Ph.D.	Section Head Analytical Development and QC Biotech Europe
Gerald Gellermann, Ph.D.	Manager, Development Analytics
Christian Hakemeyer, Ph.D.	Manager, Development Cell Culture
Jochen Felix Kepert, Ph.D.	Manager, Development Analytics
Elisabeth Kirchisner, Ph.D.	Senior Manager, Pharma Technical Regulatory
Ines Krämer, Ph.D.	Head of Pharma Technical Regulatory Development Biologics Europe
Lynne Krummen, Ph.D.	Head of Pharma Technical Regulatory Biologics
Wolfgang Kuhne, Ph.D.	Head of Bioprocess Development Purification Europe
Robert Puskeiler, Ph.D.	Manager, Development Cell Culture

Reference ID: 3209754

Rolf Schäfer, Ph.D.	Director, API Team Lead
Alfred Schnüriger	Manager, Bioassay Development
Alexander Streubel, Ph.D.,	Manager, Drug Product Process and Formulation Development
Frank Zettl, Ph.D.	Manager, Development Purification

1.0 BACKGROUND

The Sponsor is developing obinutuzumab, a recombinant, humanized, monoclonal, type II glycoengineered anti-CD20 monoclonal antibody (mAb) produced in Chinese hamster ovary (CHO) cells. The antibody targets CD20 + malignancies and is currently investigated in clinical trials for different indications (i.e., chronic lymphocytic leukemia (CLL), indolent non-Hodgkin's lymphoma (iNHL), diffuse large B-cell lymphoma (DLBCL)). In April 2013, the Sponsor intends to submit a market application for treatment of previously untreated CLL patients with comorbidities in combination with chlorambucil. On June 13, 2012 the Sponsor requested a Type C meeting with the Agency. The Agency granted that meeting on June 28, 2012.

2.0 DISCUSSION

Question 1

Does the Agency agree to the Sponsor's concept for evaluation of the biological activity and different mechanisms of action of the molecule with regard to CQA assessment?

FDA Response to Question 1:

a. *We concur that the ADCC assay is likely sufficient to identify potential CQAs impacting both ADCC and direct cell death. Please provide additional data justifying the use of ADCC in lieu of direct cell assay to identify CQAs.*

b. *It is unclear how impact rankings for obinutuzumab variants listed in Table 2 were determined. Which variants were experimentally tested in enriched form for biological activity, similarly as shown for some variant in Fig. 3?*

Additional Discussion During Meeting:

The Agency re-emphasized that the ADCC assay was likely sufficient, but that a review of a detailed justification should be included in the BLA, including an assessment of CDC as a potential mechanism of action (though the Agency believes it is not likely a mechanism of action). The Sponsor presented in slide 5 an explanation for which variants were evaluated. The Agency stated it understood that not every charge variant could be isolated or enriched, and that an assessment based on manufacturing data may be acceptable. The Sponsor clarified that the same ADCC assay was used to identify CQA's as well as for setting acceptance criteria for CQA's.

Reference ID: 3209754

Question 2

A case study presenting the QbD approach including scale-down model qualification, CPP identification, setting of CQA acceptance ranges and definition of the control strategy is presented in the briefing package. The case study focuses on a subset of CQAs.
a) Does the Agency agree with the approach to define a design space as proposed based on the CQAs included in the case study?

Specifically:
– Are the process models of the process characterization studies considered sufficiently predictive to support the claimed ranges?
– Are the data presented for scale-down model qualification sufficient to demonstrate that the models are suitable to support the claimed ranges?
b) Does the Agency agree with the proposed control strategy for the selected CQAs? Does the Agency agree with the presented tools for establishment of the control strategy and their application to the CQAs presented (b) (4) (b) (4)**?**

FDA General Response to Question 2:

Question 2 focuses on QbD concepts requesting agency agreement with exemplary proposals for design space and control strategy. In general, it is difficult to answer these questions outside of the context of an entire license application. For example, the adequacy of the process description, process validation and method validation can impact the adequacy of your QbD proposals. In addition, it is difficult to answer these questions outside of a better understanding of the obinutuzumab product quality lifecycle implications of the proposals. In your BLA, it will be helpful if you could provide greater specificity (b) (4) (b) (4)

FDA Specific Response to Question 2a (design space):

a. (b) (4)

b.

Reference ID: 3209754

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(b) (4)

Post Meeting Note (Consultative review from Biometrics)

Although Genentech's statistical approach, multivariate regression model, in the process characterization studies seems a fine approach, it is difficult to determine if their multivariate models are appropriate and are considered sufficiently predictive to support the claimed rages without looking at the actual data.

(b) (4)

(b) (4)

Reference ID: 3209754

Post Meeting Note (Consultative review from Biometrics)

First, we do not agree with the Genentech's classification of equivalence testing results.

(b) (4)

Additional Discussion During Meeting:

The Sponsor presented a revised design space definition (presented on slide 10 in the attached presentation).

(b) (4)

(b) (4)

Reference ID: 3209754

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(b) (4)

Question 3

The Sponsor plans to change the Drug Substance storage temperature from (b) (4) Does the Agency agree to the rationale, concept and intended data package to change the Drug Substance storage temperature?

FDA Response to Question 3:

We agree with the proposed plan to change the Drug Substance storage temperature from (b) (4) (b) (4)

We note that this is a good example of the necessity and value of comprehensive stability testing.

Additional Discussion During Meeting:

The Sponsor thanked the Agency for the feedback.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

There were no outstanding action items.

5.0 ATTACHMENTS AND HANDOUTS

There Sponsor had a handout to guide the discussion. The slides are presented as an attachment.

Reference ID: 3209754

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/s/

MARJORIE A SHAPIRO
10/31/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104405

MEETING MINUTES

Genentech, Inc.
Attention: Miki L. Yamamoto, Ph.D.
Scientist, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Yamamoto:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RO5072759 (GA101).

We also refer to the meeting between representatives of your firm and the FDA on June 8, 2012. The purpose of the meeting was to discuss and obtain agreement regarding the acceptability of the proposed statistical analysis plan for study B021 004 to support the initial Biologics License Application (BLA) for GA 101 in Chronic Lymphocytic Leukemia (CLL) patients (b) (4) (b) (4)

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Tyree Newman, Regulatory Project Manager at (301) 796-3907.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C.
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	C
Meeting Category:	Pre-NDA
Meeting Date and Time:	June 8, 2012 and 9:00 – 10:00 AM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 104405
Product Name:	RO5072759 (GA101)
Indication:	Treatment for Chronic Lymphocytic Leukemia (CLL) patients (b) (4)
Sponsor/Applicant Name:	Genentech, Inc.
Meeting Chair:	Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C.
Meeting Recorder:	Tyree Newman, B.S.

FDA ATTENDEES

Division of Hematology Products (DHP)

Ann Farrell, M.D., Director (Acting)
Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C., Clinical Team Leader
R. Angelo de Claro, M.D., Medical Officer
Tyree Newman, B.S., Regulatory Health Project Manager

Office of Hematology and Oncology Products (OHOP)

Anthony Murgo, M.D., M.S., F.A.C.P., Associate Director for Regulatory Science
Toyotaka Iguchi, M.D., Ph.D., Visiting Physician

Division of Biometrics V (DBV)

Mark Rothmann, Ph.D., Biostatistics Team Leader

SPONSOR ATTENDEES

Christina Baladi, Associate, Regulatory Affairs
Elina Asikanius, Statistician, Biometrics
Nafsika Kronidou Horst, Ph.D., Global Regulatory Leader, GA101
Jane Huang, M.D., Senior Medical Director, Clinical Science Leader
Carmen Ladner, Senior Director, Regulatory Affairs
Joerg Maurer, Biometric Project Leader
Nancy Valente, M.D., Hematology Development Franchise Head, Clinical Science
Michael Wenger, M.D., Global Development Team Leader, GA101
Miki Yamamoto, Ph.D., Scientist, Regulatory Affairs
Somnath Sarkar, Ph.D., Deputy Global Head Oncology & Biostatistics

1.0 BACKGROUND

On March 21, 2012, the Agency received a Type C meeting request from Genentech. The Agency granted the meeting request on March 27, 2012.

The purpose of this meeting was to obtain the Agency's feedback on the Statistical Analysis Plan (SAP) for Study BO21004. Genentech referred to the Agency's comments regarding the BO21004 study design received on July 7, 2009, in the FDA Type B Meeting minutes (Final FDA minutes dated November 18, 2009), as well as Genentech's responses to the FDA comments dated September 23, 2009, and additional comments received February 7, 2010 and June 7, 2011. In addition, we refer to the pre-meeting package dated May 26, 2009 (submitted on May 27, 2009 as Serial No. 0009) for the July 7, 2009, Type B meeting to discuss BO21004.

