

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761064Orig1s000**

**OTHER REVIEW(S)**



Center for Drug Evaluation and Research  
Office of Pharmaceutical Quality  
Office of Biotechnology Products

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### LABELS AND LABELING REVIEW

Date:	June 22, 2017
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products (OBP)
Through:	Shen Luo, PhD, Quality Reviewer OBP/Division of Biotechnology Review and Research IV  Marjorie Shapiro, PhD, Lab Chief OBP/Division of Biotechnology Review and Research I
Application:	BLA 761064/0
Product:	Rituxan Hycela (rituximab and hyaluronidase human)
Applicant:	Manufacturer as listed on FDA form 356h
Submission Dates:	August 26, 2016, May 15; May 30; June 9, 21, 2017

#### I) **RECOMMENDATION**

The labels and labeling for Rituxan Hycela (rituximab and hyaluronidase human) Injection 1,400 mg/23,400 Units per 11.7 mL and 1,600 mg/26,800 Units per 13.4 mL in single-dose vials submitted on the following dates are acceptable from a quality perspective:

- Prescribing Information and Medication Guide: June 21, 2017  
<\\cdsesub1\evsprod\bla761064\0085\m1\us\final-label-text.doc>
- Container Labels and Carton Labeling: June 9, 2017  
<\\cdsesub1\evsprod\bla761064\0082\m1\us\draft-carton-container-labels.pdf>

## II) BACKGROUND AND SUMMARY DESCRIPTION

The Applicant submitted BLA 761064/0 Rituxan Hycela (rituximab and hyaluronidase human) on August 25, 2016. This review evaluates the labeling submitted for this Application on August 25, 2016.

Table 1: Proposed Product Characteristics of Rituxan Hycela (rituximab and hyaluronidase human).

<b>Proprietary Name:</b>	Rituxan Hycela
<b>Nonproprietary Name:</b>	rituximab and hyaluronidase
<b>Dosage Form:</b>	Injection
<b>Strength and Container-Closure:</b>	1,400 mg/23,400 Units per 11.7 mL solution in a single-dose vial 1,600 mg/26,800 Units per 13.4 mL solution in a single dose vial
<b>Route of Administration:</b>	Subcutaneous
<b>Storage and Handling:</b>	Refrigerate at 36°F–46°F (2°C–8°C) in original carton to protect from light. Do not freeze.  Once transferred from the vial into the syringe, store the solution of RITUXAN HYCELA in the refrigerator at 36°F–46°F (2°C–8°C) up to 48 hours and subsequently for 8 hours at room temperature up to 30°C (86°F) in diffuse light.
<b>Indication:</b>	combination of rituximab, a CD20-directed cytolytic antibody, and hyaluronidase human, an endoglycosidase, indicated for the treatment of adult patients with: <ul style="list-style-type: none"> <li>- Follicular Lymphoma (FL)</li> <li>- Diffuse Large B-cell Lymphoma (DLBCL)</li> <li>- Chronic Lymphocytic Leukemia (CLL)</li> </ul>
<b>Dose and Frequency:</b>	<ul style="list-style-type: none"> <li>• FL: 1,400 mg/23,400 Units in subcutaneous tissue of abdomen over 5 minutes. (Frequency of dosing varies)</li> <li>• DLBCL: 1,400 mg/23,400 Units in subcutaneous tissue of abdomen over 5 minutes. (Frequency of dosing varies)</li> <li>• CLL: 1,600 mg/26,800 Units in subcutaneous tissue of abdomen over 7 minutes. (Frequency of dosing varies)</li> </ul>

### III) MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

**Table 2: Materials Considered for this Label and Labeling Review**

Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Other (n/a)	B
Relevant Code of Federal Regulations and CDER Labeling Best Practices	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

### IV) DISCUSSION

The proposed labeling was evaluated for compliance to the applicable code of federal regulations and CDER Labeling Best Practices (see Appendix C).

#### Nonproprietary Name for Hyaluronidase component

The proposed labeling uses both "hyaluronidase" and "Recombinant human hyaluronidase." We looked at labeling for currently marketed hyaluronidase products (Table 3). We noted that the majority of hyaluronidase products indicated the source (bovine, ovine, and human). Additionally, "recombinant" is part of the nonproprietary name in Hyqvia (regulated in CBER). However, "recombinant" appears to be part of the proprietary name in Hylenex recombinant.

We determined that we should include the source of the product in the name to distinguish it from bovine and ovine derived hyaluronidase. The word "recombinant" (b) (4) (b) (4) could appear within section 11 DESCRIPTION within the drug substance section. Therefore, we recommend the "hyaluronidase" portion of the nonproprietary name be "hyaluronidase human". Thus, we recommend the nonproprietary name "rituximab and hyaluronidase human" for Rituxan Hycela.

During labeling negotiations, we provided the following comment:

We agree that the name should distinguish this hyaluronidase from animal derived hyaluronidase. We recommend "hyaluronidase human". "Recombinant" (b) (4) (b) (4) detailed in section 11 in the drug substance paragraph. Within the nonproprietary name and also when describing the "hyaluronidase" component of the drug substances, revise "hyaluronidase" to "hyaluronidase human" throughout all labeling.

In response, the Applicant noted:

Per the Agency's recommendation, the Sponsor has (b) (4) the word 'recombinant' (b) (4) in Section 11 in the drug substance paragraph. However, the Sponsor proposes (b) (4)

Subsequently, we provided the following recommendation:

The nonproprietary name for Hylenex is "hyaluronidase human injection". Therefore, we find the nonproprietary name for this product should be "rituximab and hyaluronidase human".

Revise the labeling such that when naming the product or the hyaluronidase component, use "hyaluronidase human". It is appropriate to use "recombinant human hyaluronidase" when describing the hyaluronidase component in section 11.

The Applicant agreed.

**Table 3: Names of hyaluronidase products.**

	<b>BLA 761064</b>	<b>NDA 21859</b>	<b>BLA 125402*</b>	<b>NDA 21640</b>	<b>NDA 21716</b>	<b>NDA 021665</b>
<b>Names on PDP of container/ carton</b>	Rituximab/ hyaluronidase	Hylenex recombinant (hyaluronidase human injection)	Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase HYQVIA	Vitrase (hyaluronidase injection) Ovine	Hydase (hyaluronidase injection) Bovine	Amphadase (hyaluronidase injection)
<b>Name on Product Title in PI</b>	Rituximab/ hyaluronidase	Hylenex recombinant (hyaluronidase human injection)	HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase]	VITRASE (hyaluronidase injection) Ovine,	HYDASE (hyaluronidase injection) Bovine,	Amphadase (hyaluronidase injection)
<b>Names elsewhere in PI</b>	Rituximab/ hyaluronidase  recombinant human hyaluronidase (rHuPH20)	HYLENEX recombinant  Hyaluronidase recombinant human hyaluronidase	Recombinant Human Hyaluronidase	Ovine hyaluronidase (section 3)  hyaluronidase injection	hyaluronidase injection	Amphadase (hyaluronidase injection)  **Note bovine mentioned only in section 11 Description**

\*Regulated by CBER.

Proper Name

DMEPA provided the following comments to the Applicant regarding the proper name in a June 6, 2017 Information Request.

“FDA issued a final guidance entitled Nonproprietary Naming of Biological Products on January 13, 2017 stating the Agency’s intention to designate proper names for certain biological products that include distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your BLA be licensed, and intend to work with you post-approval to implement a proper name consistent with the principles outlined in the guidance. We would work with you to minimize the impact this would have to your manufacture and distribution of this product.”

## **VI) CONCLUSION**

The prescribing information, medication guide, container labels, and carton labeling for Rituxan Hycela (rituximab and hyaluronidase human) Injection 1,400 mg/23,400 Units per 11.7 mL and 1,600 mg/26,800 Units per 13.4 mL in single-dose vials were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100 and United States Pharmacopeia (USP). The labels and labeling submitted on the following dates are acceptable from a quality perspective:

- Prescribing Information and Medication Guide: June 21, 2017
- Container Labels: June 9, 2017
- Carton Labeling: June 9, 2017

## **APPENDICES**

### **Appendix A: Proposed Labeling**

- Prescribing Information and Medication Guide  
<\\cdsesub1\evsprod\bla761064\0000\m1\us\draft-labeling-text.pdf>
- Container Labels and Carton Labeling  
<\\cdsesub1\evsprod\bla761064\0000\m1\us\draft-carton-container-labels.pdf>

(b) (4)

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

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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.**  
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/s/  
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JIBRIL ABDUS-SAMAD  
06/22/2017

SHEN LUO  
06/22/2017

MARJORIE A SHAPIRO  
06/22/2017

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**LABEL AND LABELING REVIEW AMENDMENT**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Memorandum:** June 20, 2017

**Requesting Office or Division:** Division of Hematology Products (DHP)

**Application Type and Number:** BLA 761064

**Product Name and Strength:** Rituxan Hycela  
(rituximab and hyaluronidase human)  
Injection  
1,400 mg rituximab and 2,000 units/mL hyaluronidase human per 11.7 mL solution  
1,600 mg rituximab and 2,000 units/mL hyaluronidase human per 13.4 mL solution

**Applicant/Sponsor Name:** Genentech, Inc.

**Submission Date:** May 30, 2017 and June 9, 2017

**OSE RCM #:** 2016-1980-2 and 2017-59-2

**DMEPA Primary Reviewer:** Nicole Garrison, PharmD, BCPS

**DMEPA Team Leader:** Hina Mehta, PharmD

**OMEPRM Acting Deputy Director:** Lubna Merchant, MS, PharmD

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**REASON FOR AMENDMENT:**

FDA recently issued a final guidance entitled *Nonproprietary Naming of Biological Products* on January 13, 2017 stating the Agency's intention to designate proper names for certain biological products that include four-digit distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated

without a suffix [and intend to work with the applicant post-approval to implement a proper name consistent with the principles outlined in the guidance].

## **1 RECOMMENDATIONS FOR GENENTECH, INC.**

### **A. General Comments**

FDA issued a final guidance entitled *Nonproprietary Naming of Biological Products* on January 13, 2017 stating the Agency's intention to designate proper names for certain biological products that include distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying the decision of the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your BLA be licensed, and intend to work with you post-approval to implement a proper name consistent with the principles outlined in the guidance. We would work with you to minimize the impact this would have to your manufacture and distribution of this product.

## HUMAN FACTORS LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

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<b>Date of This Review:</b>	March 13, 2017
<b>Requesting Office or Division:</b>	Division of Hematology Products (DHP)
<b>Application Type and Number:</b>	BLA 761064
<b>Product Name and Strength:</b>	Rituxan subcutaneous (rituximab and hyaluronidase) Injection 1400 mg and 23,400 units, 1600 mg and 26,800 units
<b>Product Type:</b>	Multi-ingredient product
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Genentech, Inc.
<b>Submission Date:</b>	August 26, 2016, December 12, 2016, and January 6, 2017
<b>OSE RCM #:</b>	2016-1980 and 2017-59
<b>DMEPA Primary Reviewer:</b>	Nicole Garrison, PharmD, BCPS
<b>DMEPA Team Leader:</b>	Hina Mehta, PharmD
<b>DMEPA Associate Director for Human Factors:</b>	QuynhNhu Nguyen, MS
<b>OMEPRM Deputy Director (Acting):</b>	Lubna Merchant, MS, PharmD

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## **2 REASON FOR REVIEW**

The Division of Hematology Products (DHP) requested DMEPA evaluate the proposed labels and labeling and Human Factors (HF) study results submitted on August 26, 2016 and December 12, 2016, for BLA 761064, Rituxan Subcutaneous (rituximab and hyaluronidase) Injection to ensure the intended user population is able to understand the labeling of this product. This human factor study was also conducted to evaluate the intended users' ability to distinguish between the Rituxan dosage forms and strengths.

### **2.1 PRODUCT BACKGROUND**

Rituxan (rituximab) injection is currently approved for the treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Rituxan is available as 100 mg/10 mL and 500 mg/50 mL (10 mg/mL) single dose vials for intravenous use.

The proposed product, Rituximab and hyaluronidase is indicated for the treatment of patients with follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL). It is administered as a subcutaneous injection after patients receive at least full dose of Rituxan (rituximab) by intravenous infusion. Rituximab and hyaluronidase is intended for use at a dose of 1400 mg and 23,400 units/mL for patients with FL/DLBCL only and 1600 mg and 26,800 units/mL in patients with CLL. The administration of rituximab and hyaluronidase is over 5 to 7 minutes.

### **2.2 REGULATORY HISTORY**

On February 23, 2016, DMEPA participated in a face-to-face meeting between the Division of Hematology Products (DHP) and Genentech to discuss registration of subcutaneous rituximab.<sup>a</sup> We noted that the proposed subcutaneous rituximab formulation is more concentrated than the currently marketed intravenous rituximab formulation. Therefore, we expressed concern regarding the risk of medication errors if the subcutaneous and intravenous formulations are confused with each other. Additionally, we noted that the subcutaneous rituximab formulation requires a large-volume subcutaneous injection and a five to seven minute administration time, which is not the typical volume or time for subcutaneous injections. Due to the medication error risks associated with the introduction of the proposed subcutaneous rituximab formulation, we recommended that the Sponsor submit a use-related risk analysis and plans for a HF validation study that focused on product differentiation and labeling comprehension.

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<sup>a</sup> Memorandum of Type B Meeting Minutes for Rituxan (PIND 126650). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Hematology and Oncology Products, Division of Hematology Products. 2016 FEB 26.

### 3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

### 4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

#### 4.1 HUMAN FACTORS STUDY

##### 4.1.1 Methodology

Genentech submitted BLA 761064 rituximab and hyaluronidase injection for subcutaneous administration for the treatment of patients with follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL). The Applicant conducted a summative label comprehension and product differentiation study for rituximab and hyaluronidase for subcutaneous injection. DMEPA reviewed the methodology for the study on May 2, 2016<sup>b</sup> and found it acceptable in terms of focusing on product differentiation and label comprehension. However, we noted deficiencies including the omission of mockup prescriptions and the moderator's script. Additionally we noted the use of error prone abbreviations, e.g. (b) (4) in the proprietary name on the carton labeling and container labels. We provided recommendations to submit drafts of the mockup prescriptions and the moderator's script that will be used in the HF study. We recommended that the Sponsor complete the HF validation study and mitigate all identified risks prior to approval (b) (4). (b) (4). Additionally, we recommended against the use of the proprietary name (b) (4) on the labels and labeling that will be

<sup>b</sup> Whaley, E. Human Factors Study Protocol Review (PIND 126650). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 May 02. 11 p. OSE RCM No.: 2016-704.

used in the HF validation study. We have confirmed that our recommendations were implemented.

The study involved carton differentiation, vial differentiation, labeled syringe identification, and label comprehension in 15 nurses and 15 pharmacists.

#### **4.1.2 Human factors study results**

The Applicant conducted a product differentiation and a label comprehension study. The results are discussed below:

1. Carton and vial differentiation study results

There were no observed use errors performed by pharmacists and nurses. There was one observed use error (1/30, or 96.67% success) committed during the labeled syringe identification tasks. The participant was unable to identify the route of administration for a 1400 mg and 2000 units/mL hyaluronidase syringe (See Appendix C for details of the error that occurred in the Study) described in detail below.

#### **Error in determining the route of administration for a labeled syringe (n=1)**

One nurse was unable to correctly answer the syringe label question about the “dosage form or administration type” for the 1400 mg syringe. The participant was initially confused by the question and after the investigator repeated it, he then seemed to focus on the “dosage form” part of the question and provided the dose strength in response. The investigator then asked the participant about the “administration type” and he replied, “It doesn’t say. It just says injection.” The participant went on to state that the syringe label did not specify if it was subcutaneous or intravenous. During the root cause interview, the investigator redirected the participant to the medication name on the syringe and the participant then noticed “subcutaneous” in the name on the label. The participant did not provide a reason as to why he missed the word subcutaneous on the syringe label before. However, he attributed the error to the large syringe volume, which made him think it was not a subcutaneous injection. He stated the syringe volume seemed too large to be a subcutaneous injection and had only administered subcutaneous injections of 5 mL or less in the past. In his experience, a typical subcutaneous injection contains 2 to 3 mL. The Applicant proposes changes to amend the peel-off label (b) (4). After review of the proposed changes, we determined, further modifications to labels and labeling are suggested to highlight the route of administration.