The meeting package was received on May 10, 2012. On May 29, 2012, the Agency emailed Genentech the preliminary responses to the questions contained in the meeting information package dated May 9, 2012.

2. DISCUSSION

2.1. Category/Discipline A

2.2. Closed Test Procedure

Question 1: Does the Agency agree with the proposed SAP for BO21004 (CLL11)? In particular, does the Agency agree with (a) the proposed closed test procedure on the primary endpoint, investigator-assessed PFS and (b) the IRC-assessed PFS being presented as secondary endpoint following the same closed test procedure, as detailed in the SAP Section 4.4.1? As discussed previously, IRC-assessed PFS will be the basis of regulatory decisions for the Agency.

FDA Response: Please discuss the steps you have taken to ensure that you will have an adequate number of events for the IRC-assessed PFS analysis based on your event driven investigator-assessed PFS analysis.

See our previous comments on comparative claims from the July 7, 2009, meeting.

Discussion: Genentech explained their experience with the Rituxan clinical trials and feels comfortable that the trial is adequately powered for loss of events during the IRC review.

2.3. Non-Binding Futility Analysis

Question 2: Does the Agency agree with (a) the proposed non-binding futility analysis on GClb versus RClb, i.e., futility rule based on observed hazard ratio (HR) as well as on observed p-value and (b) the proposed α-spending at the non-binding futility analysis, as detailed in the SAP Section 5.3?

Reference ID: 3144822

FDA Response: Your proposed non-binding futility analysis and threshold are acceptable.

Discussion: No discussion.

2.4. Pre-Planned Analyses

Question 3: Does the Agency agree with all subsequent pre-planned analyses? In particular, as discussed on 7 July 2009, at the Type B Meeting, if a statistically significant PFS improvement of GClb over RClb is demonstrated in the Stage 2 analysis, (b) (4) (b) (4)

FDA Response: See response to question 1.

You should ensure that (b) (4) (b) (4)

Discussion: Genentech explained they intend to (b) (4) (b) (4) **Genentech intends to assess the bias to protect the rigor of the Stage 2 analysis. All patients will have completed treatment by the time of the information release.**

2.5. Submission of Data

Question 4: (b) (4) (b) (4)

FDA Response: No. Your proposal is not acceptable. (b) (4) (b) (4)

Please also explain your intended actions and all intended claims for all possible scenarios based on the results of your PFS analyses. For example, (b) (4) (b) (4)

Discussion: The Agency and Genentech agreed to the submission of the analysis datasets containing the PFS results from all treatment arms in order to assess the global test. Submission of updated [Stage 1B RClb vs Clb] data is acceptable provided there is an indicator of the data used for the global test.

Reference ID: 3144822

Additional Comments:

(b) (4)

Discussion: No discussion.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Not Applicable	FDA	N/A
Not Applicable	Sponsor	N/A

5.0 ATTACHMENTS AND HANDOUTS

See attached handout from the meeting minutes.

Reference ID: 3144822

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/s/

VIRGINIA E KWITKOWSKI
06/13/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104405

MEETING MINUTES

Genentech, Inc.
Attention: Todd W. Rich, M.D.
Vice President, Development Regulatory Affairs, Medical Communications,
Drug Safety and Development Quality and Compliance
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr Rich:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for, "Human Monoclonal Antibody to CD20 (RO5072759)."

We also refer to the meeting between representatives of your firm and the FDA on July 7, 2009. The purpose of the meeting was to obtain agreement on the proposed pre-clinical plan, the product quality manufacturing process and to discuss the proposed clinical development plan and study design for approval of RO5072759.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, MT
Regulatory Project Manager
Division of Biologics Oncology Products
Office Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure – Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

FDA RESPONSES TO GENENTECH, INC.

MEETING DATE:	July 7, 2009
TIME:	12:00 pm – 1:30 pm
APPLICATION:	IND 104405
SPONSOR:	Genentech, Inc.
DRUG NAME:	RO5072759 (GA101)
INDICATION:	For the treatment of previously untreated patients with (B-CLL)
TYPE OF MEETING:	Type B, EOP2/Pre-Phase 3
MEETING CHAIR:	Genevieve Schechter
MEETING RECORDER:	Gina Davis

LIST OF FDA ATTENDEES:
Office of Oncology Drug Products
Division of Biologic Oncology Products

Patricia Keegan
Joseph Gootenberg
Genevieve Schechter
Charles Stimler
Anne Pilaro
Michael Orr
Gina Davis

Office of Clinical Pharmacology
Division V

Hong Zhao
Angela Men

Office of Biotechnology Products
Division of Monoclonal Antibodies

Marjorie Shapiro
Eric Calvo

Office of Biostatistics
Division of Biostatistics

Hong Lu

1.0 MEETING OBJECTIVES:

Chemistry, Manufacturing and Controls (CMC)

- To obtain agreement on the plan to show product quality after introduction of changes into the manufacturing process

Nonclinical

- To obtain agreement on the proposed pre-clinical development plan

Clinical

- To discuss and obtain agreement on the proposed clinical development plan and proposed study design for approval of RO5072759 in combination with chlorambucil for the treatment of patients with previously untreated B-CLL [redacted] (b) (4) (b) (4)

2.0 BACKGROUND

RO5072759 (GA101) is a fully humanized and glycoengineered monoclonal antibody (IgG1) which binds with to the extracellular domain of the human CD20 antigen present on normal and malignant B cells. It has a molecular mass of approximately 150kDa and recognizes a CD 20 Type II epitope. Genentech, Inc. submitted an Investigational New Drug Application (IND) for RO5072759 on February 6, 2009, contained Protocol BO21003. Since the Phase 1 portion of this protocol was completed at the time of IND submission, FDA requested that Genentech submit a revised study protocol containing only the Phase 2 portion of the protocol (designated BO21003C). The IND was allowed to proceed on March 11, 2009, contingent on submission of the revised Protocol BO21003C. Protocol BO21003C was submitted to the IND on May 12, 2009.

Protocol BO21003C is an open-label, multi-center, randomized, active-control study of RO5072759 versus rituximab to be conducted in approximately 180 patients with relapsed CD20 positive indolent NHL (140 with follicular NHL and 40 with non-follicular NHL, excluding CLL). A sub study evaluating a shorter duration of infusion (SDI) enrolling up to 20 additional patients is planned. The treatment plan consists of weekly infusions (Days 1, 8, 15, 22) of RO5072759 (1000 mg) or rituximab (375 mg/m2). Patients who demonstrate stable disease or better will continue on RO5072759 (1000 mg) or rituximab (375 mg/m2) every 2 months for up to 2 years or until disease progression. The sample size for the randomized, Phase 2, was based on 80% power to detect a 15% difference in overall response rate or complete response rate between RO5072759 and rituximab, assuming an ORR of 40% in the ritixumab arm in patients with follicular NHL.

On April 16, 2009, Genentech, Inc., requested an End-of-Phase 2 (EOP2) meeting to seek FDA concurrence on the proposed chemistry, manufacturing and controls (CMC) plans, toxicology program, and Phase 3 study BO21004 to support a BLA submission. The clinical data supporting this request is derived from studies conducted outside the US IND and are summarized below (see Clinical Development Plan and Clinical Trial).

CMC

Genentech, Inc., has developed a new Drug Substance (DS) manufacturing process (b) (4) (b) (4) "as well as a new Drug Product (DP) formulation (b) (4) (b) (4) (b) (4) which changes the previously (b) (4) Based upon a plan to demonstrate acceptable Drug Substance quality between (b) (4) as well as demonstration of comparable batch analysis, and stability between (b) (4) (b) (4) Genentech seeks FDA concurrence that patients dosed with either Drug Product could be combined for data analysis and evaluation of the clinical study results.