2. Label comprehension study results

There were no observed use errors that occurred in the labeling comprehension part of the study, however during the final interview, participants were able to provide additional feedback. Of those participants who provided feedback, there were some concerns raised by the participants which are discussed below.

- Injection site guidance (n=2)
- Atypical injection time (n =2)

- Large injection volume (n =4)
- Storage information (n=3)

### **Injection site guidance (n=2)**

Two participants mentioned the injection site could be further highlighted and clarified. The participants noted that the Prescribing Information (PI) does not indicate what happens if the subcutaneous injection is administered in a site outside of the abdomen or note the reason for restricting the injection to one site. However, after review of the PI, it states that there is no available information on performing the injection at other sites of the body. Additionally, one participant recommended highlighting the injection site information to make it more visible to the intended users. Based on this feedback, we recommend highlighting the administration site (abdominal wall) in the PI by stating “Administer Rituxan subcutaneously into the abdominal wall over approximately 5-7 minutes.”

### **Atypical injection time (n=2)**

Two participants understood the atypical injection time (due to the large volume), and made comments on the injection time being long for a subcutaneous injection. It was noted that most subcutaneous injections are quick and with the large volume and longer injection time required for Rituxan subcutaneous, more guidance and practice would be needed to administer of the prescribed duration of 5 to 7 minutes. Based on this feedback, we recommend the Sponsor provide more guidance to healthcare professionals by distributing a “Dear Healthcare Provider” letter to ensure that providers are aware of the new formulation of Rituxan subcutaneous and the unique requirements for safe administration of this product. Additionally, we recommend revisions to the container label and peel off label to state, “Give the subcutaneous injection over 5 to 7 minutes”.

### **Large injection volume (n =4)**

Four participants commented on the size of the syringe injection being larger than they were used to with a subcutaneous injection. Participants had questions on how they would administer the large dose and if it would be broken up into several smaller injections. The Sponsor proposes to clarify in the PI, if the injection is interrupted, it can be continued at a different site, but restricted to the abdomen. One participant expressed concern that the large injection volume of the syringe could lead to confusion and improper administration intravenously. To address concerns from the participants, the Sponsor proposes to amend the peel off label (b) (4). Additionally, we recommend revisions to the labels and labeling to ensure the subcutaneous route of administration is prominently displayed.

### **Storage information (n=3)**

Three participants commented on the storage recommendation to protect the medication from (b) (4) light. They stated it was unclear if they meant (b) (4) all light sources

in general. After review of the PI, it states (b) (4)  
(b) (4) Thus, no further modifications are warranted to the PI at this time.

## 5 LABELS AND LABELING

In addition to the HF study results, we reviewed the proposed container label, carton labeling, and Prescribing Information to determine whether there were any areas that may be vulnerable to confusion that can lead to medication errors. The error observed in the study can be attributed to the large volume of solution required for subcutaneous injection of the product. The Applicant proposes changes to amend the peel-off label (b) (4)  
(b) (4). After review of the proposed changes, we determined, further modifications to labels and labeling are suggested to highlight the route of administration.

## 6 CONCLUSION & RECOMMENDATIONS

The HF results and feedback from interviewing study participants demonstrated that further revisions were needed to the container label, carton labeling, and Prescribing Information to ensure clarity and prominence of the information.

### 6.1 RECOMMENDATIONS FOR THE DIVISION

#### A. Prescribing Information

1. Highlights and Full Prescribing Information
  - a. As currently presented, the strength of rituximab and hyaluronidase is expressed using the dangerous abbreviation “u”. We recommend revising the strength presentation to change “u” to “USP units”<sup>c,d</sup>.
2. Section 2, Dosage and Administration
  - a. The proposed Dosage and Administration section is lengthy. Consider further separation of the text with the use of bullets to increase clarity of the information and ensure correct administration of this product.
  - b. Section 2.1 Administration of TRADENAME™ for Subcutaneous Injection
    - i. Increase the prominence of the injection site of administration by having a separate bullet that stating, “Administer Rituxan subcutaneously into the abdominal wall over approximately 5-7 minutes”.
    - ii. Revise (b) (4)  
(b) (4)

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<sup>c</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

<sup>d</sup> ISMP’s List of Error-Prone Abbreviations Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medications Practices. 2015 [2017 FEB 03]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>

(b) (4)

(b) (4) We recommend this revision based on feedback received from participants in the Human Factors study.

c. Section 2.6 Preparation for Administration

- i. The vial has a peel-off label that should be attached to the syringe after the product is withdrawn from the vial. The peel-off label is used as a tool to mitigate wrong administration errors as it is clearly labeled (b) (4). We recommend that this important information be conveyed in the Prescribing Information by revising the statement, (b) (4) (b) (4) to “Once the product is withdrawn from the vial, it should be labeled with the peel-off sticker and used immediately.”

## 6.2 RECOMMENDATIONS FOR GENENTECH, INC.

We recommend the following be implemented prior to approval of this BLA:

A. Healthcare Provider Education

1. Rituximab and hyaluronidase will be the first subcutaneous injection of rituximab in the United States. We note that there are differences between the proposed subcutaneous rituximab and hyaluronidase formulation with the currently marketed intravenous rituximab formulation. The proposed subcutaneous rituximab and hyaluronidase formulation is supplied in a larger volume (11.7 mL and 13.4 mL), requires a longer administration time than most subcutaneous injections (5 or 7 minutes) and is more concentrated than intravenous rituximab. We anticipate that providers may not review the instructions for use prior to administration of this product and medication errors may occur if the subcutaneous and intravenous formulations are confused with each other. Thus, we recommend the Applicant consider providing an education campaign to health care providers (HCP’s) that focuses on providing specific product information.

B. Container labels

1. Revise the presentation of the established name from “rituximab/hyaluronidase” to “rituximab and hyaluronidase” to be consistent with the Prescribing Information.

- Express the product strength on the principal display panel to state in terms of total quantity per total volume followed by the concentration per milliliter (mL) as per USP standards<sup>e,f</sup>.

For example:

**1400 mg and 23,400 USP units/11.7 mL**

(120 mg and 2000 USP units/mL)

- As currently presented, the strength of rituximab and hyaluronidase is expressed using the dangerous abbreviation “u”. We recommend revising the strength presentation to change “u” to “USP units”<sup>g,h</sup>.
- Revise the statement (b) (4) to “For Subcutaneous Use only. Give the subcutaneous injection over 5 to 7 minutes”. We recommend increasing the font of the statement to help minimize the risk of administering the medication via an intravenous route of administration.
- Clarify the significance of the number located next to the expiration date (10173774). If it is an internal product code, we recommend removing and/or relocating this number to mitigate the potential for confusion due to its close proximity to the expiration number.
- Reorient the barcode containing the NDC number to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to curvature of the vial.
- Peel-off Panel
  - Include the text, “For subcutaneous use only” to help minimize the risk of administering the syringe via an intravenous route of administration.
  - Include the text “Give the subcutaneous injection over 5 to 7 minutes” to ensure this important information is not overlooked.

C. Carton labeling

- See A.1 through A. 5 and revise the carton labeling accordingly.

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<sup>e</sup> USP General Chapter<1> Injections

<sup>f</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

<sup>g</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

<sup>h</sup> ISMP’s List of Error-Prone Abbreviations Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medications Practices. 2015 [2017 FEB 03]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Rituxan Subcutaneous that Genentech submitted on December 12, 2016.

<b>Table 2. Relevant Product Information for Rituxan Subcutaneous</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	Rituximab and hyaluronidase
<b>Indication</b>	For the treatment of patients with: <ul style="list-style-type: none"> <li>• Follicular Lymphoma (FL)</li> <li>• Diffuse Large B-cell Lymphoma (DLBCL)</li> <li>• Chronic Lymphocytic Leukemia (CLL)</li> </ul>
<b>Route of Administration</b>	Subcutaneous
<b>Dosage Form</b>	Injection
<b>Strength</b>	<ul style="list-style-type: none"> <li>• 1400 mg rituximab and 2000 units/mL hyaluronidase per 11.7 mL</li> <li>• 1600 mg rituximab and 2000 units/mL hyaluronidase per 13.4 mL</li> </ul>
<b>Dose and Frequency</b>	<p><b><u>FL</u></b></p> <ul style="list-style-type: none"> <li>• Administer 1400 mg rituximab and 2000 units/mL hyaluronidase may be given over 5 minutes <i>Relapsed or Refractory, Follicular Lymphoma</i></li> <li>• Administer once weekly for 3 weeks following a full intravenous Rituxan dose at week 1 (i.e. 4 weeks in total). <i>Retreatment for Relapsed or Refractory, Follicular Lymphoma</i></li> <li>• Administer once weekly for 3 weeks following a full intravenous Rituxan dose at week 1 (i.e. 4 weeks in total). <i>Previously Untreated, Follicular Lymphoma</i></li> <li>• Administer on Day 1 of Cycles 2-8 of chemotherapy, for up to 7 cycles following a full intravenous Rituxan dose on Day 1 of Cycle 1 of chemotherapy. <i>Non-progressing, Follicular Lymphoma after the first line CVP chemotherapy</i></li> <li>• Following completion of 6-8 cycles of CVP chemotherapy, administer once weekly for 3 weeks</li> </ul>

	<p>following a full intravenous Rituxan dose at week 1 (i.e. 4 weeks in total), at 6 month intervals to a maximum of 16 doses.</p> <p><b><u>DLBCL</u></b></p> <ul style="list-style-type: none"> <li>Administer 1400 mg and 2000 u/mL hyaluronidase by subcutaneous injection over 5 minutes on Day 1 of Cycles 2-8 of CHOP chemotherapy, for up to 7 cycles following a full intravenous Rituxan dose at Day 1, Cycle 1 of CHOP chemotherapy.</li> </ul> <p><b><u>CLL</u></b></p> <ul style="list-style-type: none"> <li>Administer 1600 mg rituximab and 2000 units/mL hyaluronidase may be given over 7 minutes on Day 1 of Cycles 2-6 (every 28 days) for a total of 6 cycles.</li> </ul>
<b>How Supplied</b>	<p>Individually packaged single-dose vials:</p> <ul style="list-style-type: none"> <li>1400 mg rituximab and 2000 units/mL hyaluronidase per 11.7 mL</li> <li>1600 mg rituximab and 2000 units/mL hyaluronidase per 13.4 mL</li> </ul>
<b>Storage</b>	<p>(b) (4)</p>

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On February 3, 2017, we searched the L:drive and AIMS using the terms, Rituxan to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified two previous label and labeling reviews<sup>i,j</sup>. We confirmed that our previous recommendations were implemented.

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<sup>i</sup> Whaley, E. Human Factors Study Protocol Review (PIND 126650). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 May 02. 11 p. OSE RCM No.: 2016-704

<sup>j</sup> Whaley, E. Human Factors Study Protocol Review Memo (IND 126650). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Jun 20. 03 p. OSE RCM No.: 2016-1201.

## APPENDIX C. HUMAN FACTORS STUDY

### C.1 Results

There were no observed use errors during the carton and vial differentiation tasks performed by pharmacists and nurses. There was one observed use error (1/30, or 96.67% success) committed during the labeled syringe identification tasks. All participants could read and comprehend the syringe label information. Nurses were correctly able to answer all comprehension questions on the syringe label, except for one nurse who questioned the administration type.

*Table 8. Results from Pharmacists' Product Differentiation Tasks*

Pharmacists, N = 15	Carton Differentiation			Vial Differentiation		
	Task Results		Success %	Task Results		Success %
Dose Strength (mg)	Yes	No	[(N/15)*100]	Yes	No	[(N/15)*100]
100	15	0	100%	15	0	100%
500	15	0	100%	15	0	100%
1400	15	0	100%	15	0	100%
1600	15	0	100%	15	0	100%

*Table 9. Results from Nurses' Product Differentiation Tasks*

Nurses, N = 15	Carton Differentiation			Vial Differentiation		
	Task Results		Success %	Task Results		Success %
Dose Strength (mg)	Yes	No	[(N/15)*100]	Yes	No	[(N/15)*100]
100	15	0	100%	15	0	100%
500	15	0	100%	15	0	100%
1400	15	0	100%	15	0	100%
1600	15	0	100%	15	0	100%

Table 10. Results from Pharmacists' Labeled Syringe Tasks

Pharmacists N=15	Label Comprehension						Total Outcome		Success %
	Dose Strength (mg)	Medication Name		Admin. Type		Strength	Yes	No	
		Yes	No	Yes	No				Yes
1400	15	0	15	0	15	0	15	0	[(N/15)*100] 100%

Table 11. Results from Nurses' Labeled Syringe Tasks

Nurses N=15	Label Comprehension						Total Outcome		Success %
	Dose Strength (mg)	Medication Name		Admin. Type		Strength	Yes	No	
		Yes	No	Yes	No				Yes
1400	15	0	14	1	15	0	14	1	[(N/15)*100] 93.33%
1600	15	0	15	0	15	0	15	0	100%

### Root cause of error

Table 12. Observed Use Error and Root Cause Summary

Observed Use Error	Subject #	Root Cause
Fails to/unable to identify what administration type is contained within the labeled syringe of the 1400 mg Rituxan Subcutaneous Labeled Syringe.	(b) (6)	did not identify what administration type is contained within the labeled syringe, though he was able to read subcutaneous as part of the drug name.
	-	(b) (6) did not think it was subcutaneous as he had never performed a subcutaneous injection volume that large.

### Concluding Interview

After the differentiation and identification test on the cartons, vials, and syringes were complete, participants were asked for opinion on the ease of identifying the dosage forms and strengths during the preceding activities.

#### 8.4.2.1 Ease of Identification

Before concluding the differentiation testing part of the study, the interviewer asked participants for their subjective opinion on the ease of identifying the correct dosage forms and strengths based on any of the preceding activities. Twenty-eight of the thirty participants said that the tasks were easy. When participants offered specific reasons for why the tasks were easy, use of color and red font were frequently mentioned. The two participants (b) (6) who did not respond that the tasks were easy described that they would prefer more information to be contained on the box with specific components that they then spoke in more detail about.

- More information on syringe label. (b) (6) did not find the syringe easy to use due to a reported lack of information on the syringe label, as well as the carton and vial labels. (b) (6) stated, *"Syringe not easy. These (cartons) do not say what they're mixed in...like dextrose or sodium fluoride and these (vials) do not either. I just wanna know, like, how fast are we giving this? It just has, like, sub-cu. How much is the patient to get? Do we squirt any of it out? Is there any pre-filled?"* When the investigator asked if he expected to have all that information on the syringe label, (b) (6) said *"I'd prefer it."*
- More information on IV carton. (b) (6) stated satisfaction with the amount of information on the SC carton, but noted a preference to have more information on the IV carton, stating *"So, the boxes weren't that difficult. The only thing about this one is I would put more information here [points to the front panel of the Rituxan IV 500mg box] 'cause your first view is of really this [points to the same place] and with, kind of, with our workload, and stuff like that, we have like, short, I'm not saying we're like ADD squirrel, but we have, like, [holds the Rituxan Subcutaneous 1600 mg in his hand] I know what this is in 10 seconds. This [holds the Rituxan IV 500mg] I am like okay it is this, but I have no idea whether it is an IV dose or sub-cu dose. It is well put here [points to the top panel of the Rituxan IV 500 mg box], need to put that there [points to front panel of the Rituxan IV 500 mg box] on the carton. Actually, on the vial [points to the Rituxan IV 500 mg vial] that's pretty well, it's understood on the vial. I did not have any issues with any of these vials."*

#### 8.4.2.2 Colors

Seventeen participants made some mention that they liked the use of colors on the packaging, though the actual benefit on the use of colors varied slightly. Some examples of statements are provided, divided into the common themes on the use of colors.

Some subjects liked the use of color coding and strips on the packaging.

- (b) (6) said *"I like the different colors."*
- (b) (6) noted *"really like how these are, like, coded and a different colors, these strips. The circles are easy too, but I kinda like the strips."*
- (b) (6) stated *"The color coding draws your attention to the dosage which is helpful."*
- (b) (6) said *"I think it helps that their color is different, they pop out, the numbers...the milligrams, the strength. I like that made it easy."*

Other subjects mentioned that the consistent use of different colors on vial caps and other packaging was good in differentiating between dosages and/or IV and SC formulations.

- (b) (6) said *"It did help that everything was different colors for sure...contrast to the white...the colors of the dosage...that's helpful for sure."* Regarding the vials, (b) (6) said *"It helped when the color of the cap was the same, that highlighted the strength. (IV vs. SC) Same thing, with the color that kind of match. It's a little different than these two [pointed towards different vial cap color between Rituxan IV and SC products]."*
- (b) (6) noted *"It is very good that they are different colors, that these boxes are the darker and have a different color scheme than the other two."*
- (b) (6) said *"The colors I think helped having, sort of identifying, like, sort of popped, I guess. In terms of being able to, like, see the doses with the 1600, 1400, 500, 100. The color coordination, like, as you brought the trays out, I could actually remember the colors too, so I was able to recognize things like that, although I was trying to sort of take my time to make sure it was right too, but. Definitely having the colors is there very clear. Very easy, especially if you did this every day."*
- (b) (6) stated *"I thought these (vials) were easy to distinguish -- the different colors and the does were very prominent, so that made it easy to distinguish between the different ones."*
- (b) (6) said *"I mean, I could easily identify what strength was contained in each package, and they're different colors. That helps out as well."*
- (b) (6) noted *"Definitely the colored...the colored strength on there (cartons)...how they colored the strength on there (cartons). It was more obvious for subcutaneous I think it was just the packaging, the way they ran the whole color across and subcutaneous is on there."*
- (b) (6) said *"This is good that you've also color coded the lid tops (vials). That's helpful as well, 'cause that's a distinguisher."*

#### 8.4.2.3 Font in Red

Seven participants noted that they found it helpful to have the printing on the packaging use red font to state (b) (4) because it made it stand out as a difference in SC versus IV formulations and was easy to read and pick out when highlighted in red.

- (b) (6) said "Then the red, that's a good clue to have that (cartons). I think they are labeled pretty much the same as the packaging. It's nice that there's no difference really."
- (b) (6) stated "It was a little bit easier for the sub-cu I think because it was red where this is just black. I had to read it a couple of times just to be sure I was giving the right medication. It was easy because it was like the color, the color dose and then the red is easier."
- (b) (6) said "Identifying the strengths is easy. The form is kind of small, but I mean, this one's in red so it's easy to identify."
- (b) (6) noted "Yeah the red, there for subcutaneous use is very good, but I think that they could put more emphasis on the actual wording subcutaneous or intravenous."
- (b) (6) said "The subcutaneous is in the pink, that's good, or red whatever, you know (so you can see that?) yeah, yep, I can. And you know, like I said, I just know something different about these 'cause I know with the hyaluronidase, that's just a difference and that makes me think sub-cu, because that is a drug we give to people who have, like, extravasations of drugs that are bad for you and they get out into your skin and you can actually use hyaluronidase itself as a protection from that drug that's leaked from an IV vein. So, that's why I know they're different."
- (b) (6) said "Oh, I thought it was very easy. It was very easy, yes. The subcutaneous is in red, so you can see that that's different. Yes, it's also red over here (cartons)."
- (b) (6) noted "Like I said, it's pretty well laid out. Like the sub-cu is nice and red - it's big, so it's easy to differentiate that between the IV because those (cartons) are pretty well spelled out too."

### Labeling Comprehension Tasks

No use errors were observed by pharmacists and nurses during the labeling comprehension tasks.

Table 13. Results from Pharmacists' Labeling Comprehension Tasks

Knowledge Based Assessments Pharmacists, N = 15	KBA Locate IFU		KBA Correct Response		Total Outcome		Success %
	YES	NO	YES	NO	YES	NO	
	1. How should RITUXAN SUBCUTANEOUS be stored prior to use? (confirm "at 2°C-8°C [36°F-46°F]. Do not freeze.")	15	0	15	0	15	
2. [present a vial of RITUXAN SUBCUTANEOUS to the Subject] What is the expiration date of this vial of RITUXAN SUBCUTANEOUS? (confirm correct date)	15	0	15	0	15	0	100%
3. Which RITUXAN SUBCUTANEOUS strength should be administered to a patient with FL (Follicular Lymphoma)? (confirm "1400mg")	15	0	15	0	15	0	100%

Knowledge Based Assessments Pharmacists, N = 15	KBA Locate IFU		KBA Correct Response		Total Outcome		Success %
	YES	NO	YES	NO	YES	NO	
	4. Which RITUXAN SUBCUTANEOUS strength should be administered to a patient with DLBCL (Diffuse Large B-Cell Lymphoma)? (confirm "1400mg")	15	0	15	0	15	
5. Which RITUXAN SUBCUTANEOUS strength should be administered to a patient with CLL (Chronic Lymphocytic Leukemia)? (confirm "1600mg")	15	0	15	0	15	0	100%

Table 14. Results from Nurses' Labeling Comprehension Tasks

Knowledge Based Assessments Nurses, N = 15	KBA Locate IFU		KBA Correct Response		Total Outcome		Success %
	YES	NO	YES	NO	YES	NO	
	1. How should RITUXAN SUBCUTANEOUS be stored prior to use? (confirm "at 2°C-8°C [36°F-46°F]. Do not freeze.")	15	0	15	0	15	
2. [present a vial of RITUXAN SUBCUTANEOUS to the Subject] What is the expiration date of this vial of RITUXAN SUBCUTANEOUS? (confirm correct date)	15	0	15	0	15	0	100%
3.a) Which RITUXAN SUBCUTANEOUS strength should be administered to a patient with FL (Follicular Lymphoma)? (confirm "1400mg")	15	0	15	0	15	0	100%
3.b) What is the recommended injection time for an injection of RITUXAN SUBCUTANEOUS for a patient with FL (Follicular Lymphoma)? (confirm "approximately 5 minutes")	15	0	15	0	15	0	100%
4.a) Which RITUXAN SUBCUTANEOUS strength should be administered to a patient with DLBCL (Diffuse Large B-Cell Lymphoma)? (confirm "1400mg")	15	0	15	0	15	0	100%
4.b) What is the recommended injection time for an injection of RITUXAN SUBCUTANEOUS for a patient with DLBCL (Diffuse Large B-Cell Lymphoma)? (confirm "approximately 5 minutes")	15	0	15	0	15	0	100%
5.a) Which RITUXAN SUBCUTANEOUS strength should be administered to a patient with CLL (Chronic Lymphocytic Leukemia)? (confirm "1600mg")	15	0	15	0	15	0	100%
5.b) What is the recommended injection time for an injection of RITUXAN SUBCUTANEOUS for a patient with CLL (Chronic Lymphocytic Leukemia)? (confirm "approximately 7 minutes")	15	0	15	0	15	0	100%
6. What is the correct injection site for delivering a subcutaneous injection of RITUXAN SUBCUTANEOUS? (confirm "abdominal wall")	15	0	15	0	15	0	100%

### Final Interview

During the final interview, participants were able to provide additional feedback. Of those participants who provided feedback, there were some recurring themes and comments.

- Injection site guidance. Two participants mentioned the injection site guidance could be further highlighted and/or clarified. (b) (6) suggested that the instructions highlight that the only injection site was the abdominal wall, but that other drugs allow subcutaneous injections to be administered in other locations in addition to the abdomen. (b) (6) noted that *"It doesn't really say what happens if you give it somewhere else."* (b) (6) also noted that having a reason for restricting to just the one location can help as patients often get other injections and so may want to avoid an area of a prior injection or prefer to get an injection in another location. *"I think having it restricted saying those words to where is good and important."* Both subjects expressed a desire for more guidance in the product information to explain why only the one abdominal site was recommended, as well as to give details on why other common injection sites were not suggested. Subject (b) (6) also thought the injection site information could be highlighted better in the instructions to stand out more as important information.
- Atypical injection time may be physically challenging. Two participants (b) (6) understood the atypical injection time (due to the high volume), and made comments on the injection time being a long time to have to push a subcutaneous injection. (b) (6) said *"I'm just thinking to myself, injecting something subcutaneously for 7 minutes seems like a really long time."* (b) (6) stated *"You know, most like sub-cu (subcutaneous) injections are just quick, so five minutes seemed like a long time to hold a needle over somebody. That would definitely be, I would think, an education point for people 'cause when we give sub-cu it's always jab and plunge, so if it's over five minutes that would be something people aren't used to doing."* Comments from both subjects point to the high volume and longer injection time for the SC injection time being a new process they are unfamiliar with that would be physically challenging and would require guidance and practice to carry out over the longer prescribed duration.

- Questions regarding injection volume. Four participants (b) (6) commented on the size of the syringe injection being larger than they were used to with a subcutaneous injection. Because it is a much larger dose than the subjects are used to giving subcutaneously, they had questions on how they would administer that large a dose and if it would be broken up into several smaller injections. (b) (6) also expressed concern that the larger than usual SC dose could lead to confusion and improper administration as HCPs would assume it was an IV dose, so the subject suggested the addition of the "Not for IV" warning on the syringe label for subcutaneous doses.
  - (b) (6) noted "This is a subcutaneous injection. Um, it's a larger volume though, so I would want to know if they were giving at multiple sites...would be the first thing. 'Cause normally anything over 2 mLs, we'll question if it's actually supposed to be sub-cu."
  - (b) (6) said "I'm just curious how you give that much fluid subcutaneously, do they break it up into multiple shots? I think it's pretty straight forward pharmacy wise."
  - (b) (6) indicated that the maximum amount usually administered subcutaneously is 10 mLs.
  - (b) (6) said "It is a larger than average volume for a subcutaneous injection....if it was a pre-filled syringe, you just have to have labeling "Not for IV." You know what I mean? Just because it seems like more of an IV volume dose vs. a sub-cu volume dose. Just so it doesn't [get] accidentally administered IV. Just 'cause it's outside the normal administration."

(b) (4)

### **Proposed Modifications for Risk Minimization**

The Sponsor is proposing the following changes to further optimize the Prescribing Information and labeling:

- **Injection volume:** Given the larger than usual injection volume, further guidance was requested regarding administration, specifically, if multiple-injections are required to deliver a single dose volume. The current text in the USPI specifies that the abdomen is the recommended subcutaneous injection site and that if administration is interrupted, it can be continued at the same site, or at a different site, if applicable. To avoid confusion regarding the subsequent injection site, the Sponsor proposes to clarify the text to specify that if interrupted, the injection can be continued at a different site, but restricted to the abdomen.
- **Potential for Administration Route Error:** It was also highlighted that the injection volume might raise a potential for confusion with the route of administration. In order to further optimize the labeling, the Sponsor proposes to amend the peel-off label (b) (6) [\[Appendix 2\]](#)

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>k</sup> along with postmarket medication error data, we reviewed the following Rituxan subcutaneous labels and labeling submitted by Genentech on August 26, 2016 and December 12, 2016.

- Prescribing Information
- Container labels
- Carton labeling

### **G.2 Label and Labeling Images**

#### **A. Prescribing Information**



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<sup>k</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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NICOLE B GARRISON  
06/20/2017

HINA S MEHTA  
06/20/2017

LUBNA A MERCHANT  
06/20/2017

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Memorandum:** June 15, 2017

**Requesting Office or Division:** Division of Hematology Products (DHP)

**Application Type and Number:** BLA 761064

**Product Name and Strength:** Rituxan Hycela  
(rituximab and hyaluronidase human)  
Injection  
1,400 mg rituximab and 2,000 units/mL hyaluronidase  
human per 11.7 mL solution  
1,600 mg rituximab and 2,000 units/mL hyaluronidase  
human per 13.4 mL solution

**Applicant/Sponsor Name:** Genentech, Inc.

**Submission Date:** May 30, 2017 and June 9, 2017

**OSE RCM #:** 2016-1980-1 and 2017-59-1

**DMEPA Primary Reviewer:** Nicole Garrison, PharmD, BCPS

**DMEPA Team Leader:** Hina Mehta, PharmD

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#### 1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised container labels and carton labeling for Rituxan Hycela (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous Human Factors label and labeling review.<sup>a</sup>

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<sup>a</sup> Garrison N. Human Factors Label and Labeling Review for Rituxan Subcutaneous (BLA 761064). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAR 13 RCM No.: 2016-1980 and 2017-59.

## **2 CONCLUSION**

The revised container label and carton labeling for Rituxan Hycela is acceptable from a medication error perspective. We have no further recommendations at this time.

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NICOLE B GARRISON  
06/15/2017

HINA S MEHTA  
06/15/2017

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: April 28, 2017

To: Ann Farrell, MD  
Director  
**Division of Hematology Products (DHP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Sharon R. Mills, BSN, RN, CCRP  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

L. Shenee' Toombs, Pharm. D.  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): RITUXAN HYCELA (rituximab and hyaluronidase)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761064

Applicant: Genentech, Inc.

## 1 INTRODUCTION

On August 26, 2016, Genentech, Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761064 for RITUXAN HYCELA (rituximab/hyaluronidase) injection seeking approval of a subcutaneous injection formulation of rituximab and hyaluronidase, in the treatment of patients with follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL). The reference product is RITUXAN (rituximab) injection, for intravenous use (BLA 103705).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on September 30, 2016 and September 16, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for RITUXAN HYCELA (rituximab and hyaluronidase) injection, for subcutaneous injection.

## 2 MATERIAL REVIEWED

- Draft RITUXAN HYCELA (rituximab and hyaluronidase) injection MG received on August 26, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 13, 2017.
- Draft RITUXAN HYCELA (rituximab and hyaluronidase) injection Prescribing Information (PI) received on August 26, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 13, 2017.
- Approved RITUXAN (rituximab) injection labeling dated August 12, 2014.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/  
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SHARON R MILLS  
04/28/2017

LATOYA S TOOMBS  
04/28/2017

LASHAWN M GRIFFITHS  
04/28/2017

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

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

*Memorandum*

Date: April 27, 2017

To: Laura Wall, Regulatory Project Manager  
Division of Hematology Products (DHP)

From: L. Shenee Toombs, Regulatory Review Officer (OPDP)  
Elaine Cunningham, Senior Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)  
Michael Wade, Regulatory Health Project Manager (OPDP)  
Kathleen Davis, Team Leader (OPDP)

Subject: BLA 761064  
OPDP labeling comments for RITUXAN HYCELA™ (rituximab and  
hyaluronidase) injection, for subcutaneous use  
Labeling Review

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OPDP has reviewed the proposed package insert (PI), Medication Guide and carton and container labeling for RITUXAN HYCELA™ (rituximab and hyaluronidase) injection, for subcutaneous use (Rituxan Hycela) that was submitted for consult on September 16, 2016. Comments on the proposed PI and Medication Guide are based on the version sent via email from Laura Wall (RPM) on April 13, 2017, entitled "BLA 761064 Rituximab SC PI and MG 3.15.17.docx" and the draft carton/container labeling emailed on April 26, 2017.

Comments regarding the PI are provided on the marked version below.

Please note that comments on the Medication Guide will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Program (DMPP).

OPDP has no comments on the draft carton and container labeling at this time.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or [latoya.toombs@fda.hhs.gov](mailto:latoya.toombs@fda.hhs.gov).

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

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/s/  
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LATOYA S TOOMBS  
04/27/2017

**MEMORANDUM**

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

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DATE: April 26, 2017

TO: Ann T. Farrell, M.D.  
Director  
Division of Hematology Products (DHP)  
Office of Hematology and Oncology Products (OHOP)  
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.  
Visiting Associate  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.  
Deputy Director  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspections of five clinical sites including  
1) Institut Paoli-Calmettes, Marseille, France; 2)  
N.n.blokhin Russian Cancer Research Center, Moscow, Russia;  
3) Hospital Duran I Reynals, Barcelona, Spain; 4) Institute  
Of Hematology, Belgrade, Serbia; and 5) General University  
Hospital, Praha, Czech.

**Inspection Summary:**

The Office of Study Integrity and Surveillance (OSIS) arranged inspections of the clinical portion of the following studies submitted to **BLA 761064**:

- 1) **Study BP22333** conducted by Institut Paoli-Calmettes, Marseille, France and N.n.blokhin Russian Cancer Research Center, Moscow, Russia.
- 2) **Study BO22334** conducted by Hospital Duran I Reynals, Barcelona, Spain and Institute Of Hematology, Belgrade, Serbia.
- 3) **Study BO25341** conducted by General University Hospital, Praha, Czech.

Page 2 - Surveillance inspections of five clinical sites including 1) Institut Paoli-Calmettes, Marseille, France; 2) N.n.blokhin Russian Cancer Research Center, Moscow, Russia; 3) Hospital Duran I Reynals, Barcelona, Spain; 4) Institute Of Hematology, Belgrade, Serbia; and 5) General University Hospital, Praha, Czech

The ORA investigators who audited the sites did not observe significant deficiencies and did not issue form FDA 483 at the conclusion of the inspections. The final inspection classifications for all sites are No Action Indicated (NAI).