Toxicology

To date, the following cynomolgous monkey studies have been completed with RO5072759 (Table taken from Sponsor briefing document):

Study Type	Study Report	Dose Per Week	Treatment Duration	Additional Assessments
Pilot toxicology study	1024829	1 mg/kg 10 mg/kg	2 weeks	No evidence of cytokine release 4 hours after treatment
GLP intravenous study	1024830	10 mg/kg 30 mg/kg 100 mg/kg	13 weeks	Local tolerance Safety pharmacology (no effect on blood pressure, heart rate and cardiac conduction times in conscious non-telemetered animals)
GLP subcutaneous study	1024838	30 mg/animal 120 mg/animal	4 weeks	Local tolerance
Tissue cross-reactivity in Human and Cynomolgus Tissues	1024159 1024158	NA	NA	NA
Cytokine release and neutrophil activation in human whole blood	1025124	NA	NA	NA

In addition, Genentech, Inc., has proposed the following additional primate studies (Table taken from Sponsor briefing document):

Study Type	Treatment Duration	Species/ Test System
GLP intravenous study	26 weeks	Cynomolgus monkey
Embryo-fetal and pre/postnatal development	17 weeks [a]	Cynomolgus monkey

[a] Maternal animals will be dosed weekly for 17 weeks. Loading doses will be administered prior to study dose.

Genentech believes that the 13-week study (1024830) is sufficient to support the proposed dosing for the proposed study BO21004 and seeks FDA concurrence that the planned 26-week repeat-dose toxicity, and embryo-fetal and pre/postnatal development studies are acceptable

Genentech seeks concurrence that neither genotoxicity testing and carcinogenicity studies for RO5072759 are not necessary.

Clinical Development Plan and Clinical Trial

Limited clinical experience is available from two clinical studies (BO21003 and BO20999):

- BO21003, as noted above, was initiated outside the US to patients with relapsed indolent B-cell NHL and received a reduced start dose of 50% of the dose for their respective cohort followed by three subsequent weekly infusions at the cohort dose level. The treatment plan was weekly dosing for the first 4 doses then one dose every 2 months for up to 2 years. Fifteen patients have been enrolled in 5 cohorts, 3 patients per cohort [cohort 1 (100/200 mg); cohort 2 (200/400 mg), cohort 3 (400/800 mg) cohort 4 (800/1200 mg) and cohort 5 (1200/2000 mg)]. A planned interim analysis of Study BO21003 was undertaken in November 2008, and included data from the first 15 evaluable patients enrolled into the study. Among these 15 patients with NHL, there were no CRs and 6 PRs (1 in cohort 1, 3 in cohort 2, and 2 in cohort 3) with no obvious dose-response relationship. Six patients were continued into the maintenance phase. The RO5072759 dose for the Phase 2 portion of the protocol was determined to be 1000 mg/dose administered weekly for 4 doses.

- BO20999 was also a combined safety/tolerability and activity study of R05072759 monotherapy, in which 1000 mg was determined to be the Phase 2 dose. In BO20999, 27 (21 NHL and 6 CLL) patients have been enrolled sequentially across 7 cohorts. Patients received a reduced start dose of 50% of the dose for their respective cohort. The briefing document states that three NHL patients were enrolled in each of the first three cohorts [cohort 1 (50mg/100mg), cohort 2 (100 mg/200 mg) and cohort 3 (200 mg/400 mg)], 3 patients with NHL and 3 with CLL in both cohorts 4 (400 mg/800 mg) and 5 (800 mg/1200 mg), and three patients with NHL each for cohorts 6 (1200 mg/2000 mg) and 7 (1600 mg

cycle 1 and 800 mg cycles 2-8). In the Phase 2 portion of this study, RO5072759 is administered as a single infusion once every 3 weeks, with an additional dose on Day 8 of Cycle 1 for a maximum of 8 Cycles (a total of 9 doses). A planned interim analysis of Study BO20999 was undertaken in October 2008 and included data from the first 27 evaluable patients (21 NHL and 6 CLL) enrolled into the study. Among the 21 patients with NHL, there have been 3 patients with CRs (1 each in cohorts 1, 3, and 4) and 5 with PRs (1 each in cohorts 2, 3, 4, 5, and 6). Information about drug activity in CLL is not available.

The safety data, summarized in the briefing package with a data cut-off date of March 2009, includes 49 patients who received monotherapy at doses over the dose range of 50 mg to 2000 mg. As compared to Rituxan®, an increased incidence of Grade 3-4 neutropenia and infusion-related toxicity in patients with CLL was noted. Among the 13 CLL patients treated in study BO20999, all (13/13) experienced an infusion related reaction (IRR) with the first infusion of RO5072759. These IRRs were Grade < 2 and decreased in number and severity with subsequent infusions. Grade 3/4 neutropenia was observed in 9/13 patients with recovery either spontaneously or with the use of growth factors.

The meeting package contains the protocol for the proposed registrational study, BO21004, entitled "An open-label, multi-center, three-arm randomized Phase 3 study to compare the efficacy and safety of RO5072759 + chlorambucil (GClb), rituximab + chlorambucil (RClb) or chlorambucil (Clb) alone in previously untreated chronic lymphocytic leukemia (CLL) patients not eligible for fludarabine-based chemoimmunotherapy". Randomization is 2 (331 patients): 2 (331 patients): 1 (118 patients) in the GClb, RClb, and Clb arms, respectively. Stratification factors are Binet stage, country/region, and cytogenetic profile (favorable vs. unfavorable). The proposed treatment plan for GClb includes RO5072759 1000 mg on days 1, 8, 15 of Cycle 1 with chlorambucil 0.5 mg/kg PO on days 1, 15 of each cycle. For the RClb arm, rituximab 375 mg/m2 on day 1 Cycle 1, then 500 mg/m2 day 1 of subsequent cycles will be given with chlorambucil 0.5 mg/kg on days 1 and 15. Chlorambucil (Clb) will be given as a single agent at 0.5 mg/kg on day 1, 15 of each cycle. Treatment plan for each arm is six cycles of twenty-eight days duration.

The proposed study has two stages. During Stage 1, patients will be randomized to the three treatment arms: GClb, RClb, or Clb alone. At the Stage 1 analysis, the primary endpoint of PFS will be evaluated with a two-sided log-rank test at an alpha level of 5%, testing the global hypothesis of no treatment differences between the three treatment arms. If this hypothesis is rejected the comparison of GClb with Clb alone and RClb with Clb alone will also be performed at an alpha level of 5%. At this stage a futility analysis on the comparison of GClb with RClb based on the primary endpoint will also be performed: specifically, the Stage 2 randomization will continue when the one-sided p-value is less than 0.25. At the end of the Stage 1 analysis, Stage 2 randomization will be stopped if any of the

following occurs: 1) a non-significant test for any difference between the 3 arms; 2) a non-significant test for GClb versus Clb alone; or 3) a failed futility analysis for GClb versus RClb. In this case, patients will be followed for PFS events and overall survival according to the follow-up schedule.

If at Stage 1, the test for GClb vs. Clb is statistically significant ($p < 0.025$, one-sided), this data will be submitted for approval for the indication: "RO5072759 in combination with chlorambucil is indicated for the treatment of previously untreated B-CLL patients (b) (4) (b) (4) (b) (4) (b) (4)

Disclaimer: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the face-to face meeting scheduled for July 7, 2009, between Genentech Inc., and the Division of Biologic Oncology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments.

If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the Regulatory Project Manager). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, the purpose of the meeting, or questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

At the end of the meeting, key discussion points, agreements, clarifications, and action items will be summarized. We request that you take the responsibility for summarizing what you have heard at the meeting. This will help ensure that there is mutual understanding of the advice given and meeting outcomes and actions.

These comments were provided to Genentech, Inc., on July 2, 2009.

Sponsor Submitted Questions and FDA Responses:

All of the answers provided are in the context of indications related to cancer such as CLL. [redacted] (b) (4)

Chemistry, Manufacturing and Controls (CMC)

1. Changes were made for the [redacted] (b) (4) Drug Substance manufacturing process, which included [redacted] (b) (4) Does the Agency agree with the plan to demonstrate product quality?

   FDA Response: The proposed comparability assessment plan to demonstrate the [redacted] (b) (4) DS quality appears adequate from a CMC perspective. FDA will review all data upon submission and provide an assessment of comparability. Please include the rationale for the formulation change when the data are submitted to the IND.

   Discussion During the Meeting: *Genentech had no questions or clarifications regarding FDA's response to question 1. No discussion occurred.*

Multidisciplinary: CMC/Clinical

2. The Sponsor proposes to supply the pivotal registration Study BO21004 with both [redacted] (b) (4) Drug Product derived from the [redacted] (b) (4) drug substance process and the proposed liquid dosage form derived from the [redacted] (b) (4) Drug Substance manufacturing process, [redacted] (b) (4) Based upon demonstration of acceptable Drug Substance quality discussed in Question 1, as well as demonstration of comparable batch analysis (as applicable) and stability of [redacted] (b) (4) derivedDrug Product lots, does the Agency agree that patients dosed with either Drug Product could be combined for data analysis and evaluation of the study results?