After reviewing the establishment inspection reports (EIR) and inspectional findings, I found the clinical data generated by all five sites for the three studies (**BP22333**, **BO22334**, and **BO25341**) to be reliable and recommend that the data be accepted for further Agency review, except for the following items.

1. For **Study BP22333**, various pharmacokinetic (PK) and antibody samples were centrifuged outside the timeframes specified by the study protocol at Institut Paoli-Calmettes, Marseille, France (**Site ID: 163460**). Because there is limited information regarding the stability of rituximab and rHuPH20 in whole blood under the protocol specified conditions (**Attachment #1**), I cannot determine the impact of this finding on the measured concentrations of analytes. Therefore, the review division should consider requesting additional whole blood stability data for rituximab and rHuPH20 from the study sponsor. Until the information is received, these samples should not be accepted for further Agency review (**Attachment #2**).
2. For **Study BP22333**, Subjects (b) (6) enrolled at Institut Paoli-Calmettes, Marseille, France received incorrect doses of investigational medicinal product (IMP) at certain study visits. The review division should evaluate the impact of the finding on study data.
3. For **Study BO22334**, Subjects (b) (6) enrolled at Institute Of Hematology, Belgrade, Serbia (**Site ID: 206451**) experienced adverse events (AEs) which were not reported to the Agency. The review division should evaluate the impact of these AEs on the study data (**Attachment #3**).

**Audited in vivo bioavailability studies:**

**Study Number #1:** BP22333

**Study Title:** "A Two-Stage Phase Ib Study To Investigate the Pharmacokinetics, Safety and Tolerability of Rituximab Subcutaneous (SC) Formulation in Patients with Follicular Lymphoma (FL) as Part of Maintenance Treatment"

**Study Conduct:** Sep 8, 2009 - Jul 15, 2013 (Clinical cutoff date)

Page 3 - Surveillance inspections of five clinical sites including 1) Institut Paoli-Calmettes, Marseille, France; 2) N.n.blokhin Russian Cancer Research Center, Moscow, Russia; 3) Hospital Duran I Reynals, Barcelona, Spain; 4) Institute Of Hematology, Belgrade, Serbia; and 5) General University Hospital, Praha, Czech

**Clinical Site #1: Institut Paoli-Calmettes, Onco Hematologie 1 (Site ID: 163460)**

232 Boulevarde Sainte Marguerite  
Marseille 13273, France

ORA investigator Richard W. Berning (b) (4) audited the clinical portion of **Study BP22333** at Institut Paoli-Calmettes, Marseille, France from February 20 - 24, 2017.

The audit covered all Informed Consent Forms (ICF), source documents, case report forms, drug administration records, compliance with protocol inclusion/exclusion criteria, safety assessments, concomitant medications, and AEs. No significant issues were observed and there was no under-reporting of protocol deviations and AEs. At the conclusion of the inspection, no Form FDA 483 was issued. However, Investigator Berning discovered the following findings during the inspection.

1. Various PK and antibody samples were centrifuged outside the timeframes specified by the study protocol (within 30-60 minutes of sample collection for Rituximab and within 30 minutes for rHuPH20). The discrepancies in time of centrifugation ranged from 1 minute to 925 minutes exceeding the specified timeframes (**Attachment #2**). In addition, the documentation of the collection of blood samples was incomplete on several occasions.
2. **Subjects** (b) (6) received incorrect doses of IMP at certain study visits because the site used a calculation different from the algorithm in the study protocol. Specifically, **Subject** (b) (6) received 656.25 mg of IMP instead of the planned 648.75 mg dose for study cycles 5, 8, and 10; **Subject** (b) (6) received 750 mg of IMP instead of the planned 821.25 mg dose at cycle 5.

**Firm's response:** The firm submitted a written response (**Attachment #4**) and acknowledged the above findings. For *Finding #1*, the firm stated that the timing discrepancies occurred because they subcontracted routine laboratory activities to an external service provider, which operated only on working days, from 8:30am through 6:30pm, during the conduct of the study. As corrective action, the firm made an agreement with the external service provider to improve their compliance with timeframes as specified in future study protocols. They also proposed to re-train all the nurses for better practice.

For *Finding #2*, the firm used software to calculate IMP doses based on maximum body surface area (BSA) of 2m<sup>2</sup>, instead of actual subject height and weight. As a result, subjects (b) (6) received lower

Page 4 - Surveillance inspections of five clinical sites including 1) Institut Paoli-Calmettes, Marseille, France; 2) N.n.blokhin Russian Cancer Research Center, Moscow, Russia; 3) Hospital Duran I Reynals, Barcelona, Spain; 4) Institute Of Hematology, Belgrade, Serbia; and 5) General University Hospital, Praha, Czech

doses of IMP than originally planned. Following notification of these deviations by the sponsor, the site began to use the correct algorithm provided in the protocol to calculate the dose.

**OSIS Evaluation:**

For *Finding #1*, the timing discrepancies of early and late centrifugation were reported to the Agency in "Table 1b030\_A\_001, Listing Of Antibodies Values Over Time - Stage 1 and 2", of Primary Clinical Study Report of **Study BP22333** (Report No.1044859 - October 2012). Therefore, the review division is probably aware of the timing discrepancies.

However, the reported discrepancies occurred at following time points only:

- **Stage 1** (study cohorts A, B, C & D), Visit 1 Pre-Dose, Visit 1 Day 17, Visit 2 Pre-Dose, follow-up (FU) 3 months, and follow-up (FU) 9 months, if applicable.
- **Stage 2** (study cohorts E & F), Visit 1 Pre-Dose, Visit 1 Day 22, Visit 2 Pre-Dose, and Visit 2 Day 1, if applicable.

Please refer to **Attachment #2** for a full list of all affected samples.

(b) (4) conducted the bioanalytical analysis for PK and antibody determination of Rituximab in subject serum samples; while (b) (4) conducted the bioanalytical analysis for PK and antibody determination of rHuPH20. However, there is limited information about analytes stability in whole blood for the above bioanalytical analysis. Consequently, I could not determine the impact of delayed centrifugation on the stability of analytes. The review division should consider requesting whole blood stability data for rituximab and rHuPH20 from the study Sponsor. Until the stability information is received, the results of PK and antibody determination of Rituximab and rHuPH20 from samples with delayed centrifugation should not be accepted for further Agency review.

For *Finding #2*, the dosing discrepancies for **Subject** (b) (6) and **Subject** (b) (6) were 1.1% higher and 8.7% lower than the planned doses, respectively. The OND reviewer(s) should evaluate if the pharmacokinetic parameters and antibody values calculated from those specific cycles were impacted.

**Clinical Site #2: N.n.blokhin Russian Cancer Research Center, Dept. Of Chemotherapy & Hemoblastosis (Site ID: 163523)  
24, Kashirskoye Shosse  
Moscow 115478, Russian Federation**

Page 5 - Surveillance inspections of five clinical sites including 1) Institut Paoli-Calmettes, Marseille, France; 2) N.n.blokhin Russian Cancer Research Center, Moscow, Russia; 3) Hospital Duran I Reynals, Barcelona, Spain; 4) Institute Of Hematology, Belgrade, Serbia; and 5) General University Hospital, Praha, Czech

ORA investigator Annette Melendez (b) (4) audited the clinical portion of the above study at N.n.blokhin Russian Cancer Research Center, Moscow, Russia from March 27 - 31, 2017.

The audit covered the review of all subjects' ICFs, source documents, case report forms, regulatory binder containing sponsor/monitor/IRB correspondence, test article accountability, and adverse events. No significant issues were observed and there was no under-reporting of protocol deviations and AEs. At the conclusion of the inspection, no Form FDA 483 was issued.

**Study Number #2: BO22334**

**Study Title:** "Two-stage Phase III, International, Multi-Center, Randomized, Controlled, Open-label Study to Investigate the Pharmacokinetics, Efficacy and Safety of Rituximab SC in Combination With CHOP or CVP Versus Rituximab IV in Combination With CHOP or CVP in Patients With Previously Untreated Follicular Lymphoma Followed by Maintenance Treatment With Either Rituximab SC or Rituximab IV"

**Study Conduct:** Feb 4, 2010 - Jan 11, 2016 (Clinical cutoff date)

**Clinical Site #1: Hospital Duran I Reynals, Servicio De Hematologia Hospitalet De Llobregat (Site ID: 205755)**  
Avda. Gran Via, S/n, Km 2.7  
Barcelona 08907, Spain

ORA investigator Margaret N. Torres Vazquez (b) (4) audited the clinical portion of **Study BO22334** at Hospital Duran I Reynals, Barcelona, Spain from February 20 - 24, 2017.

The audit covered all twelve subjects' ICFs, drug accountability records, temperature records of the refrigerators where IMPs were stored, compliance with protocol inclusion/exclusion criteria, case report forms, study subjects source documents, study monitoring log, AEs and Serious AEs. No significant issues were observed and there was no under-reporting of protocol deviations and AEs. At the conclusion of the inspection, no Form FDA 483 was issued.

**Clinical Site #2: Institute of Hematology (Site ID: 206451)**  
Koste Todorovica 2  
Belgrade 11000, Serbia

Page 6 - Surveillance inspections of five clinical sites including 1) Institut Paoli-Calmettes, Marseille, France; 2) N.n.blokhin Russian Cancer Research Center, Moscow, Russia; 3) Hospital Duran I Reynals, Barcelona, Spain; 4) Institute Of Hematology, Belgrade, Serbia; and 5) General University Hospital, Praha, Czech

ORA investigator Marcia A. Worley (b) (4) audited the clinical portion of **Study BO22334** at Institute Of Hematology, Belgrade, Serbia from March 6 - 10, 2017.

The audit covered all subjects' ICFs, source records, inclusion/exclusion criteria, sponsor correspondence, IRB approvals and correspondence, test article accountability records, and other regulatory documentation. Investigator Worley discovered under-reporting of AEs at this site. Specifically, 15 AEs were discovered by the site during a quality review in February 2017 (**Attachment #3**). These AEs were not reported to the Agency. The site reported these AEs to the sponsor who will include the events in the next report to the Agency.

At the conclusion of the inspection, no Form FDA 483 was issued.

**OSIS Evaluation:** Out of the 15 late reported AEs, at least 5 AEs were considered as associated with administration of investigational product (subcutaneous rituximab). Three of those AEs were resolved without intervention and the other two AEs were resolved with concomitant medications. Although those AEs were not considered as severe by the clinical investigator, the OND reviewers should determine the safety impact of the unreported AEs.

**Study Number #3: BO25341**

**Study Title:** "An adaptive, comparative, randomized, parallel-group, multi-center, Phase Ib study of subcutaneous (SC) rituximab versus intravenous (IV) rituximab both in combination with chemotherapy (fludarabine and cyclophosphamide), in patients with previously untreated CLL"

**Study Conduct:** Apr 13, 2011 - Mar 7, 2014 (Clinical cutoff date)

**Clinical Site:** **General University Hospital, 1 Th Department Of Medicine - Clinic Of Hematooncology (Site ID: 205357)**  
U Nemocnice 2  
Praha 2 12808, Czech Republic

ORA investigator Marcia A. Worley (b) (4) audited the clinical portion of **Study BO25341** at General University Hospital, Praha, Czech from March 13 - 17, 2017.

The audit covered all subjects' ICFs, source records, inclusion/exclusion criteria, sponsor correspondence, IRB approvals

Page 7 - Surveillance inspections of five clinical sites including 1) Institut Paoli-Calmettes, Marseille, France; 2) N.n.blokhin Russian Cancer Research Center, Moscow, Russia; 3) Hospital Duran I Reynals, Barcelona, Spain; 4) Institute Of Hematology, Belgrade, Serbia; and 5) General University Hospital, Praha, Czech

and correspondence, test article accountability records, and other regulatory documentation. No significant issues were observed and there was no under-reporting of protocol deviations and AEs. At the conclusion of the inspection, no Form FDA 483 was issued.

**Conclusion:**

After reviewing the EIRs and inspectional findings, I found the clinical data from **Studies BP22333, BO22334, and BO25341** submitted to **BLA761064** to be reliable and recommend that the data be accepted for further Agency review, except for the following pending items.

1. For **Study BP22333**, various PK and antibody samples were not centrifuged according to the study protocol at Institut Paoli-Calmettes, Marseille, France (**Attachment #2**). The review division should consider requesting additional whole blood stability data for rituximab and rHuPH20 from the study sponsor to mitigate the concern about the impact of delayed sample centrifugation on analyte stability under the protocol specified conditions. Until then, data obtained from the affected samples should not be accepted for further Agency review.
2. For **Study BP22333**, the review division should evaluate the impact of incorrect dosing in Subjects (b) (6) enrolled at Institut Paoli-Calmettes, Marseille, France on the PK and safety data from these subjects.
3. For **Study BO22334**, the review division should evaluate the impact of unreported AEs from Subjects (b) (6) enrolled at Institute Of Hematology, Belgrade, Serbia on the study's safety data (**Attachment #3**).

Yiyue Zhang, Ph.D.  
DNDBE, OSIS

**Final Classification:**

**Clinical Sites**

- NAI:** Institut Paoli-Calmettes, Marseille, France (FEI: 3006039416)
- NAI:** N.n.blokhin Russian Cancer Research Center, Moscow, Russia (FEI: 3013216589)
- NAI:** Hospital Duran I Reynals, Barcelona, Spain (FEI: 3006364396)
- NAI:** Institute Of Hematology, Belgrade, Serbia (FEI: 3013168653)
- NAI:** General University Hospital, Praha, Czech (FEI: 3013167413)

Page 8 - Surveillance inspections of five clinical sites including 1) Institut Paoli-Calmettes, Marseille, France; 2) N.n.blokhin Russian Cancer Research Center, Moscow, Russia; 3) Hospital Duran I Reynals, Barcelona, Spain; 4) Institute Of Hematology, Belgrade, Serbia; and 5) General University Hospital, Praha, Czech

**Attachments:**

1. Sample Collection, Handling and Storage Instructions for pharmacokinetic Rituximab, anti-Rituximab antibody, pharmacokinetic rHuPH20 and anti-rHuPH20 antibody samples.
2. List of subject samples centrifuged outside of the timeframe specified in Study BP22333 protocol
3. List of unreported adverse events at Institute Of Hematology, Belgrade, Serbia
4. Institut Paoli-Calmettes' written response

CC:

OTS/OSIS/Kassim/Choe/Taylor/Kadavil/[CDER-OSIS-BEQ@fda.hhs.gov](mailto:CDER-OSIS-BEQ@fda.hhs.gov)

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala/Zhang

OTS/OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Au

ORA/CE-FO [REDACTED] (b) (4) -IB/Berning

ORA/SE-FO [REDACTED] -IB/Melendez

ORA/CE-FO [REDACTED] -IB/Torres-Vazquez

ORA/CE-FO [REDACTED] -IB/Worley

Draft: YZ 4/18/2017, 4/21/2017, 4/25/2017

Edit: RCA 4/20/2017, 4/24/2017, 4/25/2017; AD 4/25/2017, 4/26/2017

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/Institut Paoli-Calmettes, Marseille, France  
.../Clinical Sites/N.n.blokhin Russian Cancer Research Center, Moscow, Russia  
.../Clinical Sites/Hospital Duran I Reynals, Barcelona, Spain  
.../Clinical Sites/Institute Of Hematology, Belgrade, Serbia  
.../Clinical Sites/General University Hospital, Praha, Czech

BE File#: 7317

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/s/  
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YIYUE ZHANG  
04/26/2017

RUBEN C AYALA  
04/26/2017

ARINDAM DASGUPTA  
04/26/2017

MEMORANDUM

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

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DATE: April 12, 2017

TO: Ann T. Farrell, M.D.  
Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Office of New Drugs

FROM: Kara A. Scheibner, Ph.D.  
Pharmacologist  
Division of Generic Drug Bioequivalence Evaluation  
(DGDBE)  
Office of Study Integrity and Surveillance (OSIS)

AND

Gajendiran Mahadevan, Ph.D.  
Pharmacologist  
Division of New Drug Bioequivalence Evaluation  
(DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Sam H Haidar, Ph.D., R.Ph.  
Deputy Director,  
Division of Generic Drug Bioequivalence Evaluation  
(DGDBE)  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Analytical inspection (b) (4)

(b) (4)

**Inspection Summary:**

At the request of the Division of Hematology Products (DHP) in the Office of Hematology and Oncology Products (OHOP), the Office of Study Integrity and Surveillance (OSIS) initiated an inspection of assays for anti-drug antibodies (ADA) and pharmacokinetic (PK) concentrations for rituximab. The assays associated with studies BP22333, B022334, and B025341 were conducted at (b) (4)

(b) (4)

. Based upon the results of this inspection, we

recommend that ADA and PK analytical data from studies BP22333, B022334, and B025341 be accepted for Agency review. However, DHP reviewers should note that a relevant and reliable low positive control for system suitability was not present in confirmatory assays for all inspected studies. The instrument signals (optical density; OD) for some of the study samples that were reported as ADA-negative were close to OD signals for the low positive control samples. Please see below for details.