   FDA Response: Given the multiple manufacturing changes between [redacted] (b) (4) and the critical stage of the product development, we recommend you conduct a clinical pharmacokinetic and pharmacodynamic comparability study in addition to CMC comparability assessment to support the use of [redacted] (b) (4) in 5-10% of the population in the registration trial.

If upon review of all data for [redacted] (b) (4) materials, the FDA concurs comparability is established, it would be acceptable to use both [redacted] (b) (4) materials in the pivotal study.

Discussion During the Meeting: *Genentech had no questions or clarifications regarding FDA's response to question 2. No discussion occurred.*

Nonclinical

3. Based on RO5072759's lack of binding specificity to DNA, it is not expected that RO5072759 would directly interact with DNA or other chromosomal material. Does the Agency agree that standard genotoxicity tests are not necessary for RO5072759?

   FDA Response: Yes.

   Discussion During the Meeting: *Genentech had no questions or clarifications regarding FDA's response to question 3. No discussion occurred.*

4. Does the agency agree that carcinogenicity studies are not required forRO5072759?

   FDA Response: Yes.

   Discussion During the Meeting: *Genentech had no questions or clarifications regarding FDA's response to question 4. No discussion occurred.*

5. Does the Agency agree that the proposed toxicology plan is adequate to support a marketing application of RO5072759? (see Section 7)

   FDA Response: Yes, this is a reasonable toxicology plan.

   Discussion During the Meeting: *Genentech had no questions or clarifications regarding FDA's response to question 5. No discussion occurred.*

   a. Does the Agency agree that the 13-weekly intravenous administration toxicity study in cynomolgus monkeys with a 37-week recovery phase (Report No. 1024830) appears to be reasonable to support the proposed intermittent dosing of up to 6 months in Study BO21004?

      FDA Response: Yes.

      Discussion During the Meeting: *Genentech had no questions or clarifications regarding FDA's response to question 5a. No discussion occurred.*

b. Does the Agency agree with the planned 26-week repeat-dose toxicity study? In particular, is the proposal to combine assessments of safety pharmacology (effects on the central nervous system, cardiovascular system, and respiratory system) and male fertility assessment in the planned 26-week toxicity study acceptable? (see Section 7.3)

FDA Response: Yes.

Discussion During the Meeting: *Genentech had no questions or clarifications regarding FDA's response to question 5b. No discussion occurred.*

c. Does the Agency agree that a combined study on embryo-fetal and pre/postnatal development in cynomolgus monkeys is acceptable to address the potential reproductive toxicity of RO5072759? (see Section 7.3).

FDA Response: Yes

Discussion During the Meeting: *Genentech had no questions or clarifications regarding FDA's response to question 5c. No discussion occurred.*

Clinical

6. Does the Agency agree that the proposed Phase 3 design and planned first analysis of Study BO21004 are adequate to demonstrate the efficacy and safety of RO5072759 + chlorambucil (GClb) for the treatment of patients with previously untreated B-CLL (b) (4) (b) (4) (see Section 11)

FDA Response: No. FDA has the following comments:

- FDA does not agree with the trial design in particular the inclusion of rituximab + chlorambucil arm. (See answer to question #8 below)
- FDA does not agree that the study (b) (4) (b) (4) (See answer to question #6a below)
- FDA does not agree with inclusion of CLL patients defined as Binet B and C. (see additional clinical comments)
- FDA does not agree with the proposed dose/dosing schedule for the chlorambucil only arm. (See answer to question #6b below)

- FDA does not agree with the planned crossover to the GClb arm with progression on chlorambucil. (See additional clinical comment below)

- FDA does not agree that the primary analysis of PFS should be based on investigator-assessment. (See answer to question #6e below)

- FDA does not agree with proposed assessment plan for response/progression. (See answer to question #6d below)

a. [redacted] (b) (4)

FDA Response: No. [redacted] (b) (4) patients having renal failure (creatinine clearance < 70 cc/minutes) or other general co-morbidities as defined by the Cumulative Illness Rating Scale (CIRS). [redacted] (b) (4) Therefore the eligibility criteria should be revised to include only patients with creatinine clearance $\leq$ 30 cc/minute.

With regard to CIRS, this co-morbidity index has not been validated for use in CLL or in any other cancer setting. FDA would consider patients having any of the following to be unsuitable candidates for fludarabine:

- Impaired performance status requiring assistance with activities of daily living (ADLs), e.g. Karnofsky PS $\leq$ 60.
- Known hypersensitivity to fludarabine.
- Serious co-morbid condition.

Serious co-morbid conditions would include:

- Chronic active infection.
- History of opportunistic infection.
- Autoimmune disease including hemolytic anemia, thrombocytopenia.
- Grade 3 or higher motor or sensory neuropathy.
- Clinically significant organ dysfunction including :
  - Pulmonary disease (e.g COPD with $FEV_1 \leq 60\%$ predicted or DCLO $\leq$ 60% predicted).

- Diabetes mellitus requiring chronic treatment with oral agents or insulin.
- NYHA Grade 3/4 heart failure or ischemic heart disease.
- Severe renal insufficiency (CrCl < 30 cc/min).
- Hepatic insufficiency (Child-Pugh A classification or worse).

All co-morbid conditions which make a patient unsuitable for fludarabine therapy must be clearly documented in the case report form.

Discussion During the Meeting: *During the meeting Genentech stated that their intent to change the proposed indication from* (b) (4) (b) (4) *to* (b) (4) *FDA requested that Genentech define the term* (b) (4) *in objective terms as it pertains to the proposed study population and provide data to support the definition. Genentech stated that they plan to use the CIRS scale. Genentech noted that the CIRS is used by the German CLL Study Group and by the 2008 CLL NCI-IWG to identify patients from whom FCR chemotherapy may not be appropriate. FDA advised that use of this scale might result in the inclusion of patients who have multiple conditions that are not incapacitating conditions; classification of these patients as* (b) (4) *may not be appropriate. FDA advised that the condition(s) that result in the classification of the patient as* (b) (4) *must be collected on the case report forms.* (b) (4) (b) (4) (b) (4) *The label claim sought should be based on characteristics of the population enrolled and rather than the vague term* (b) (4)

b. Is chlorambucil in the control arm an acceptable treatment for previously untreated B-CLL patients who are unsuitable for fludarabine-based therapy?

FDA Response: Chlorambucil is an acceptable active control treatment for previously untreated B-CLL patients unsuitable for fludarabine-based therapy. The chlorambucil dose of 0.5 mg/kg biweekly for 6 months proposed for the chlorambucil only arm based on review of the literature is a suboptimal dose. Provide evidence from the medical literature to support the proposed dose. Please discuss the dose titration of chlorambucil generally used in CLL patients receiving chlorambucil.

Chlorambucil therapy is generally continued until there is evidence of CR, stable PR, progression or unacceptable toxicity, a treatment period usually much longer than six months. Please discuss the adequacy of your proposal for only six months of therapy on the chlorambucil only arm and

on the combination arms. Please provide literature evidence to support the appropriateness of a six month schedule of therapy.

Discussion During the Meeting: *Genentech stated they would treat patients until best response was achieved or until 6 months whichever is sooner. Chlorambucil therapy until CR, or stable PR for one year is considered standard in the US. FDA requested that Genentech provide literature to support their contention that chlorambucil treatment for six months is adequate. Genentech agreed to provide the requested information.*

c. Does the Agency agree with the proposed safety monitoring plan, including the real-time safety assessment of the first 6 patients receiving GClb?

FDA Response: Genentech's proposal to conduct an in-depth safety assessment in lieu of conducting a Phase 1 safety and tolerability study of the combination may be sufficient to minimize risks provided that intensive safety monitoring continue beyond the first 6 patients receiving the untested combination and that comparative assessments of safety between study arms also be provided after twenty-five to fifty patients have been accrued on the RO5072759 plus chlorambucil arm. This alternative approach to determination of safety and tolerability may be inefficient should safety concerns regarding the combination occur which would require modification of one or both doses of the planned combination. FDA suggests that a separate single arm study to determine the safety of the combination of RO5072759 with chlorambucil be conducted in patients with impaired renal function and/or other significant co-morbidities. A small study with an adequate sample size and careful dose escalation of chlorambucil with RO5072759 to determine the appropriate dose and the dose adjustments for hematologic or other unexpected toxicities as well as to gain information about the activity would provide useful information for a pivotal trial. Dose modification and stopping rules similar to those used in the study (Table 1 Dose Modification, page 9) would be appropriate.