Please note that ADA and PK assays for hyaluronidase, associated with studies BP22333, B022334, and B025341, were conducted at two other study sites. Reviews of the Establishment Inspection Reports (EIRs) for these additional sites will be reported in separate memos.

**Studies audited during this inspection:**

**Study Number:** BP22333 (BLA 761064)  
**Study Title:** "A Two-Stage Phase Ib Study To Investigate the Pharmacokinetics, Safety, and Tolerability of Rituximab Subcutaneous (SC) Formulation in Patients with Follicular Lymphoma (FL) as Part of Maintenance Treatment"  
**Study Dates:** May 22, 2012 through July 23, 2013

**Study Number:** B022334 (BLA 761064)  
**Study Title:** "A Two-stage Phase III, International, Multi-Center, Randomized, Controlled, Open-label Study to Investigate the Pharmacokinetics, Efficacy and Safety of Rituximab SC in Combination With CHOP or CVP Versus Rituximab IV in Combination With CHOP or CVP in Patients With Previously Untreated Follicular Lymphoma Followed by Maintenance Treatment With Either Rituximab SC or Rituximab IV"  
**Study Dates:** June 4, 2012 through January 18, 2017 (ongoing)

**Study Number:** B025341 (BLA 761064)  
**Study Title:** "An adaptive, comparative, randomized, parallel-group, multi-center, Phase Ib study of subcutaneous (SC) rituximab versus intravenous (IV) rituximab both in combination with chemotherapy (fludarabine and cyclophosphamide), in patients with previously untreated CLL"  
**Study Dates:** June 21, 2012 through March 29, 2016

OSIS inspectors Gajendiran Mahadevan, Ph.D. and Kara A. Scheibner, Ph.D. conducted the inspection of ADA

ab associated with the studies above,

The audit included a thorough review of applicable Standard Operating Procedures (SOPs), method validations, laboratory notebooks and journals, paper and electronic records of raw data, correspondence during method validation and study conduct, bioanalytical study data, and comparison of original results to data submitted to Agency. The inspection also covered the current facilities for receipt of samples, sample handling, sample storage, and bioanalysis.

At the conclusion of the inspection, a two-item Form FDA-483 was issued (**Attachment 1**).

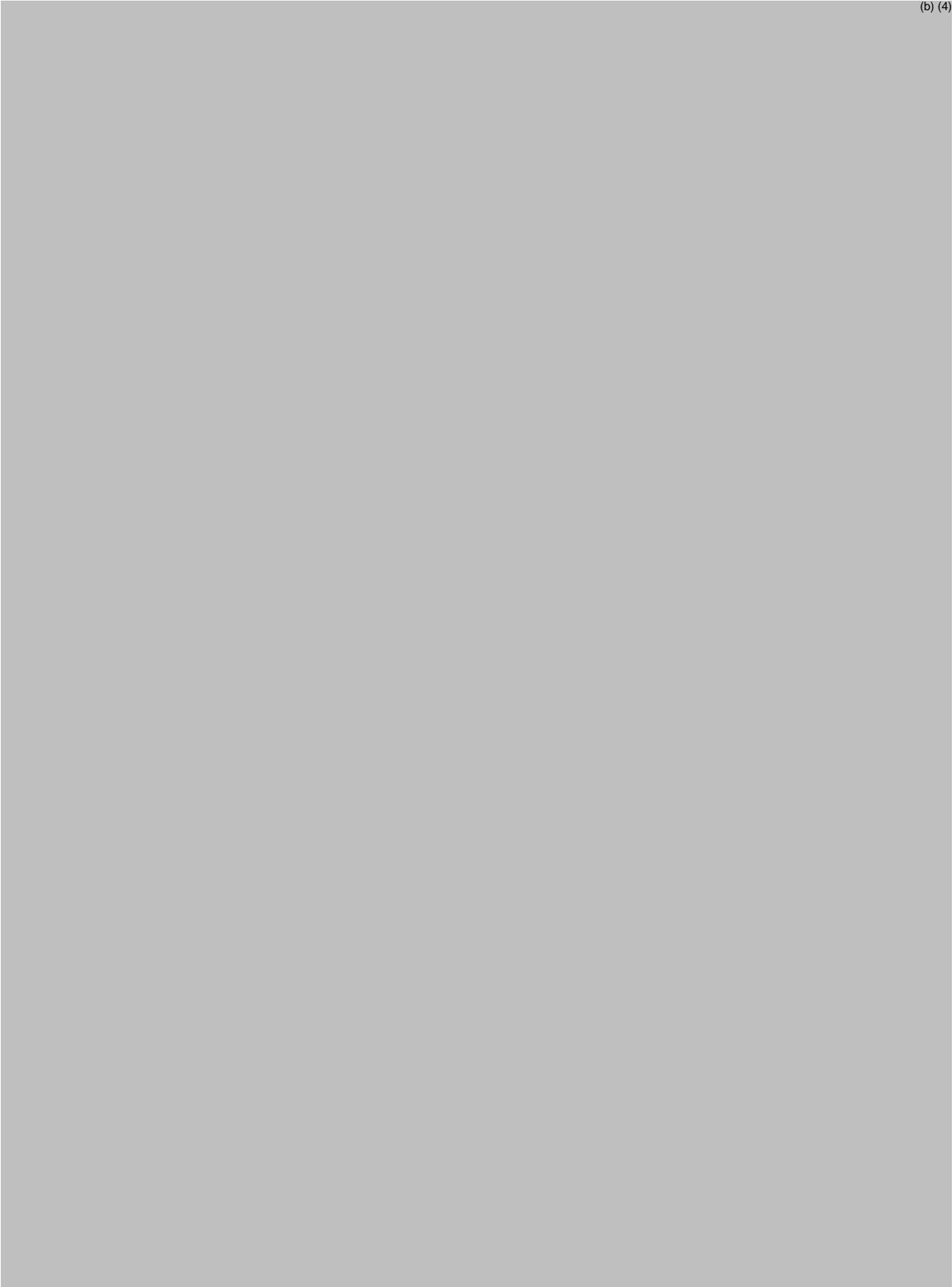


on

(b) (4)

(b) (4)

(b) (4)



**Recommendation:**

Following review of the EIR and inspectional findings, we conclude that the analytical data from ADA and PK assays for rituximab associated with studies BP22333, BO22334, and BO25341 are reliable. Therefore, we recommend that the analytical

portions of the audited studies (b) (4) be  
accepted for further Agency review.

Kara A. Scheibner, Ph.D.  
DGDBE, OSIS

Gajendiran Mahadevan, Ph.D.  
DNDBE, OSIS

**Final Classification:**

VAI:

(FEI#: (b) (4))

CC:

OTS/OSIS/Kassim/Choe/Taylor/Turner-Rinehardt/Fenty-  
Stewart/Nkah/Miller/Kadavil/ Mitchell

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala/Mahadevan

OTS/OSIS/DGDBE/Cho/Haidar/Skelly/Choi/Au/Scheibner

Draft: KAS 04/10/2017; GM 04/11/2017

Edit: MFS 04/10/2017, 04/11/2017; SHH 04/11/2017

OSIS file #: BE7317

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical  
Sites/ (b) (4)

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/s/  
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KARA A SCHEIBNER  
04/12/2017

GAJENDIRAN MAHADEVAN  
04/12/2017

SAM H HAIDAR  
04/12/2017

**MEMORANDUM**

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

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DATE: April 11, 2017

TO: Ann Farrell, M.D.  
Director  
Office of New Drugs  
Division of Hematology Products

AND

Atiqur Rahman, Ph.D.  
Director  
Office of Clinical Pharmacology  
Division of Clinical Pharmacology V

FROM: Xiaohan Cai, Ph.D.  
Visiting Associate  
Division of Generic Drug Bioequivalence Evaluation  
(DGDBE)  
Office of Study Integrity and Surveillance (OSIS)

Mohsen Rajabi Abhari, Ph.D.  
Pharmacologist  
Division of New Drug Bioequivalence Evaluation  
(DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho  
Director,  
Division of Generic Drug Bioequivalence Evaluation  
(DGDBE)  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Analytical inspection (b) (4)  
(b) (4) covering BLAs 761064 (b) (4)  
(b) (4)

**Inspection Summary:**

At the request of the Division of Hematology and the Division of Clinical Pharmacology V, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical

(b) (4)

portions of studies BP22333, B022334, and B025341 submitted for  
BLA 761064 and (b) (4)

(b) (4) Based upon the results of this inspection, we recommend that bioanalytical data all studies be accepted for Agency review, but with several considerations and exceptions. Details are included in the Recommendation section below.

**Studies audited during this inspection:**

**Study Number:** BP22333 (b) (4)  
**Study Title:** "A Two-Stage Phase Ib Study To Investigate the Pharmacokinetics, Safety, and Tolerability of Rituximab Subcutaneous (SC) Formulation in Patients with Follicular Lymphoma (FL) as Part of Maintenance Treatment"

**Analytical Study Dates:** 07/29/10-07/10/13

**Study Number:** B022334 (b) (4)  
**Study Title:** "A Two-stage Phase III, International, Multi-Center, Randomized, Controlled, Open-label Study to Investigate the Pharmacokinetics, Efficacy and Safety of Rituximab SC in Combination With CHOP or CVP Versus Rituximab IV in Combination With CHOP or CVP in Patients With Previously Untreated Follicular Lymphoma Followed by Maintenance Treatment With Either Rituximab SC or Rituximab IV"

**Analytical Study Dates:** 12/2/12-03/09/16

**Study Number:** B025341 (b) (4)  
**Study Title:** "An adaptive, comparative, randomized, parallel-group, multi-center, Phase Ib study of subcutaneous (SC) rituximab versus intravenous (IV) rituximab both in combination with chemotherapy (fludarabine and cyclophosphamide), in patients with previously untreated CLL"

**Analytical Study Dates:** 12/1/11-04/16/15

NON-RESPONSIVE

(b) (4)  
**NON-RESPONSIVE**

OSIS scientists Xiaohan Cai, Ph.D. and Mohsen Rajabi Abhari, Ph.D. conducted an inspection of the analytical portions of the above studies during (b) (4). The audit included a thorough review of facilities, current bioanalytical SOPs, study records and correspondence, method validation records, and interviews and discussions with (b) (4) management and staff.

At the conclusion of the inspection, we issued a three-item Form FDA-483 (b) (4). We also discussed additional items during the inspection and at the closing meeting. We received formal responses to the FDA-483 observations

(b) (4)



(b) (4)

(b) (4)

[redacted] (b) (4)

[redacted] (b) (4)



(b) (4)

(b) (4)

**OSIS Evaluation:** (b) (4) response is acceptable.

(b) (4)

NON-RESPONSIVE

Xiaohan Cai, Ph.D.  
DGDBE, OSIS

Mohsen Rajabi Abhari, Ph.D.  
DNDBE, OSIS

**Final Classification:**

VAI: (b) (4)  
(FEI# (b) (4))

CC:  
OTS/OSIS/Kassim/Choi/Taylor/Fenty-Stewart/Nkah/Miller/Kadavil

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala/Rajabi  
OTS/OSIS/DGDBE/Cho/Haidar/Skelly/Choi/Au/Cai  
Draft: XHC 04/02/2017, MR 04/02/2017, XHC 04/03/2017, MR  
04/04/2017, XHC 04/06/17, XHC 04/11/17  
Edit: YMC 04/06/2017, JC 04/09/2017, 4/11/2017

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical  
Sites/ (b) (4)

OSIS file #: 7317 (BLA 761064)

**NON-RESPONSIVE**

**FACTS:**

(b) (4)

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/s/  
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XIAOHAN CAI  
04/11/2017

MOHSEN RAJABI ABHARI  
04/11/2017

YOUNG M CHOI  
04/11/2017

SEONGEUN CHO  
04/11/2017

**MEMORANDUM**

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

---

DATE: April 10, 2017

TO: Ann Farrell, M.D.  
Director  
Division of Hematology Products (DHP)  
Office of New Drugs

FROM: Melkamu Getie-Kebtie, R.Ph., Ph.D.  
Division of Generic Drug Bioequivalence Evaluation (DGDBE)  
Office of Study Integrity and Surveillance (OSIS)

Yiyue Zhang, Ph.D.  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance

THROUGH: Seongeun (Julia) Cho, Ph.D.  
Director  
Division of Generic Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance

SUBJECT: Review of analytical establishment inspection report (EIR), covering BLA 761064, rituximab/hyaluronidase, (Genentech, USA)

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**Inspection summary**

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion of studies BP22333, BO22334, and BO25341 evaluating hyaluronidase (rHuPH20) activity tivity that was performed

(b) (4)

These reviewers recommend that the PK data from studies BP22333 and BO25341 are acceptable for further FDA review. However, one Form FDA 483 item was issued for the neutralizing anti-rHuPH20 antibody data in studies BP22333, BO22334, and BO25341. The neutralizing anti-rHuPH20 antibody data from these studies are found unreliable due to use of inappropriate assay cut point. In response to the Form FDA 483 observation, (b) (4) stated that in 2015, a new version of the neutralizing anti-rHuPH20

antibody method was developed. Please note that we were not informed of the new method validation during the current inspection nor (b) (4) submitted the data with the response to Form FDA observation. These reviewers recommend that the DHP reviewer request the sponsor to submit the validation report for the new method and determine if the new method supports the neutralizing anti-rHuPH20 antibody assay results that were included in the current bioanalytical reports for studies BP22333, BO22334, and BO25341.

### Inspected studies

At the request of the Division of Hematology Products, the Office of Study Integrity and Surveillance audited the bioanalytical portion of the following studies.

**Study number:** BP22333, (b) (4) project numbers: PF09B-0110 (PK assay: 2/18/2010-3/22/2012) and PF09B-0111 (NAb assay: 10/26/2009-7/17/2013)

**Study Title:** A Two-Stage Phase Ib Study To Investigate the Pharmacokinetics, Safety, and Tolerability of Rituximab Subcutaneous (SC) Formulation in Patients with Follicular Lymphoma (FL) as Part of Maintenance Treatment

**Study number:** BO22334, (b) (4) project numbers: PF11B-0300 (NAb assay: 2/20/2012- 1/27/2016 (interim); study is ongoing)

**Study Title:** A Two-stage Phase III, International, Multi-Center, Randomized, Controlled, Open-label Study to Investigate the Pharmacokinetics, Efficacy and Safety of Rituximab SC in Combination with CHOP or CVP Versus Rituximab IV in Combination with CHOP or CVP in Patients with Previously Untreated Follicular Lymphoma Followed by Maintenance Treatment with Either Rituximab SC or Rituximab IV

**Study number:** BO25341, (b) (4) project numbers: PF11B-0262 (PK assay: 2/2/2012-6/24/2015) and PF11B-0263 (NAb assay: 2/10/2012-5/6/2015)\*

**Study Title:** An adaptive, comparative, randomized, parallel-group, multi-center, Phase Ib study of subcutaneous (SC) rituximab versus intravenous (IV) rituximab both in combination with chemotherapy (fludarabine and cyclophosphamide), in patients with previously untreated CLL

(b) (4)

(\*Note: The final bioanalytical reports for study B025341 were provided by the firm during the inspection. The reports include results from the PK assay ( (b) (4) , dated November 5, 2015) and the NAb assay ( (b) (4) , dated November 10, 2015). Since these reports have not been submitted to FDA, a copy of each report was collected (Attachment-1 and Attachment-2).

(b) (4) stated that they submitted the reports to the sponsor, but did not have information regarding whether the reports were submitted to FDA. During the inspection, (b) (4) contacted the sponsor regarding plans for submitting the reports to FDA. The sponsor replied that they plan to submit the bioanalytical reports as part of the final clinical report tentatively scheduled to be submitted in November 2017.)