Discussion During the Meeting : *FDA stated that Genentech did not provide sufficient safety and tolerability information regarding the combination of RO5072759 plus chlorambucil. FDA recommends that Genentech conduct a small study with careful monitoring, with dose escalation of chlorambucil in combination with RO5072759 to obtain safety and activity information. Genentech acknowledged the risk of choosing less than optimal doses for the two drugs in combination but chooses to proceed with the proposed trial design. FDA stated that* ***all*** *patients, including the first six to receive RO5072759 plus chlorambucil*

should be randomized; thus all patients enrolled can be included in the comparative analyses of safety and efficacy. Genentech and FDA agreed that the safety data from the first twenty-five patients randomized to each arm will be reviewed by an independent data safety monitoring committee to determine if the toxicities of the combination of GClb and Clb are acceptable. The DSMC would then review safety data at 3 to 6 month intervals (interval dependent on prior safety results). The final protocol will also have dose modification and early termination rules for unacceptable toxicity.

d. Is the primary endpoint of progression-free survival (PFS) based on investigator assessment an appropriate endpoint for demonstration of clinical benefit in the proposed patient population? Does the Agency agree with the proposed primary analysis of PFS? (See Section 11.6.1.)

FDA Response: Although PFS is an acceptable primary endpoint for this study the FDA does not agree that the proposed analysis of PFS should be based on investigator assessment in this open-label trial (See Question 6e), (b) (4)

The accurate measurement of organomegaly as well as changes in the extent of organomegaly and lymphadenopathy over time by physical examination alone has been shown to be unreliable. Recently the ODAC panel expressed the opinion that determination of disease progression on the basis of organomegaly and/or lymphadenopathy requires confirmation by radiological testing (eg., CT scan) in the context of a clinical trial for registration purposes. CT scans of the chest, abdomen, and pelvis (and neck if clinically involved) should be scheduled every 3 months while on study to evaluate hepatomegaly, splenomegaly, and lymphadenopathy, and be continued during the follow-up period every 3 months until disease progression.
Please see the statistical comments about the proposed analysis of PFS.

Discussion During the Meeting: *FDA stated that CT scans must be performed at baseline (within one month prior to enrollment) for all patients, be obtained to confirm objective response, and to confirm PD in those patients who progress based on physical examination only (i.e. new or increased lymph node size; new or increasing organomegaly). Genentech agreed to require CT scans at these timepoints. Genentech agreed to provide data to support statements during the meeting that radiographs contributed to determination of disease progression in only 15% of patients undergoing first-line treatment for CLL.*

FDA agreed that doubling of lymphocyte counts could be used to define progression.

e. Is the proposed plan for the supportive IRC (independent review committee) – assessed PFS evaluation acceptable?

FDA Response: No. IRC review of PFS should be the primary endpoint. Progression should be assessed by an independent radiologic assessment of PFS and include correlation with clinical information from the CRFs with the reviewers masked to the therapy that the subject received. IRC review should be done in real time to avoid investigator bias in this unblined study regarding removal from study of patients who have not actually progressed. For any patient enrolled on this study IRC confirmation of progression should be obtained prior to the initiation of a new CLL therapy.

Discussion During the Meeting: *FDA stated that verification of investigator-determined PFS events by the independent radiologist occur in real time. Genentech stated that a group of CLL experts, blinded to treatment assignment, would be given data to confirm response or disease progression but not in real time. Genentech stated their intent that the IRC would not review films but would only review the reports of CT scans. FDA stated that use of reports would be acceptable only if the clinical site radiology review was comprehensive (inclusive of all scans from baseline forward) at each reading and that lesions measurements would be described in the report for use in determining percent change in individual lesions and sum of the largest diameters of all measurable disease at each time-point. FDA stated that all CT scans should be available for FDA review and audit and it would be more desirable if these scan were available for review by the IRC. Genentech agreed to store images and have them available for review by the IRC as needed.*

f. Is the planned first formal Stage 1 analysis of GClb versus Clb alone, as defined, sufficiently adequate to support approval of GClb for the proposed indication? (See Section 11.6.1.)

FDA Response: Please be advised that two Phase 3 studies are generally required for licensure. FDA would accept a single pivotal study to support licensure if the results demonstrate a highly significant effect on the primary endpoint that in internally consistent across subgroups. The results of a single pivotal trial must be sufficiently robust and so compelling that if would be unethical to the repeat the study. For further information please refer to the FDA document entitled: "Guidance for

Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biologic Products" at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf

Note that a second randomized trial could be performed in a different CLL population.

Discussion During the Meeting: *Genentech had no questions or clarifications regarding FDA's response to question 6f. No discussion occurred.*

7. Provided that a robust magnitude of treatment effect and favorable benefit-risk profile of GClb would be demonstrated based on the Stage 1 result, does the Agency agree that the single pivotal Phase III Study BO21004 is adequate to support full approval of GClb for the treatment of previously untreated B-CLL patients (b) (4)

FDA Response: As noted in FDA's response to Question # 6e the study would have to demonstrate robust evidence of clinical efficacy, a favorable risk/benefit profile, highly statistical significant endpoints with supportive information from secondary endpoints, and internal consistency across subgroups.

Discussion During the Meeting: *Genentech had no questions or clarifications regarding FDA's response to question 7. No discussion occurred.*

8. (b) (4)

(b) (4)

Additional Comments:

Clinical

9. FDA recommends that patients treated on this study not be crossed over to another study treatment at documented progression as this will obscure survival results. Note that other therapies are available for patients who progress on this study.

   Discussion During the Meeting: *Genentech had no questions or clarifications regarding FDA's additional clinical comment 9. No discussion occurred.*

10. The CLL population to be enrolled should meet criteria for treatment consistent with current clinical practice guidelines. The following inclusion criteria for initiating CLL therapy should be used (See NCCN guidelines):

    a. Significant disease-related symptoms (B symptoms):

       1) Fever due to CLL
       2) Night sweats
       3) Weight loss
       4) Extreme fatigue

    b. Bulky disease which would include any of the following (should be documented by CT);

       1) Progressive enlargement of lymph nodes or progression of hepatomegaly or splenomegaly.
       2) Spleen > 6 cm beneath costal margin Lymph nodes > 10cm unidimensionally.
       3) Obstructive adenopathy.

    c. Documented progressive anemia or Hemoglobin < 10 g/dl.

    d. Documented progressive thrombocytopenia or platelet count < 100,000 cells/mm^3.

    e. Documented rapid lymphocyte doubling time ($\leq$ 6 months).

    f. Evidence of end organ dysfunction requiring treatment.

    The basis for the decision to treat CLL should be clearly captured in the case

report form.

Discussion During the Meeting: *Genentech agreed to provide the reason for initiation of treatment for all patients enrolled on this study.*

11. Hypotension is described as an "expected" infusion-related reaction (IRR) (see IB section 6.1.2, p 68) and has been demonstrated in all (13/13) CLL patients in study BO20999 who experienced IRRs. Discuss the frequency, duration, and magnitude of hypotension observed during initial and subsequent infusions among patients in earlier studies. Would an expectation of hypotension contraindicate participation by patients with recent CVA, TIA, or carotid stenosis?

    Discussion During the Meeting: *Genentech had no questions or clarifications regarding FDA's additional clinical comment 11. No discussion occurred.*

12. Patients with AST or ALT > 2.5 x ULN should be excluded unless liver infiltration by leukemia is suspected as should patients with bilirubin > 2x ULN.

    Discussion During the Meeting: *Genentech agreed to make the requested change. Genentech noted that chlorambucil labeling does not specify dose modification for liver toxicity and agreed to provide data to justify the safety of the proposed chlorambucil dosing schedule in patients with abnormal liver function tests.*

13. The protocol should include a standardized comprehensive management plan for treatment of IRR due to RO5072759.

    Discussion During the Meeting: *Genentech agreed to provide a comprehensive management plan for treatment of infusion related reactions in the protocol.*

14. How will the presence of autoimmune hemolytic anemia be detected without a screening Coombs test?

    Discussion During the Meeting: *Genentech agreed to perform a Coombs test for the detection of autoimmune hemolytic anemia on all patients at entry onto the study.*

15. Allopurinol is not included as a required prophylactic medication on this protocol. Based on the previous experience with RO5072759 and other monoclonal antibodies how likely is Tumor Lysis Syndrome (TLS) to occur in the CLL population? In this frail population with co-morbidities including renal failure is this more of a concern? FDA notes that one of thirteen patients with CLL treated with RO5072759 developed TLS.