The inspection was conducted by OSIS scientists Melkamu Getie-Kehtie, (b) (4) Zhang, Ph.D. (DNDBE), from (b) (4)

(b) (4) The inspection included a thorough examination of study records, facilities and equipment, and interviews and discussions with the firm's management and staff.

At the conclusion of the inspection, one Form FDA 483 item was issued ( (b) (4)

(b) (4)

(b) (4)

Final Classification

(b) (4)

**VAI:**

(b) (4)

(b) (4)

CC:

OTS/OSIS/Kassim/Taylor/ Kadavil/Fenty-

Stewart/Nkah/Miller/Johnson

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala/Zhang

OTS/OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Au/Getie-Kebtie

OND/DHP/Farrell/Wall

Draft: MG 3/24/2017, 3/30/2017, 3/31/2017, 4/5/2017, 4/7/2017;

YZ 3/28/2017

Edit: SA 03/30/2017, 3/31/2017; JC 4/4/2017, 4/6/2017, 4/8/2017

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical  
Sites/ (b) (4)

OSI:

**FACTS**

(b) (4)

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/s/  
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MELKAMU GETIE KEBTIE  
04/10/2017

YIYUE ZHANG  
04/10/2017

STANLEY AU  
04/10/2017  
Acting Team Lead

SEONGEUN CHO  
04/10/2017

## CLINICAL INSPECTION SUMMARY

<b>Date</b>	April 6, 2017
<b>From</b>	Anthony Orenca, M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman, M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D. M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation/OSI
<b>To</b>	Alexandria Schwarsin, M.D., Vishal Bhatnagar, M.D., Medical Officers R. Angelo de Claro, M.D., CDTL Ann Farrell, M.D., Division Director Laura C. Wall, Regulatory Project Manager Division of Hematology Products/OHOP
<b>BLA</b>	761064
<b>Applicant</b>	(b) (4)
<b>Drug</b>	rituximab-hyaluronidase
<b>NME</b>	No
<b>Therapeutic Classification/Review</b>	Standard
<b>Proposed Indication</b>	Treatment of patients with: <ul style="list-style-type: none"> <li>• Follicular Lymphoma</li> <li>• Diffuse Large B-cell Lymphoma</li> <li>• Chronic Lymphocytic Leukemia</li> </ul>
<b>Consultation Request Date</b>	November 18, 2016 (signed)
<b>Summary Goal Date</b>	April 22, 2017
<b>Action Goal Date</b>	June 26, 2017
<b>PDUFA Date</b>	June 26, 2017

### 1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Mercadal Vilchez and Tani) were selected for inspection. Additionally the contract research organization (CRO), (b) (4) responsible for site monitoring and monitoring record retention for Study MO28107 and sponsor, Genentech Inc. (South San Francisco, CA), were inspected.

The preliminary classification for the inspections of Drs. Mercadal Vilchez, (b) (4) (CRO) and sponsor (Genentech, Inc., a Member of the Roche Group) is No Action Indicated (NAI). The preliminary classification for Dr. Tani is Voluntary Action Indicated (VAI) based on communications with the field investigator. The study data derived from these clinical sites are considered reliable in support of the requested indication.

## **2. BACKGROUND**

Rituximab is a CD20-directed cytolytic antibody approved for the treatment of patients with Non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA) in combination with methotrexate in adult patients with moderately- to severely-active RA who have inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies, granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) and microscopic polyangiitis (MPA) in adult patients in combination with glucocorticoids. The approved rituximab is administered as an intravenous infusion.

Rituximab solution for subcutaneous (SC) injection (hereafter referred to as rituximab SC) is a new dosage form of rituximab associated with a new route of administration. It is a co-formulation of the CD20-directed cytolytic antibody rituximab and recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. The rituximab SC injection is administered subcutaneously into the abdominal wall. Compared with intravenous (IV) infusions which typically range from 1.5 to 6 hours in clinical practice, the administration time with rituximab SC injections is reduced to approximately 5-7 minutes.

In this BLA application, the sponsor proposes rituximab SC injection for the treatment indication of follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and CLL.

The sponsor submitted two clinical trials (BO22334/SABRINA and MO28107/MabEase) and three supportive clinical trials (BO25341/SAWYER, MO28457/PrefMab, and BP22333/AparkThera) to support the proposed indication.

In review of this BLA, the Division of Hematology Products (DHP) requested two clinical sites, and CRO and sponsor inspections for two clinical trials (BO22334/SABRINA and MO28107/MabEase) and one supportive clinical trial (BO25341/SAWYER). The CRO and sponsor inspections were requested by DHP primarily for review of monitoring of study conduct at the CI sites.

### **BO22334 (SABRINA)**

This trial was a Phase 3, multicenter, two-stage, open-label, randomized trial of rituximab SC versus rituximab IV induction followed by maintenance in patients with previously untreated CD20+ FL. Induction treatment consisted of R-CHOP or R-CVP followed by maintenance with rituximab only (either IV or SC).

The primary objective at stage 1 was to estimate the ratio of trough serum concentrations of rituximab obtained at Cycle 7, 21 days after subcutaneous administration to that obtained after intravenous administration. The primary objective at stage 2 was to estimate the overall response rate (ORR) in each treatment arm at the end/completion of induction treatment.

The primary efficacy endpoint for stage 1 was observed rituximab serum trough concentration levels at Cycle 7 during induction treatment. The primary efficacy endpoint for stage 2 was overall response rate (ORR) at the end of induction, with progression free survival (PFS) as a secondary endpoint.

The main inclusion criteria were adult patients with previously untreated histologically confirmed CD20-positive, follicular NHL grade 1, 2 or 3a, according to the WHO classification system. A tumor biopsy (lymph node, bone marrow, etc.) must have been performed within 6 months before study entry with material available for central review.

A total of 410 subjects were enrolled, with 205 in each group. The study was conducted in 31 countries. The first subject screened in this study was on February 4, 2010 and the clinical data cutoff date for the submission was on February 12, 2016.

### **MO28107 (MabEase)**

This study was a Phase 3b, multicenter, open-label, randomized trial evaluating rituximab SC versus rituximab IV in patients with previously untreated DLBCL. Treatment consisted of rituximab in combination with CHOP-14 or CHOP-21.

The primary objective for this study was to estimate the efficacy of rituximab administered subcutaneously (SC) or intravenously (IV) in combination with cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP), as measured by complete response rate (including complete response unconfirmed; CR/CRu) approximately one month after the end of rituximab based treatment.

The primary endpoint was CR at the end of treatment with PFS as a secondary efficacy endpoint. The main inclusion criteria are adult patients with previously untreated CD20-positive DLBCL, according to the WHO classification system.

A total of 572 subjects were enrolled with 381 subjects in the rituximab SC group and 195 subjects in the rituximab IV group. The study was conducted in 25 countries. The study period was from August 22, 2012 to December 31, 2015.

### **BO25341(SAWYER)**

This study was a Phase 1b/2, two-part, open-label, randomized trial (part 2) comparing rituximab SC with rituximab IV in patients with previously untreated CD20+ chronic lymphocytic leukemia. Part 1 was dose-finding and part 2 was dose-confirmation.

The primary objective was to confirm a selected SC rituximab dose results in trough drug concentration levels that are comparable to IV rituximab in part 1 and to establish non-inferiority in observed trough drug concentration levels between the confirmed SC rituximab dose and the reference IV rituximab dose in part 2.

Pharmacokinetic parameter of trough drug concentration level was the primary endpoint of the study. Efficacy endpoints included ORR and CRR at the end of treatment were considered as exploratory. The main inclusion criteria are adult patients with previously untreated documented CD20+ B-CLL of Binet stage A, B or C requiring treatment.

A total of 192 subjects were enrolled with 16 subjects in part 1 and 176 subjects in part 2. The study was conducted in 12 countries. The first subject screened in this study was on April 13, 2011 and the clinical data cutoff date was on May 07, 2014.

### 3. RESULTS (by site):

Name of CI, Address	Protocol #, Site #, and # of Enrolled Subjects	Inspection Date	Classification
Santiago Mercadal Vilchez M.D. ICO (Instituto Catalán de Oncología) Hospital Duran i Reynals Avenida Gran Via, 199-203, 7 <sup>a</sup> planta, unidad de hematología. 08908 Hospitalet del Llobregat Barcelona Spain	BO22334 (SABRINA)  Site #205755  12 randomized	February 20-23, 2017	Pending: Preliminary NAI
Monica Tani, M.D. Az. Osp. S. Maria Delle Croci; U.o. Di Ematologia Viale Randi 5 48100 Ravenna Emilia-romagna Italy	MO28107 (MabEase)  Site #247526  17 randomized	February 13- 17, 2017	Pending: Preliminary VAI
CRO: (b) (4) (b) (4)	Study Protocol: MO28107 (MabEase)	February 27 – March 2, 2017	Pending: Preliminary NAI
SPONSOR: Genentech Inc. 1 DNA Way South San Francisco, CA 94080	Study Protocols: 1. BO22334 (SABRINA) 2. BO25341 (SAWYER)	January 23 to February 1, 2017	Pending: Preliminary NAI

#### Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data are unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

## **Clinical Investigator**

### **1. Santiago Mercadal Vilchez, M.D., Barcelona, Spain**

The inspection was conducted from February 20 to 23, 2017. A total of 12 subjects were screened and enrolled, and 12 study subjects were randomized. Eleven subjects completed the study. An audit of 12 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

### **2. Monica Tani, M.D., Rome Italy**

The inspection was conducted from February 13 to 17, 2017. A total of 17 subjects were screened and were enrolled, and 17 subjects were randomized. A total of 11 study subjects completed the study. Five subjects died during the study and one study subject was lost to follow-up. An audit of the 17 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection for failure to conduct the investigation in accordance with the investigational plan. Adverse events were not reported according to the protocol-required time intervals.

- A. Late serious adverse event reports for three separate patients were communicated by the clinical site to the sponsor more than 24 hours after the onset of the event (“atrial fibrillation” [Subject (b) (6) rituximab i.v. subgroup], “abdominal pain and sepsis” [Subject (b) (6)], and “transitional cell cancer” [also Subject (b) (6), rituximab i.v. subgroup]).
- B. Late completions of the adverse events of special interest forms, each for three distinct study subjects.

Reviewer Comment:

*The delayed reporting for a subject with atrial fibrillation occurred after the clinical investigator (CI) at the site learned that the subject was hospitalized in another hospital ward. Delayed reporting for the subject hospitalized for abdominal pain and sepsis was due to a delay in the CI informing the study coordinator of the event. These serious adverse events were ultimately reported (relatively soon) after awareness of the events and appear to be relatively isolated.*

*Adverse events of special interest (AESIs) or administration-related reactions for three subjects (# (b) (6) five episodes, (b) (6) one episode, and (b) (6) one episode), were not signed by the sub-investigator and reported until just prior to the inspection in February 2017. There are no AEs reported in the BLA data listing for AEs corresponding to these episodes. The CI response to the Form FDA 483 states that AESIs at this site were documented in a specific section of the chart (i.e. nursing records) and not noted by physician, study coordinator, or site monitor. In preparation for inspection these findings were observed in nursing notes and subsequently reported, however this is not reflected in the BLA.*

Dr. Tani responded adequately to the Form FDA 483 observation issued on March 9, 2017.

Notwithstanding the concern about potentially unreported AESIs (administration-related reactions) at this site as outlined above, data submitted by this clinical site appear acceptable in support of this specific indication. An information request to the sponsor inquiring about AESI reporting at this site after database lock and potential for this problem to have occurred at other CI sites participating in the study should be considered by DHP. (b) (4) was responsible for study monitoring for Study MO28107.

**Sponsor/CRO**

3. **CRO:** (b) (4) (Study MO28107 [MabEase] study monitoring)

This inspection was conducted from February 27 to March 2, 2017.

(b) (4) (Contract Research Organization) records reviewed included the following: regulatory site set up, financial disclosures, site management and monitoring visits. Monitoring visits reports including study site closeout visit were reviewed. Monitoring reports indicated that the five audited sites received adequate periodic monitoring. IRB approvals, site study protocol deviations and serious adverse event were assessed, and the CRO oversight appeared to be adequate. (b) (4)

standard operating procedure (SOP) index likewise revealed document identification, title, revision, document status, scope, effective date, and periodic review dates.

Records reviewed indicated that the CRO maintained adequate oversight of the clinical trial and monitoring activities were appropriate.

**4. SPONSOR: Genentech Inc., San Francisco, CA, (Study BO22334 [SABRINA] and BO25341 [SAWYER] study monitoring)**

This inspection was conducted from January 23 to February 1, 2017.

Monitoring visit reports including study site closeout visits were reviewed. Monitoring reports indicated that the 10 audited sites (five study sites each for Study SABRINA and Study SAWYER, respectively) received adequate periodic monitoring. IRB approvals, and site study protocol deviations and serious adverse events reporting were assessed. CRO monitoring oversight appeared to be adequate. Appropriate steps were taken by the sponsor monitor per their standard operating procedures and trial monitoring plans. The sponsor maintained adequate oversight of the clinical trial and monitoring activities were appropriate.

*{See appended electronic signature page}*

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

CONCURRENCE:

*{See appended electronic signature page}*

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

CONCURRENCE:

*{See appended electronic signature page}*

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

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/s/  
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ANTHONY J ORENCIA  
04/06/2017

JANICE K POHLMAN  
04/06/2017

KASSA AYALEW  
04/07/2017

**MEMORANDUM**

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

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DATE: March 29, 2017

TO: Ann T. Farrell, M.D.  
Director  
Division of Hematology Products  
Office of New Drugs

FROM: Ruben C. Ayala, Pharm.D.  
Lead Pharmacologist  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.  
Deputy Director  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct biopharmaceutical inspection**

RE: BLA 761064 (Rituximab and Hyaluronidase for subcutaneous injection).

The Division of New Drug Bioequivalence Evaluation within the Office of Study Integrity and Surveillance declines to conduct a bioequivalence inspection of one clinical site involved with **study B025341** submitted in support of BLA 761064. The rationale for this decision follows.

The ORA investigator is unable to travel to Penza, Russia in a reasonable timeframe to complete the inspection and to provide a finalized Establishment Inspection Report (EIR) prior to the impending PDUFA goal date of June 26, 2017. The earliest possible travel date is the end of May 2017.

Given the updated travel timeline, ORA could provide preliminary inspectional findings, but the OSIS final EIR review, which may include the site's response to a potential form FDA 483, may not be

available before June 26, 2017. Therefore, we decline to inspect Penza Regional Oncology Dispensary located in Penza, Russia.

We note that the inspection of the second clinical site (General University Hospital, Czech Republic) associated with Study B025341 is still scheduled as planned. OSIS should be able to provide a recommendation on the reliability and acceptability of data prior to the PDUFA goal date based on findings from the second site only.

Requested Site Inspections for Study B025341

OSIS Decision	Facility Type	Facility Name	Facility Address
Declined to inspect	Clinical site	Penza Regional Oncology Dispensary	Pr Stroiteley 37a, Penza, 454080, Russia
Scheduled for inspection	Clinical site	General University Hospital, 1 Th Department of Medicine - Clinic of Hematooncology	U Nemocnice 2, Praha 2 128 08, Czech Republic

Ruben C. Ayala, Pharm.D.  
Lead Pharmacologist  
DNDBE

CC:

OTS/OSIS/Kassim/Taylor/Choe/Kadavil/Turner-Rinehardt/Fenty-Stewart/Nkah/Miller/Johnson  
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Zhang  
OTS/OSIS/DGDBE/Cho/Haidar/Skelly/Choi/Au

Draft: RCA 3/28/2017; 3/29/2017

Edits: AD 3/29/2017

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/  
Clinical Sites/Penza Regional Oncology Dispensary

BE File #: 7317 (BLA 761064)

**FACTS: 11700968**

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/s/  
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RUBEN C AYALA  
03/29/2017

ARINDAM DASGUPTA  
03/29/2017

**HUMAN FACTORS LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** March 13, 2017

**Requesting Office or Division:** Division of Hematology Products (DHP)

**Application Type and Number:** BLA 761064

**Product Name and Strength:** Rituxan subcutaneous  
(rituximab and hyaluronidase)  
Injection  
1400 mg and 23,400 units, 1600 mg and 26,800 units

**Product Type:** Multi-ingredient product

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Genentech, Inc.