Discussion During the Meeting: *FDA stated that all patients must be pre-medicated with allopurinol to avoid TLS. Genentech responded that TLS was not objectively confirmed in about one-third of cases and often there were no elevated creatinines noted. Genentech agreed to provide FDA with updated information regarding TLS events that have occurred.*

16. Molecular confirmation of complete response in CLL is strongly encouraged.

    Discussion During the Meeting: *Genentech confirmed that all complete responses will be confirmed molecularly.*

17. Justify the dosing schedule you have proposed for RO5072759 in combination with chlorambucil as well as for rituximab in combination with chlorambucil to treat CLL. Specifically, provide evidence that 6 months of treatment with either combination is likely to provide clinical benefit in CLL. Explain why therapy with chlorambucil in both combination arms is not continued until achieving PR or CR.

    Discussion During the Meeting: *Genentech will provide information to support the efficacy of the proposed six-month schedule of administration of chlorambucil alone and to support the proposed schedule for the combination of chlorambucil and rituximab.*

Statistical

18. Missing data/assessments of progression should be kept at a minimum. Additionally, you should provide sensitivity analyses to study the impact on the analysis of PFS due to any missing data/assessments, and any loss to follow-up or discontinuation of assessments of PFS not due to an event.

    Discussion During the Meeting: *Genentech had no questions or clarifications regarding FDA's additional statistical comment 18. No discussion occurred.*

19. Independent review of scans and clinical information should occur simultaneously or shortly after the investigator's review. Patients should continue to undergo clinical visit/follow up and CT scans until progression has been confirmed by the independent review committee.

    Discussion During the Meeting: *Genentech agreed to perform CT scans at the time of enrollment, and collect, and store them. Images will also be collected at time of response and at time of progression if progression is noted on physical examination (i.e. palpable lymph nodes, new lymph nodes, new or recurrent organomegaly). FDA commented that independent review of scans should be done at real time at least for those patients determined as PD by study investigators. If the independent review committee can not confirm PD, these*

patients should continue to be assessed for response until PD is confirmed or the end of study.

20. Please submit a detailed statistical analysis plan (SAP). The timing of analysis for overall survival should be included in the SAP.

    Discussion During the Meeting: *Genentech had no questions or clarifications regarding FDA's additional statistical comment 20. No discussion occurred.*

21. [redacted] (b) (4)

Clinical Pharmacology

22. Please provide the detailed testing plans for pharmacokinetics and immunogenicity for the proposed Phase 3 study.

    Discussion During Teleconference: *Genentech had no questions or clarifications regarding FDA's additional clinical pharmacology comment 22. No discussion occurred.*

23. Please provide the ECG monitoring plan for the proposed study.

    Discussion During Teleconference: *Genentech had no questions or clarifications regarding FDA's additional clinical pharmacology comment 23. No discussion occurred.*

24. During the drug development, please determine the potential pharmacokinetic drug-drug interaction between RO5072759 and chlorambucil. Conducting such study using a subset of the proposed Phase III study is acceptable.

    Discussion During Teleconference: *Genentech had no questions or clarifications regarding FDA's additional clinical pharmacology comment 24. No discussion occurred.*

Additional Comment from the Meeting

- *FDA stated that Genentech would need a study for drug-drug interaction assessment between RO5072759 and chlorambucil. Genentech agreed.*

Additional Action Items

- Genentech agreed to provide updated information on Phase 1 and 2 studies.
- Genentech plans to submit the revised protocol in the next few months and to initiate the "run-in" phase in December 2009. The randomized phase of the study is likely to begin in the first quarter of 2010.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
IND 104405	GI 1		Human Monoclonal Antibody (RO5072759, Genentech) to CD20
IND 104405	GI 1		Human Monoclonal Antibody (RO5072759, Genentech) to CD20

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/s/

GINA M DAVIS
08/04/2009

LATE-CYCLE COMMUNICATION DOCUMENTS

From: Kirchisner, Elisabeth
To: Hennessey, Lyndsay
Cc: Stephane Avella; Kallungal, Beatrice
Subject: Re: Obinutuzumab (GA101) - Follow-up from late cycle meeting dated Sept 24, 2013
Date: Thursday, October 10, 2013 1:14:10 PM

Dear Lyndsay,

thank you very much for this information. I can confirm [redacted] (b) (4) .
Concerning the meeting minutes from the last two teleconference calls, I will share them with the CMC team and would let you know in case the team has significant comments.

Kind regards,
Elisabeth.

Roche Diagnostics GmbH
Werk Penzberg; Nonnenwald 2; D-82377 Penzberg; Telefon +49-8856-60-0; Telefax +49-8856-60-3896
Sitz der Gesellschaft: Mannheim - Registergericht: AG Mannheim HRB 3962 - Geschäftsführung:
Thomas Schmid, Sprecher; Edgar Vieth - Aufsichtsratsvorsitzender: Dr. Severin Schwan

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On Thu, Oct 10, 2013 at 6:50 PM, Hennessey, Lyndsay <Lyndsay.Hennessey@fda.hhs.gov> wrote:

> Dear Elisabeth,
>
> The review team stated that as long as the [redacted] (b) (4) , which are considered final, it is okay to go ahead [redacted] (b) (4) . Also, please find attached the minutes from the last two teleconferences.
>
> Kind regards,
> Lyndsay
>
> **Lyndsay Hennessey**
>
> Regulatory Health Project Manager
>
> FDA/CDER/OPS/OBP-IO

10903 New Hampshire Ave.

WO Building 21 Room 1523

Silver Spring, Maryland 20993-0002

Lyndsay.Hennessey@fda.hhs.gov

240-402-3746

From: Kirchisner, Elisabeth [mailto:elisabeth.kirchisner@roche.com]
Sent: Monday, October 07, 2013 12:41 PM
To: Hennessey, Lyndsay
Cc: Stephane Avella; Kallungal, Beatrice

Subject: Obinutuzumab (GA101) - Follow-up from late cycle meeting dated Sept 24, 2013

Dear Lyndsay,

based on the discussion which took place during the late-cycle meeting for obinutuzumab on Sept 24, 2013, the CMC team intends to go ahead with (b) (4) commercial launch (b) (4)

The batches will be released according to the updated release specifications for Drug Substance and Drug Product as they were submitted to Module 3 of the BLA with the submission package on Oct 04, 2013 (including all updates according to Q&A).

The CMC team assumes that these release specifications are final and no further adaptations are necessary. It would be very helpful if you could inform us should this assumption not be valid.

Thank you very much in advance and kind regards,

Elisabeth.

Dr. Elisabeth Kirchisner

Director Technical Regulatory Affairs

Roche Diagnostics GmbH
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Nonnenwald 2
82377 Penzberg / Germany

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Sitz der Gesellschaft: Mannheim - Registergericht: AG Mannheim HRB 3962 - Geschäftsführung:
Thomas Schmid, Sprecher; Edgar Vieth - Aufsichtsratsvorsitzender: Dr. Severin Schwan

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/s/

LYNDSAY J HENNESSEY
10/10/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

LATE-CYCLE MEETING MINUTES

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Obinutuzumab (GA101, RO5072759) liquid single use vial (1000mg/40mL (25 mg/mL)) for intravenous infusion.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 24, 2013.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, M.S., RN, ACNP-BC
Lead Clinical Analyst, Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 24, 2013 9:00 AM – 10:00 AM EDT

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: BLA 125486
Product Name: Obinutuzumab (GA101, RO5072759)
Applicant Name: Genentech

Meeting Chair: Virginia Kwitkowski, M.S., RN, ACNP-BC
Meeting Recorder: Beatrice Kallungal, B.S.