**Submission Date:** August 26, 2016, December 12, 2016, and January 6, 2017

**OSE RCM #:** 2016-1980 and 2017-59

**DMEPA Primary Reviewer:** Nicole Garrison, PharmD, BCPS

**DMEPA Team Leader:** Hina Mehta, PharmD

**DMEPA Associate Director for Human Factors:** QuynhNhu Nguyen, MS

**OMEPRM Deputy Director (Acting):** Lubna Merchant, MS, PharmD

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## **1 REASON FOR REVIEW**

The Division of Hematology Products (DHP) requested DMEPA evaluate the proposed labels and labeling and Human Factors (HF) study results submitted on August 26, 2016 and December 12, 2016, for BLA 761064, Rituxan Subcutaneous (rituximab and hyaluronidase) Injection to ensure the intended user population is able to understand the labeling of this product. This human factor study was also conducted to evaluate the intended users' ability to distinguish between the Rituxan dosage forms and strengths.

### **1.1 PRODUCT BACKGROUND**

Rituxan (rituximab) injection is currently approved for the treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Rituxan is available as 100 mg/10 mL and 500 mg/50 mL (10 mg/mL) single dose vials for intravenous use.

The proposed product, Rituximab and hyaluronidase is indicated for the treatment of patients with follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL). It is administered as a subcutaneous injection after patients receive at least full dose of Rituxan (rituximab) by intravenous infusion. Rituximab and hyaluronidase is intended for use at a dose of 1400 mg and 23,400 units/mL for patients with FL/DLBCL only and 1600 mg and 26,800 units/mL in patients with CLL. The administration of rituximab and hyaluronidase is over 5 to 7 minutes.

### **1.2 REGULATORY HISTORY**

On February 23, 2016, DMEPA participated in a face-to-face meeting between the Division of Hematology Products (DHP) and Genentech to discuss registration of subcutaneous rituximab.<sup>a</sup> We noted that the proposed subcutaneous rituximab formulation is more concentrated than the currently marketed intravenous rituximab formulation. Therefore, we expressed concern regarding the risk of medication errors if the subcutaneous and intravenous formulations are confused with each other. Additionally, we noted that the subcutaneous rituximab formulation requires a large-volume subcutaneous injection and a five to seven minute administration time, which is not the typical volume or time for subcutaneous injections. Due to the medication error risks associated with the introduction of the proposed subcutaneous rituximab formulation, we recommended that the Sponsor submit a use-related risk analysis and plans for a HF validation study that focused on product differentiation and labeling comprehension.

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<sup>a</sup> Memorandum of Type B Meeting Minutes for Rituxan (PIND 126650). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Hematology and Oncology Products, Division of Hematology Products. 2016 FEB 26.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

### 3.1 HUMAN FACTORS STUDY

#### 3.1.1 Methodology

Genentech submitted BLA 761064 rituximab and hyaluronidase injection for subcutaneous administration for the treatment of patients with follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL). The Applicant conducted a summative label comprehension and product differentiation study for rituximab and hyaluronidase for subcutaneous injection. DMEPA reviewed the methodology for the study on May 2, 2016<sup>b</sup> and found it acceptable in terms of focusing on product differentiation and label comprehension. However, we noted deficiencies including the omission of mockup prescriptions and the moderator's script. Additionally we noted the use of error prone abbreviations, e.g. (b) (4) in the proprietary name on the carton labeling and container labels. We provided recommendations to submit drafts of the mockup prescriptions and the moderator's script that will be used in the HF study. We recommended that the Sponsor complete the HF validation study and mitigate all identified risks prior to approval (b) (4). (b) (4). Additionally, we recommended against the use of the proprietary name (b) (4) on the labels and labeling that will be

<sup>b</sup> Whaley, E. Human Factors Study Protocol Review (PIND 126650). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 May 02. 11 p. OSE RCM No.: 2016-704.

used in the HF validation study. We have confirmed that our recommendations were implemented.

The study involved carton differentiation, vial differentiation, labeled syringe identification, and label comprehension in 15 nurses and 15 pharmacists.

### **3.1.2 Human factors study results**

The Applicant conducted a product differentiation and a label comprehension study. The results are discussed below:

#### **1. Carton and vial differentiation study results**

There were no observed use errors performed by pharmacists and nurses. There was one observed use error (1/30, or 96.67% success) committed during the labeled syringe identification tasks. The participant was unable to identify the route of administration for a 1400 mg and 2000 units/mL hyaluronidase syringe (See Appendix C for details of the error that occurred in the Study) described in detail below.

#### **Error in determining the route of administration for a labeled syringe (n=1)**

One nurse was unable to correctly answer the syringe label question about the “dosage form or administration type” for the 1400 mg syringe. The participant was initially confused by the question and after the investigator repeated it, he then seemed to focus on the “dosage form” part of the question and provided the dose strength in response. The investigator then asked the participant about the “administration type” and he replied, “It doesn’t say. It just says injection.” The participant went on to state that the syringe label did not specify if it was subcutaneous or intravenous. During the root cause interview, the investigator redirected the participant to the medication name on the syringe and the participant then noticed “subcutaneous” in the name on the label. The participant did not provide a reason as to why he missed the word subcutaneous on the syringe label before. However, he attributed the error to the large syringe volume, which made him think it was not a subcutaneous injection. He stated the syringe volume seemed too large to be a subcutaneous injection and had only administered subcutaneous injections of 5 mL or less in the past. In his experience, a typical subcutaneous injection contains 2 to 3 mL. The Applicant proposes changes to amend the peel-off label [REDACTED] <sup>(b) (4)</sup>. After review of the proposed changes, we determined, further modifications to labels and labeling are suggested to highlight the route of administration.

#### **2. Label comprehension study results**

There were no observed use errors that occurred in the labeling comprehension part of the study, however during the final interview, participants were able to provide additional feedback. Of those participants who provided feedback, there were some concerns raised by the participants which are discussed below.

- Injection site guidance (n=2)
- Atypical injection time (n =2)

- Large injection volume (n =4)
- Storage information (n=3)

### **Injection site guidance (n=2)**

Two participants mentioned the injection site could be further highlighted and clarified. The participants noted that the Prescribing Information (PI) does not indicate what happens if the subcutaneous injection is administered in a site outside of the abdomen or note the reason for restricting the injection to one site. However, after review of the PI, it states that there is no available information on performing the injection at other sites of the body. Additionally, one participant recommended highlighting the injection site information to make it more visible to the intended users. Based on this feedback, we recommend highlighting the administration site (abdominal wall) in the PI by stating “Administer Rituxan subcutaneously into the abdominal wall over approximately 5-7 minutes.”

### **Atypical injection time (n=2)**

Two participants understood the atypical injection time (due to the large volume), and made comments on the injection time being long for a subcutaneous injection. It was noted that most subcutaneous injections are quick and with the large volume and longer injection time required for Rituxan subcutaneous, more guidance and practice would be needed to administer of the prescribed duration of 5 to 7 minutes. Based on this feedback, we recommend the Sponsor provide more guidance to healthcare professionals by distributing a “Dear Healthcare Provider” letter to ensure that providers are aware of the new formulation of Rituxan subcutaneous and the unique requirements for safe administration of this product. Additionally, we recommend revisions to the container label and peel off label to state, “Give the subcutaneous injection over 5 to 7 minutes”.

### **Large injection volume (n =4)**

Four participants commented on the size of the syringe injection being larger than they were used to with a subcutaneous injection. Participants had questions on how they would administer the large dose and if it would be broken up into several smaller injections. The Sponsor proposes to clarify in the PI, if the injection is interrupted, it can be continued at a different site, but restricted to the abdomen. One participant expressed concern that the large injection volume of the syringe could lead to confusion and improper administration intravenously. To address concerns from the participants, the Sponsor proposes to amend the peel off label (b) (4). Additionally, we recommend revisions to the labels and labeling to ensure the subcutaneous route of administration is prominently displayed.

### **Storage information (n=3)**

Three participants commented on the storage recommendation to protect the medication from (b) (4) light. They stated it was unclear if they meant (b) (4) all light sources

in general. After review of the PI, it states (b) (4). Thus, no further modifications are warranted to the PI at this time.

#### 4 LABELS AND LABELING

In addition to the HF study results, we reviewed the proposed container label, carton labeling, and Prescribing Information to determine whether there were any areas that may be vulnerable to confusion that can lead to medication errors. The error observed in the study can be attributed to the large volume of solution required for subcutaneous injection of the product. The Applicant proposes changes to amend the peel-off label (b) (4). After review of the proposed changes, we determined, further modifications to labels and labeling are suggested to highlight the route of administration.

#### 5 CONCLUSION & RECOMMENDATIONS

The HF results and feedback from interviewing study participants demonstrated that further revisions were needed to the container label, carton labeling, and Prescribing Information to ensure clarity and prominence of the information.

##### 5.1 RECOMMENDATIONS FOR THE DIVISION

###### A. Prescribing Information

1. Highlights and Full Prescribing Information
  - a. As currently presented, the strength of rituximab and hyaluronidase is expressed using the dangerous abbreviation “u”. We recommend revising the strength presentation to change “u” to “USP units”<sup>c,d</sup>.
2. Section 2, Dosage and Administration
  - a. The proposed Dosage and Administration section is lengthy. Consider further separation of the text with the use of bullets to increase clarity of the information and ensure correct administration of this product.
  - b. Section 2.1 Administration of TRADENAME™ for Subcutaneous Injection
    - i. Increase the prominence of the injection site of administration by having a separate bullet that stating, “Administer Rituxan subcutaneously into the abdominal wall over approximately 5-7 minutes”.
    - ii. Revise (b) (4)

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<sup>c</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

<sup>d</sup> ISMP’s List of Error-Prone Abbreviations Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medications Practices. 2015 [2017 FEB 03]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>

(b) (4)

(b) (4) We recommend

this revision based on feedback received from participants in the Human Factors study.

c. Section 2.6 Preparation for Administration

- i. The vial has a peel-off label that should be attached to the syringe after the product is withdrawn from the vial. The peel-off label is used as a tool to mitigate wrong administration errors as it is clearly labeled (b) (4). We recommend that this important information be conveyed in the Prescribing Information by revising the statement, (b) (4) (b) (4) to “Once the product is withdrawn from the vial, it should be labeled with the peel-off sticker and used immediately.”

## 5.2 RECOMMENDATIONS FOR GENENTECH, INC.

We recommend the following be implemented prior to approval of this BLA:

A. Healthcare Provider Education

1. Rituximab and hyaluronidase will be the first subcutaneous injection of rituximab in the United States. We note that there are differences between the proposed subcutaneous rituximab and hyaluronidase formulation with the currently marketed intravenous rituximab formulation. The proposed subcutaneous rituximab and hyaluronidase formulation is supplied in a larger volume (11.7 mL and 13.4 mL), requires a longer administration time than most subcutaneous injections (5 or 7 minutes) and is more concentrated than intravenous rituximab. We anticipate that providers may not review the instructions for use prior to administration of this product and medication errors may occur if the subcutaneous and intravenous formulations are confused with each other. Thus, we recommend the Applicant consider providing an education campaign to health care providers (HCP's) that focuses on providing specific product information.

B. Container labels

1. Revise the presentation of the established name from “rituximab/hyaluronidase” to “rituximab and hyaluronidase” to be consistent with the Prescribing Information.

2. Express the product strength on the principal display panel to state in terms of total quantity per total volume followed by the concentration per milliliter (mL) as per USP standards<sup>e,f</sup>.

For example:

**1400 mg and 23,400 USP units/11.7 mL**

(120 mg and 2000 USP units/mL)

3. As currently presented, the strength of rituximab and hyaluronidase is expressed using the dangerous abbreviation “u”. We recommend revising the strength presentation to change “u” to “USP units”<sup>g,h</sup>.
4. Revise the statement (b) (4) to “For Subcutaneous Use only. Give the subcutaneous injection over 5 to 7 minutes”. We recommend increasing the font of the statement to help minimize the risk of administering the medication via an intravenous route of administration.
5. Clarify the significance of the number located next to the expiration date (10173774). If it is an internal product code, we recommend removing and/or relocating this number to mitigate the potential for confusion due to its close proximity to the expiration number.
6. Reorient the barcode containing the NDC number to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to curvature of the vial.
7. Peel-off Panel
  - i. Include the text, “For subcutaneous use only” to help minimize the risk of administering the syringe via an intravenous route of administration.
  - ii. Include the text “Give the subcutaneous injection over 5 to 7 minutes” to ensure this important information is not overlooked.

C. Carton labeling

1. See A.1 through A. 5 and revise the carton labeling accordingly.

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<sup>e</sup> USP General Chapter<1> Injections

<sup>f</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

<sup>g</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

<sup>h</sup> ISMP’s List of Error-Prone Abbreviations Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medications Practices. 2015 [2017 FEB 03]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rituxan Subcutaneous that Genentech submitted on December 12, 2016.

<b>Table 2. Relevant Product Information for Rituxan Subcutaneous</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	Rituximab and hyaluronidase
<b>Indication</b>	For the treatment of patients with: <ul style="list-style-type: none"> <li>• Follicular Lymphoma (FL)</li> <li>• Diffuse Large B-cell Lymphoma (DLBCL)</li> <li>• Chronic Lymphocytic Leukemia (CLL)</li> </ul>
<b>Route of Administration</b>	Subcutaneous
<b>Dosage Form</b>	Injection
<b>Strength</b>	<ul style="list-style-type: none"> <li>• 1400 mg rituximab and 2000 units/mL hyaluronidase per 11.7 mL</li> <li>• 1600 mg rituximab and 2000 units/mL hyaluronidase per 13.4 mL</li> </ul>
<b>Dose and Frequency</b>	<p><b><u>FL</u></b></p> <ul style="list-style-type: none"> <li>• Administer 1400 mg rituximab and 2000 units/mL hyaluronidase may be given over 5 minutes <i>Relapsed or Refractory, Follicular Lymphoma</i></li> <li>• Administer once weekly for 3 weeks following a full intravenous Rituxan dose at week 1 (i.e. 4 weeks in total). <i>Retreatment for Relapsed or Refractory, Follicular Lymphoma</i></li> <li>• Administer once weekly for 3 weeks following a full intravenous Rituxan dose at week 1 (i.e. 4 weeks in total). <i>Previously Untreated, Follicular Lymphoma</i></li> <li>• Administer on Day 1 of Cycles 2-8 of chemotherapy, for up to 7 cycles following a full intravenous Rituxan dose on Day 1 of Cycle 1 of chemotherapy. <i>Non-progressing, Follicular Lymphoma after the first line CVP chemotherapy</i></li> <li>• Following completion of 6-8 cycles of CVP chemotherapy, administer once weekly for 3 weeks</li> </ul>

	<p>following a full intravenous Rituxan dose at week 1 (i.e. 4 weeks in total), at 6 month intervals to a maximum of 16 doses.</p> <p><b><u>DLBCL</u></b></p> <ul style="list-style-type: none"> <li>Administer 1400 mg and 2000 u/mL hyaluronidase by subcutaneous injection over 5 minutes on Day 1 of Cycles 2-8 of CHOP chemotherapy, for up to 7 cycles following a full intravenous Rituxan dose at Day 1, Cycle 1 of CHOP chemotherapy.</li> </ul> <p><b><u>CLL</u></b></p> <ul style="list-style-type: none"> <li>Administer 1600 mg rituximab and 2000 units/mL hyaluronidase may be given over 7 minutes on Day 1 of Cycles 2-6 (every 28 days) for a total of 6 cycles.</li> </ul>
<b>How Supplied</b>	<p>Individually packaged single-dose vials:</p> <ul style="list-style-type: none"> <li>1400 mg rituximab and 2000 units/mL hyaluronidase per 11.7 mL</li> <li>1600 mg rituximab and 2000 units/mL hyaluronidase per 13.4 mL</li> </ul>
<b>Storage</b>	<p>(b) (4)</p>

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On February 3, 2017, we searched the L:drive and AIMS using the terms, Rituxan to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified two previous label and labeling reviews<sup>i,j</sup>. We confirmed that our previous recommendations were implemented.

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<sup>i</sup> Whaley, E. Human Factors Study Protocol Review (PIND 126650). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 May 02. 11 p. OSE RCM No.: 2016-704

<sup>j</sup> Whaley, E. Human Factors Study Protocol Review Memo (IND 126650). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Jun 20. 03 p. OSE RCM No.: 2016-1201.