FDA ATTENDEES

CDER Participants:

Office of New Drugs
John Jenkins, M.D., Director

Office of Hematology and Oncology Products (OHOP)
Richard Pazdur, M.D., Director

Division of Hematology Products
Ann Farrell, M.D., Division Director
Robert Kane, M.D., Ph.D., Deputy Director Safety
Virginia Kwitkowski, M.S., RN, ACNP-BC, Lead Clinical Analyst, Clinical Team Leader
Hyon-Zu Lee, Pharm.D., Clinical Reviewer
Barry Miller, M.S., CRNP, Clinical Reviewer
Diane Leaman, B.S., Safety Regulatory Project Manager
Ebla Ali Ibrahim, M.S., Lead Regulatory Health Project Manager
Beatrice Kallungal, B.S., Regulatory Project Manager

Office of Biostatistics
Lei Nie, Ph.D., Team Leader
Chia-Wen Ko, Ph.D., Reviewer

Division of Hematology Oncology Toxicology
Haleh Saber, Ph.D., Supervisory Pharmacologist
Stacy Ricci, Ph.D., Reviewer

Pedro DelValle, Ph.D., Reviewer

Office of Clinical Pharmacology
Julie Bullock, Pharm.D., Team Leader

Office of Pharmacovigilance and Epidemiology, Division of Pharmacovigiliance
Tracy Salaam, Pharm.D., Safety Evaluator Team Leader
Afrouz Nayernama, Safety Evaluator

Office of Planning and Informatics (OPI)
Kimberly Taylor, Operations Research Analyst

Office of Biotechnology Products
Marjorie Shapiro, Ph.D., Lab Chief, DMA
Laurie Graham, M.S., Team Lead, DMA
Mate Tolnay, Ph.D., Product Quality Reviewer, DMA

Office of Manufacturing and Product Quality (OMPQ)
Patricia Hughes, Ph.D., Product Quality Microbiology, Team Leader
Colleen Thomas, Ph.D., Product Quality Microbiology Reviewer, BMAB
Kalavati Suvarna, Ph.D., Product Quality Microbiology Reviewer, BMAB

EASTERN RESEARCH GROUP ATTENDEES
Patrick Zhou, Independent Assessor

APPLICANT ATTENDEES
Michael Adler, Process Development Drug Product
Elina Asikanius, Biometrics
Stephane Avella Regulatory Program Manager
Christina Baladi, Regulatory Affairs Associate
Batu Berkok, Product Supply Chain Leader
Jacques Bourquin, Ph.D., Technical Team Leader
Michael Brewster, Clinical Pharmacology
Thomas Buechele, M.D., Global Lifecycle Leader
Hanns-Christian Mahler, Process Development Drug Product
Guenter Fingerle-Rowson, Associate PD Medical Director
Kathryn Humphrey, Clinical Science
Ines Kraemer, Ph.D., Head Technical Regulatory Biologics EU Development
Nafsika Kronidou Horst, Ph.D., Global Regulatory Leader
Hanna Piper-Lepoutre, Safety Scientist Lead
Joerg Maurer, Global Development Leader
Jeffrey Miller, US Regulatory Team Leader-Hematology
Ettore Ohage, Ph.D. IMP Product Quality Leader
Sarah Oliver, Ph.D., US Regulatory Lead
Elisabeth Kirchisner, Ph.D. Technical Regulatory Lead

Reference ID: 3381796

Meik Sacher, Microbiology Drug Product
Alexander Streubel, Process Development Drug Product
Holger Raviol, Technical Regulatory

1.0 BACKGROUND

BLA 125486/0 was submitted on April 22, 2013 for Obinutuzumab (GA101, RO5072759), and is currently under review by the FDA. The application has been granted priority review designation.

Proposed indication: Obinutuzumab in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).

PDUFA goal date: December 20, 2013

FDA issued a Background Package in preparation for this meeting, on September 10, 2013.

2.0 DISCUSSION

1. Introductory Comments

   Welcome, Introductions, Ground rules, Objectives of the meeting

   Discussion: FDA stated that the purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (not planned for this application), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

2. Discussion of Substantive Review Issues

   Each issue was introduced by FDA and followed by a discussion.

   - Product Quality Microbiology

   Discussion: Genentech confirmed that data from the microbial retention study that was repeated for the (b) (4) will be submitted to the BLA the week of October 7, 2013.

   - (b) (4)

   Discussion: Genentech presented the attached slide deck for discussion of (b) (4) (b) (4).

Reference ID: 3381796

Highlights of the presentation included the following:

- (b) (4)
- (b) (4)
- Leptospira testing (b) (4) was completed and was negative.
- (b) (4)
- Information was submitted to the Agency on 08/30/13 with responses to the IR dated 08/12/13 (b) (4) .
- (b) (4)
- Genentech requested written feedback from the Agency (in the form of written meeting minutes including the presentation as an appendix) (b) (4)
- (b) (4)
- (b) (4)

3. Additional Applicant Data

Discussion: No discussion occurred.

4. Information Requests

Product Quality Microbiology
An information request regarding a microbial hold time study was sent on August 26, 2013. A response is requested by September 10, 2013.

Reference ID: 3381796

Discussion: The drug product quality microbiology reviewer stated that the response to this information request was satisfactory. In addition, general discussions occurred regarding existing information requests and expected response dates.

5. Post-marketing Requirements/Post-marketing Commitments

Discussion: A formal verification for hold times of [redacted] (b) (4) from manufacturing scale samples for [redacted] (b) (4) will be completed in December 2013. The final study report will be submitted to the Agency.

6. Major labeling issues

Clinical and Statistics
Your proposed label contains data on [redacted] (b) (4) which was not a pre-specified primary or secondary endpoint in trial BO21004. Since median PFS was the primary endpoint, [redacted] (b) (4)

Your proposed label contains data on "median duration of response". Duration of response is a descriptive endpoint intended for responders only. [redacted] (b) (4) the trial did not adjust for multiplicity for secondary endpoints. Should we retain duration of response as a descriptor for response rates, [redacted] (b) (4).

Discussion: The Agency stated that it is not the usual practice to include secondary endpoints in the product labeling for which there was no statistical alpha control. Exceptions may occur if the endpoints are clinically meaningful for prescribers. The Agency stated that at this time, if median duration of response was considered for inclusion in the PI, it would be presented as a descriptive analysis [redacted] (b) (4), because it is a non-ITT analysis.

Regarding the Agency's disagreement with the proposal to include [redacted] (b) (4), [redacted] (b) (4) Labeling negotiations will continue in writing when the Agency sends amended labeling to the Application in October.

7. Review Plans

- Proposed labeling and, if necessary, any post-marketing requirement/commitment requests will be communicated by October 25, 2013.
- The user fee goal date is December 20, 2013.

Discussion: The Agency stated that attempts will be made to communicate proposed labeling earlier in October in order to expedite possible launch.

8. Wrap-up and Action Items

Reference ID: 3381796

- Timeline for submission of revised protocol synopses for post-marketing requirements and post-marketing commitments.
- Timeline for submission of revised labeling to the FDA.

Discussion:
The timeline for submission of the revised labeling to the FDA will be communicated to the Applicant with the proposed revisions in October.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

19 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3381796

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/s/

VIRGINIA E KWITKOWSKI
10/01/2013

October 1, 2013

This version of the late-cycle meeting minutes did not include the presentation slides used by the sponsor. Refer to the corrected communication issued on October 1, 2013.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

LATE-CYCLE MEETING MINUTES

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Obinutuzumab (GA101, RO5072759) liquid single use vial (1000mg/40mL (25 mg/mL)) for intravenous infusion.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 24, 2013.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, M.S., RN, ACNP-BC
Lead Clinical Analyst, Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 24, 2013 9:00 AM – 10:00 AM EDT

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: BLA 125486
Product Name: Obinutuzumab (GA101, RO5072759)
Applicant Name: Genentech

Meeting Chair: Virginia Kwitkowski, M.S., RN, ACNP-BC
Meeting Recorder: Beatrice Kallungal, B.S.