## APPENDIX C. HUMAN FACTORS STUDY

### C.1 Results

There were no observed use errors during the carton and vial differentiation tasks performed by pharmacists and nurses. There was one observed use error (1/30, or 96.67% success) committed during the labeled syringe identification tasks. All participants could read and comprehend the syringe label information. Nurses were correctly able to answer all comprehension questions on the syringe label, except for one nurse who questioned the administration type.

*Table 8. Results from Pharmacists' Product Differentiation Tasks*

Pharmacists, N = 15	Carton Differentiation			Vial Differentiation		
	Task Results		Success %	Task Results		Success %
	Yes	No	[(N/15)*100]	Yes	No	[(N/15)*100]
<b>Dose Strength (mg)</b>						
<b>100</b>	15	0	100%	15	0	100%
<b>500</b>	15	0	100%	15	0	100%
<b>1400</b>	15	0	100%	15	0	100%
<b>1600</b>	15	0	100%	15	0	100%

*Table 9. Results from Nurses' Product Differentiation Tasks*

Nurses, N = 15	Carton Differentiation			Vial Differentiation		
	Task Results		Success %	Task Results		Success %
Dose Strength (mg)	Yes	No	[(N/15)*100]	Yes	No	[(N/15)*100]
<b>100</b>	15	0	100%	15	0	100%
<b>500</b>	15	0	100%	15	0	100%
<b>1400</b>	15	0	100%	15	0	100%
<b>1600</b>	15	0	100%	15	0	100%

Table 10. Results from Pharmacists' Labeled Syringe Tasks

Pharmacists N=15	Label Comprehension						Total Outcome		Success %
	Dose Strength (mg)	Medication Name		Admin. Type		Strength	Yes	No	
		Yes	No	Yes	No				Yes
1400	15	0	15	0	15	0	15	0	[(N/15)*100] 100%

Table 11. Results from Nurses' Labeled Syringe Tasks

Nurses N=15	Label Comprehension						Total Outcome		Success %
	Dose Strength (mg)	Medication Name		Admin. Type		Strength	Yes	No	
		Yes	No	Yes	No				Yes
1400	15	0	14	1	15	0	14	1	[(N/15)*100] 93.33%
1600	15	0	15	0	15	0	15	0	100%

### Root cause of error

Table 12. Observed Use Error and Root Cause Summary

Observed Use Error	Subject #	Root Cause
Fails to/unable to identify what administration type is contained within the labeled syringe of the 1400 mg Rituxan Subcutaneous Labeled Syringe.	(b) (6)	did not identify what administration type is contained within the labeled syringe, though he was able to read subcutaneous as part of the drug name.
	-	(b) (6) did not think it was subcutaneous as he had never performed a subcutaneous injection volume that large.

### Concluding Interview

After the differentiation and identification test on the cartons, vials, and syringes were complete, participants were asked for opinion on the ease of identifying the dosage forms and strengths during the preceding activities.

#### 8.4.2.1 Ease of Identification

Before concluding the differentiation testing part of the study, the interviewer asked participants for their subjective opinion on the ease of identifying the correct dosage forms and strengths based on any of the preceding activities. Twenty-eight of the thirty participants said that the tasks were easy. When participants offered specific reasons for why the tasks were easy, use of color and red font were frequently mentioned. The two participants (b) (6) who did not respond that the tasks were easy described that they would prefer more information to be contained on the box with specific components that they then spoke in more detail about.

- More information on syringe label. (b) (6) did not find the syringe easy to use due to a reported lack of information on the syringe label, as well as the carton and vial labels. (b) (6) stated, *"Syringe not easy. These (cartons) do not say what they're mixed in...like dextrose or sodium fluoride and these (vials) do not either. I just wanna know, like, how fast are we giving this? It just has, like, sub-cu. How much is the patient to get? Do we squirt any of it out? Is there any pre-filled?"* When the investigator asked if he expected to have all that information on the syringe label, (b) (6) said *"I'd prefer it."*
- More information on IV carton. (b) (6) stated satisfaction with the amount of information on the SC carton, but noted a preference to have more information on the IV carton, stating *"So, the boxes weren't that difficult. The only thing about this one is I would put more information here [points to the front panel of the Rituxan IV 500mg box] 'cause your first view is of really this [points to the same place] and with, kind of, with our workload, and stuff like that, we have like, short, I'm not saying we're like ADD squirrel, but we have, like, [holds the Rituxan Subcutaneous 1600 mg in his hand] I know what this is in 10 seconds. This [holds the Rituxan IV 500mg] I am like okay it is this, but I have no idea whether it is an IV dose or sub-cu dose. It is well put here [points to the top panel of the Rituxan IV 500 mg box], need to put that there [points to front panel of the Rituxan IV 500 mg box] on the carton. Actually, on the vial [points to the Rituxan IV 500 mg vial] that's pretty well, it's understood on the vial. I did not have any issues with any of these vials."*

#### 8.4.2.2 Colors

Seventeen participants made some mention that they liked the use of colors on the packaging, though the actual benefit on the use of colors varied slightly. Some examples of statements are provided, divided into the common themes on the use of colors.

Some subjects liked the use of color coding and strips on the packaging.

- (b) (6) said *"I like the different colors."*
- (b) (6) noted *"really like how these are, like, coded and a different colors, these strips. The circles are easy too, but I kinda like the strips."*
- (b) (6) stated *"The color coding draws your attention to the dosage which is helpful."*
- (b) (6) said *"I think it helps that their color is different, they pop out, the numbers...the milligrams, the strength. I like that made it easy."*

Other subjects mentioned that the consistent use of different colors on vial caps and other packaging was good in differentiating between dosages and/or IV and SC formulations.

- (b) (6) said *"It did help that everything was different colors for sure...contrast to the white...the colors of the dosage...that's helpful for sure."* Regarding the vials, (b) (6) said *"It helped when the color of the cap was the same, that highlighted the strength. (IV vs. SC) Same thing, with the color that kind of match. It's a little different than these two [pointed towards different vial cap color between Rituxan IV and SC products]."*
- (b) (6) noted *"It is very good that they are different colors, that these boxes are the darker and have a different color scheme than the other two."*
- (b) (6) said *"The colors I think helped having, sort of identifying, like, sort of popped, I guess. In terms of being able to, like, see the doses with the 1600, 1400, 500, 100. The color coordination, like, as you brought the trays out, I could actually remember the colors too, so I was able to recognize things like that, although I was trying to sort of take my time to make sure it was right too, but. Definitely having the colors is there very clear. Very easy, especially if you did this every day."*
- (b) (6) stated *"I thought these (vials) were easy to distinguish -- the different colors and the does were very prominent, so that made it easy to distinguish between the different ones."*
- (b) (6) said *"I mean, I could easily identify what strength was contained in each package, and they're different colors. That helps out as well."*
- (b) (6) noted *"Definitely the colored...the colored strength on there (cartons)...how they colored the strength on there (cartons). It was more obvious for subcutaneous I think it was just the packaging, the way they ran the whole color across and subcutaneous is on there."*
- (b) (6) said *"This is good that you've also color coded the lid tops (vials). That's helpful as well, 'cause that's a distinguisher."*

#### 8.4.2.3 Font in Red

Seven participants noted that they found it helpful to have the printing on the packaging use red font to state (b) (4) because it made it stand out as a difference in SC versus IV formulations and was easy to read and pick out when highlighted in red.

- (b) (6) said "Then the red, that's a good clue to have that (cartons). I think they are labeled pretty much the same as the packaging. It's nice that there's no difference really."
- (b) (6) stated "It was a little bit easier for the sub-cu I think because it was red where this is just black. I had to read it a couple of times just to be sure I was giving the right medication. It was easy because it was like the color, the color dose and then the red is easier."
- (b) (6) said "Identifying the strengths is easy. The form is kind of small, but I mean, this one's in red so it's easy to identify."
- (b) (6) noted "Yeah the red, there for subcutaneous use is very good, but I think that they could put more emphasis on the actual wording subcutaneous or intravenous."
- (b) (6) said "The subcutaneous is in the pink, that's good, or red whatever, you know (so you can see that?) yeah, yep, I can. And you know, like I said, I just know something different about these 'cause I know with the hyaluronidase, that's just a difference and that makes me think sub-cu, because that is a drug we give to people who have, like, extravasations of drugs that are bad for you and they get out into your skin and you can actually use hyaluronidase itself as a protection from that drug that's leaked from an IV vein. So, that's why I know they're different."
- (b) (6) said "Oh, I thought it was very easy. It was very easy, yes. The subcutaneous is in red, so you can see that that's different. Yes, it's also red over here (cartons)."
- (b) (6) noted "Like I said, it's pretty well laid out. Like the sub-cu is nice and red - it's big, so it's easy to differentiate that between the IV because those (cartons) are pretty well spelled out too."

### Labeling Comprehension Tasks

No use errors were observed by pharmacists and nurses during the labeling comprehension tasks.

Table 13. Results from Pharmacists' Labeling Comprehension Tasks

Knowledge Based Assessments Pharmacists, N = 15	KBA Locate IFU		KBA Correct Response		Total Outcome		Success %
	YES	NO	YES	NO	YES	NO	
	1. How should RITUXAN SUBCUTANEOUS be stored prior to use? (confirm "at 2°C-8°C [36°F-46°F]. Do not freeze.")	15	0	15	0	15	
2. [present a vial of RITUXAN SUBCUTANEOUS to the Subject] What is the expiration date of this vial of RITUXAN SUBCUTANEOUS? (confirm correct date)	15	0	15	0	15	0	100%
3. Which RITUXAN SUBCUTANEOUS strength should be administered to a patient with FL (Follicular Lymphoma)? (confirm "1400mg")	15	0	15	0	15	0	100%

Knowledge Based Assessments Pharmacists, N = 15	KBA Locate IFU		KBA Correct Response		Total Outcome		Success %
	YES	NO	YES	NO	YES	NO	
	4. Which RITUXAN SUBCUTANEOUS strength should be administered to a patient with DLBCL (Diffuse Large B-Cell Lymphoma)? (confirm "1400mg")	15	0	15	0	15	
5. Which RITUXAN SUBCUTANEOUS strength should be administered to a patient with CLL (Chronic Lymphocytic Leukemia)? (confirm "1600mg")	15	0	15	0	15	0	100%

Table 14. Results from Nurses' Labeling Comprehension Tasks

Knowledge Based Assessments Nurses, N = 15	KBA Locate IFU		KBA Correct Response		Total Outcome		Success %
	YES	NO	YES	NO	YES	NO	
	1. How should RITUXAN SUBCUTANEOUS be stored prior to use? (confirm "at 2°C-8°C [36°F-46°F]. Do not freeze.")	15	0	15	0	15	
2. [present a vial of RITUXAN SUBCUTANEOUS to the Subject] What is the expiration date of this vial of RITUXAN SUBCUTANEOUS? (confirm correct date)	15	0	15	0	15	0	100%
3.a) Which RITUXAN SUBCUTANEOUS strength should be administered to a patient with FL (Follicular Lymphoma)? (confirm "1400mg")	15	0	15	0	15	0	100%
3.b) What is the recommended injection time for an injection of RITUXAN SUBCUTANEOUS for a patient with FL (Follicular Lymphoma)? (confirm "approximately 5 minutes")	15	0	15	0	15	0	100%
4.a) Which RITUXAN SUBCUTANEOUS strength should be administered to a patient with DLBCL (Diffuse Large B-Cell Lymphoma)? (confirm "1400mg")	15	0	15	0	15	0	100%
4.b) What is the recommended injection time for an injection of RITUXAN SUBCUTANEOUS for a patient with DLBCL (Diffuse Large B-Cell Lymphoma)? (confirm "approximately 5 minutes")	15	0	15	0	15	0	100%
5.a) Which RITUXAN SUBCUTANEOUS strength should be administered to a patient with CLL (Chronic Lymphocytic Leukemia)? (confirm "1600mg")	15	0	15	0	15	0	100%
5.b) What is the recommended injection time for an injection of RITUXAN SUBCUTANEOUS for a patient with CLL (Chronic Lymphocytic Leukemia)? (confirm "approximately 7 minutes")	15	0	15	0	15	0	100%
6. What is the correct injection site for delivering a subcutaneous injection of RITUXAN SUBCUTANEOUS? (confirm "abdominal wall")	15	0	15	0	15	0	100%

### Final Interview

During the final interview, participants were able to provide additional feedback. Of those participants who provided feedback, there were some recurring themes and comments.

- Injection site guidance. Two participants mentioned the injection site guidance could be further highlighted and/or clarified. (b) (6) suggested that the instructions highlight that the only injection site was the abdominal wall, but that other drugs allow subcutaneous injections to be administered in other locations in addition to the abdomen. (b) (6) noted that *"It doesn't really say what happens if you give it somewhere else."* (b) (6) also noted that having a reason for restricting to just the one location can help as patients often get other injections and so may want to avoid an area of a prior injection or prefer to get an injection in another location. *"I think having it restricted saying those words to where is good and important."* Both subjects expressed a desire for more guidance in the product information to explain why only the one abdominal site was recommended, as well as to give details on why other common injection sites were not suggested. Subject (b) (6) also thought the injection site information could be highlighted better in the instructions to stand out more as important information.
- Atypical injection time may be physically challenging. Two participants (b) (6) understood the atypical injection time (due to the high volume), and made comments on the injection time being a long time to have to push a subcutaneous injection. (b) (6) said *"I'm just thinking to myself, injecting something subcutaneously for 7 minutes seems like a really long time."* (b) (6) stated *"You know, most like sub-cu (subcutaneous) injections are just quick, so five minutes seemed like a long time to hold a needle over somebody. That would definitely be, I would think, an education point for people 'cause when we give sub-cu it's always jab and plunge, so if it's over five minutes that would be something people aren't used to doing."* Comments from both subjects point to the high volume and longer injection time for the SC injection time being a new process they are unfamiliar with that would be physically challenging and would require guidance and practice to carry out over the longer prescribed duration.

- Questions regarding injection volume. Four participants (b) (6) commented on the size of the syringe injection being larger than they were used to with a subcutaneous injection. Because it is a much larger dose than the subjects are used to giving subcutaneously, they had questions on how they would administer that large a dose and if it would be broken up into several smaller injections. (b) (6) also expressed concern that the larger than usual SC dose could lead to confusion and improper administration as HCPs would assume it was an IV dose, so the subject suggested the addition of the "Not for IV" warning on the syringe label for subcutaneous doses.
  - (b) (6) noted "This is a subcutaneous injection. Um, it's a larger volume though, so I would want to know if they were giving at multiple sites...would be the first thing. 'Cause normally anything over 2 mLs, we'll question if it's actually supposed to be sub-cu."
  - (b) (6) said "I'm just curious how you give that much fluid subcutaneously, do they break it up into multiple shots? I think it's pretty straight forward pharmacy wise."
  - (b) (6) indicated that the maximum amount usually administered subcutaneously is 10 mLs.
  - (b) (6) said "It is a larger than average volume for a subcutaneous injection...if it was a pre-filled syringe, you just have to have labeling "Not for IV." You know what I mean? Just because it seems like more of an IV volume dose vs. a sub-cu volume dose. Just so it doesn't [get] accidentally administered IV. Just 'cause it's outside the normal administration."

(b) (4)

### **Proposed Modifications for Risk Minimization**

The Sponsor is proposing the following changes to further optimize the Prescribing Information and labeling:

- **Injection volume:** Given the larger than usual injection volume, further guidance was requested regarding administration, specifically, if multiple-injections are required to deliver a single dose volume. The current text in the USPI specifies that the abdomen is the recommended subcutaneous injection site and that if administration is interrupted, it can be continued at the same site, or at a different site, if applicable. To avoid confusion regarding the subsequent injection site, the Sponsor proposes to clarify the text to specify that if interrupted, the injection can be continued at a different site, but restricted to the abdomen.

- **Potential for Administration Route Error:** It was also highlighted that the injection volume might raise a potential for confusion with the route of administration. In order to further optimize the labeling, the Sponsor proposes to amend the peel-off label

(b) (6) [Appendix 2]

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>k</sup> along with postmarket medication error data, we reviewed the following Rituxan subcutaneous labels and labeling submitted by Genentech on August 26, 2016 and December 12, 2016.

- Prescribing Information
- Container labels
- Carton labeling

### **G.2 Label and Labeling Images**

#### **A. Prescribing Information**



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

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<sup>k</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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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.**  
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/s/  
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