FDA ATTENDEES

CDER Participants:

Office of New Drugs
John Jenkins, M.D., Director

Office of Hematology and Oncology Products (OHOP)
Richard Pazdur, M.D., Director

Division of Hematology Products
Ann Farrell, M.D., Division Director
Robert Kane, M.D., Ph.D., Deputy Director Safety
Virginia Kwitkowski, M.S., RN, ACNP-BC, Lead Clinical Analyst, Clinical Team Leader
Hyon-Zu Lee, Pharm.D., Clinical Reviewer
Barry Miller, M.S., CRNP, Clinical Reviewer
Diane Leaman, B.S., Safety Regulatory Project Manager
Ebla Ali Ibrahim, M.S., Lead Regulatory Health Project Manager
Beatrice Kallungal, B.S., Regulatory Project Manager

Office of Biostatistics
Lei Nie, Ph.D., Team Leader
Chia-Wen Ko, Ph.D., Reviewer

Division of Hematology Oncology Toxicology
Haleh Saber, Ph.D., Supervisory Pharmacologist
Stacy Ricci, Ph.D., Reviewer

Pedro DelValle, Ph.D., Reviewer

Office of Clinical Pharmacology
Julie Bullock, Pharm.D., Team Leader

Office of Pharmacovigilance and Epidemiology, Division of Pharmacovigiliance
Tracy Salaam, Pharm.D., Safety Evaluator Team Leader
Afrouz Nayernama, Safety Evaluator

Office of Planning and Informatics (OPI)
Kimberly Taylor, Operations Research Analyst

Office of Biotechnology Products
Marjorie Shapiro, Ph.D., Lab Chief, DMA
Laurie Graham, M.S., Team Lead, DMA
Mate Tolnay, Ph.D., Product Quality Reviewer, DMA

Office of Manufacturing and Product Quality (OMPQ)
Patricia Hughes, Ph.D., Product Quality Microbiology, Team Leader
Colleen Thomas, Ph.D., Product Quality Microbiology Reviewer, BMAB
Kalavati Suvarna, Ph.D., Product Quality Microbiology Reviewer, BMAB

EASTERN RESEARCH GROUP ATTENDEES
Patrick Zhou, Independent Assessor

APPLICANT ATTENDEES
Michael Adler, Process Development Drug Product
Elina Asikanius, Biometrics
Stephane Avella Regulatory Program Manager
Christina Baladi, Regulatory Affairs Associate
Batu Berkok, Product Supply Chain Leader
Jacques Bourquin, Ph.D., Technical Team Leader
Michael Brewster, Clinical Pharmacology
Thomas Buechele, M.D., Global Lifecycle Leader
Hanns-Christian Mahler, Process Development Drug Product
Guenter Fingerle-Rowson, Associate PD Medical Director
Kathryn Humphrey, Clinical Science
Ines Kraemer, Ph.D., Head Technical Regulatory Biologics EU Development
Nafsika Kronidou Horst, Ph.D., Global Regulatory Leader
Hanna Piper-Lepoutre, Safety Scientist Lead
Joerg Maurer, Global Development Leader
Jeffrey Miller, US Regulatory Team Leader-Hematology
Ettore Ohage, Ph.D. IMP Product Quality Leader
Sarah Oliver, Ph.D., US Regulatory Lead
Elisabeth Kirchisner, Ph.D. Technical Regulatory Lead

Reference ID: 3380773

Meik Sacher, Microbiology Drug Product
Alexander Streubel, Process Development Drug Product
Holger Raviol, Technical Regulatory

1.0 BACKGROUND

BLA 125486/0 was submitted on April 22, 2013 for Obinutuzumab (GA101, RO5072759), and is currently under review by the FDA. The application has been granted priority review designation.

Proposed indication: Obinutuzumab in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).

PDUFA goal date: December 20, 2013

FDA issued a Background Package in preparation for this meeting, on September 10, 2013.

2.0 DISCUSSION

1. Introductory Comments

   Welcome, Introductions, Ground rules, Objectives of the meeting

   Discussion: FDA stated that the purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (not planned for this application), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

2. Discussion of Substantive Review Issues

   Each issue was introduced by FDA and followed by a discussion.

   - Product Quality Microbiology

   Discussion: Genentech confirmed that data from the microbial retention study that was repeated for the (b) (4) will be submitted to the BLA the week of October 7, 2013.

   - (b) (4)

   Discussion: Genentech presented the attached slide deck for discussion of the (b) (4)

Reference ID: 3380773

Highlights of the presentation included the following:

- (b) (4)
- Leptospira testing (b) (4) was completed and was negative.
- (b) (4)
- Information was submitted to the Agency on 08/30/13 with responses to the IR dated 08/12 (b) (4)
- Genentech requested written feedback from the Agency (in the form of written meeting minutes including the presentation as an appendix) (b) (4)
  (b) (4)

3. Additional Applicant Data

   Discussion: No discussion occurred.

4. Information Requests

   Product Quality Microbiology
   An information request regarding a microbial hold time study was sent on August 26, 2013. A response is requested by September 10, 2013.

Reference ID: 3380773

Discussion: The drug product quality microbiology reviewer stated that the response to this information request was satisfactory. In addition, general discussions occurred regarding existing information requests and expected response dates.

5. Post-marketing Requirements/Post-marketing Commitments

Discussion: A formal verification for hold times of (b) (4) from manufacturing scale samples for (b) (4) will be completed in December 2013. The final study report will be submitted to the Agency.

6. Major labeling issues

Clinical and Statistics
Your proposed label contains data on (b) (4) which was not a pre-specified primary or secondary endpoint in trial BO21004. Since median PFS was the primary endpoint. (b) (4)

Your proposed label contains data on "median duration of response". Duration of response is a descriptive endpoint intended for responders only. (b) (4) the trial did not adjust for multiplicity for secondary endpoints. Should we retain duration of response as a descriptor for response rates, (b) (4)

Discussion: The Agency stated that it is not the usual practice to include secondary endpoints in the product labeling for which there was no statistical alpha control. Exceptions may occur if the endpoints are clinically meaningful for prescribers. The Agency stated that at this time, if median duration of response was considered for inclusion in the PI, it would be presented as a descriptive analysis (b) (4) because it is a non-ITT analysis.

Regarding the Agency's disagreement with the proposal to include (b) (4) , (b) (4) Labeling negotiations will continue in writing when the Agency sends amended labeling to the Application in October.

7. Review Plans

- Proposed labeling and, if necessary, any post-marketing requirement/commitment requests will be communicated by October 25, 2013.
- The user fee goal date is December 20, 2013.

Discussion: The Agency stated that attempts will be made to communicate proposed labeling earlier in October in order to expedite possible launch.

8. Wrap-up and Action Items

Reference ID: 3380773

- Timeline for submission of revised protocol synopses for post-marketing requirements and post-marketing commitments.
- Timeline for submission of revised labeling to the FDA.

Discussion:
The timeline for submission of the revised labeling to the FDA will be communicated to the Applicant with the proposed revisions in October.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

Reference ID: 3380773

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/s/

VIRGINIA E KWITKOWSKI
09/28/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

LATE CYCLE MEETING
BACKGROUND PACKAGE

Genentech, Inc.
Attention: Michelle H. Rohrer, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Rohrer:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Obinutuzumab (GA101, RO5072759) liquid single use vial (1000mg/40mL (25 mg/mL)) for intravenous infusion.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 24, 2013. Attached is our background package, including our agenda for this meeting.

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, M.S., RN, ACNP-BC
Lead Clinical Analyst, Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: September 24, 2013 9:00 AM – 10:00 AM EDT

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: BLA 125486
Product Name: Obinutuzumab (GA101, RO5072759)
Indication: Obinutuzumab in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).
Sponsor/Applicant Name: Genentech

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Reference ID: 3371190

- Product Quality Microbiology

As discussed previously, the microbial retention study for the [redacted] (b) (4) will be repeated and the data is expected to be available the week of October 7, 2013. Submit summary data and the validation report to the BLA file promptly, and notify the Agency if data submission to the BLA file will be delayed.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 25 minutes

   Each issue will be introduced by FDA and followed by a discussion.
   - Product Quality Microbiology
   - [redacted] (b) (4)

3. Additional Applicant Data – 5 minutes (Applicant)

4. Information Requests – 5 minutes

   Product Quality Microbiology
   An information request regarding a microbial hold time study was sent on August 26, 2013. A response is requested by September 10, 2013.

5. Post-marketing Requirements/Post-marketing Commitments – 5 minutes

   (TO BE DETERMINED)

6. Major labeling issues – 5 minutes

   Clinical and Statistics
   Your proposed label contains data on [redacted] (b) (4) which was not a pre-specified primary or secondary endpoint in trial BO21004. Since median PFS was the primary endpoint, [redacted] (b) (4).

   Your proposed label contains data on "median duration of response". Duration of response is a descriptive endpoint intended for responders only. [redacted] (b) (4)

Reference ID: 3371190

(b) (4) the trial did not adjust for multiplicity for secondary endpoints. Should we retain duration of response as a descriptor for response rates, hazard ratios and p-values will not be included.

7. Review Plans – 5 minutes

   - Proposed labeling and, if necessary, any post-marketing requirement/commitment requests will be communicated by October 25, 2013.
   - The user fee goal date is December 20, 2013.

8. Wrap-up and Action Items – 5 minutes

   - Timeline for submission of revised protocol synopses for post-marketing requirements and post-marketing commitments.
   - Timeline for submission of revised labeling to the FDA.

Reference ID: 3371190

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/s/

VIRGINIA E KWITKOWSKI
09/10/2013