CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761064Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA STN 761064

USAN: Rituximab/hyaluronidase (human recombinant)
INN: Rituximab/vorhyaluronidase alfa

Sponsor Genentech

OBP Product Reviewer (Rituximab): Marjorie Shapiro DBRR1
OBP Product Reviewer (Hyaluronidase): Shen Luo DBRR4
OPF/DMA DS Microbiology Reviewer: Candace Gomez-Broughton
OPF/DMA, DP Microbiology Reviewer: Natalia Pripuzova
OPF/DIA Facilities Reviewer: Thuy Nguyen
OPRO RBPM: Melinda Bauerlien
ATL: Marjorie Shapiro

OPQ CMC BLA Review Data Sheet

1. **BLA#:** STN 760164

2. **REVIEW DATE:**

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Alexandra Schwarsin
CDTL: Angelo DeClaro
Pharm/Tox: Natalie Simpson
Product Quality Team: Marjorie Shapiro, DBRR1, Shen Luo DBRR4
CMC Microbiology: Candace Gomez-Broughton and
Facilities: Natalia Pripuzova
Clinical Pharmacology: Olanrewaju Okusanua
Statistics: Jingjing Ye
OBP Labeling:
RPM: Laura Wall

4. **MAJOR 21st Century Review DEADLINES**
Filing Meeting: 10/11/2016
Mid-Cycle Meeting: 1/18/2017
Wrap-Up Meeting: 5/17/2017
Primary Review Due: 5/8/2017
Secondary Review Due: 5/15/2017
PDUFA Action Date: 6/12/2017

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
Information Request #1	8/31/2016 –DP products manufactured on the same line.
Information Request #2	10/18/2016 DP microbiology
Information Request #3	11/15/2015 DS microbiology, rituximab and hyaluronidase
Information Request #4	11/21/2016 (b) (4) facility information
Information Request #5	12/1/2016 PQ rituximab and immunogenicity
Information Request #6	1/18/2017 PQ hyaluronidase and DP microbiology
Information Request #7	2/16/2017 DP microbiology
Information Request #8	2/17/2017 PQ hyaluronidase and DP microbiology
Information Request #9	3/7/17 updated DP stability
Information Request #10	3/31/2017 hyaluronidase HCP spec
Information Request #11	4/19/2017 Identity testing per 21 CFR 610.14

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

Submission	Date Received	Review Completed
Original Submission	8/26/2016	Yes
Amendment 2 manufacturing schedule	9/6/2016	Yes
Amendment 3 Response to IR #1	9/7/2016	Yes
Amendment 19 Response to IR #2	10/25/2016	Yes
Amendment 20 Response to IR #2	11/4/2016	Yes
Amendment 31 Response to IR #5	11/30/2016	Yes
Amendment 34 Response to IR #3	12/5/2016	Yes
Amendment 38 Inspection Waiver	12/9/2016	Yes
Amendment 45 Response to IR #5	12/22/2016	Yes
Amendment 46 Response to IR#5	1/5/2017	Yes
Amendment 61 Response to IR #7	1/30/2017	Yes
Amendment 62 Response to IR #7	2/6/2017	Yes
Amendment 67 Response to inspection	2/10/2017	Yes
Amendment 69 Response to IR #8	2/23/2017	Yes
Amendment 70 Response to IR #7	3/1/2017	Yes
Amendment 71 Response to IR # 9	3/13/2017	Yes
Amendment 73 Response to IR #6	3/31/2017	Yes
Amendment 74 Response to IR #10	4/7/2017	Yes
Amendment 75 Response to IR #10	4/14/17	Yes
Amendment 77 Response to IR #11	4/27/2017	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: RITUXAN HYCELA
   b. Trade Name: RITUXAN HYCELA
   c. Non-Proprietary/USAN: rituximab
   d. CAS name: 174722-31-7
   e. Common name: C2B8
   f. INN Name: rituximab
   g. Compendial Name:
   h. OBP systematic name:
   i. Other Names: MabThera

8. **PHARMACOLOGICAL CATEGORY:**
9. **DOSAGE FORM:** solution for injection
10. **STRENGTH/POTENCY:**
11. **ROUTE OF ADMINISTRATION:** subcutaneous
12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
[redacted] (b) (4)			yes	
			yes	
			yes	

13. **INSPECTIONAL ACTIVITIES**

Rituximab DS manufacturing at Genentech, Vacaville – inspection waived
Hyaluronidase PLI at [redacted] (b) (4)
Hyaluronidase release testing at [redacted] (b) (4) -
Rituximab/Hyaluronidase DP manufacturing at F. Hoffman La Roche Kaiseraugst, covered by ORA during surveillance inspection.
All other sites listed for DS and DP testing were found acceptable and did not need to be inspected.

14. **CONSULTS REQUESTED BY OBP**

None

15. QUALITY BY DESIGN ELEMENTS

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

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

15. **PRECEDENTS**

The BLA describes rituximab formulated with recombinant hyaluronidase for subcutaneous administration. The hyaluronidase acts as a tissue dispersion agent to facilitate the subcutaneous administration of 1400 mg rituximab in 11.7 mL for CLL or 1600 mg rituximab in 13.4 mL in about 15 minutes as opposed to the several hours that may be needed for intravenous administration of rituximab.

A combination of recombinant hyaluronidase and IVIg was approved by CBER in 2014. In this case, the hyaluronidase was co-packaged with the10% IVIg and administered 15 minutes prior to the Immune Globulin Infusion of 25 up to 300 mL, depending on the dosage required. CBER considered the hyaluronidase to be an adjuvant because by itself, it had been approved at a concentration of 150 U/mL as an adjuvant "to increase the absorption and dispersion of other injected drugs, for SC fluid administration (hypodermoclysis), and as an adjunct in SC urography for improving resorption of radiopaque agents." (From CBER Review memo)

However, for the purpose of this BLA, the hyaluronidase is considered an active ingredient.

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761064 for Rituxan HYCELA, manufactured by Genentech pending acceptable compliance checks. The data submitted in this application are adequate to support the conclusion that the manufacture of Rituxan HYCELA is well controlled and leads to a product that is pure and potent. We recommend that Rituxan HYCELA be approved for human use under the conditions specified in the package insert.

We recommend an expiration dating period of (b) (4) months for rituximab drug substance when stored at (b) (4).

We recommend an expiration dating period of (b) (4) months for hyaluronidase drug substance when stored a (b) (4)

We recommend an expiration dating period of 30 months for rituximab/hyaluronidase drug product (1400 mg rituximab/23,400 Units hyaluronidase per vial and 1600 mg rituximab/26,800 Units hyaluronidase per vial) when stored at 2-8°C.

We recommend approval of the proposed release and shelf life specifications for rituximab drug substance, hyaluronidase drug substance and rituximab/hyaluronidase drug product.

II. List Of Deficiencies To Be Communicated

None

III. List Of Post-Marketing Commitments/Requirement

None

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment or Claim Of Categorical Exclusion

A categorical exclusion is claimed from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c). The claim of categorical exemption is accepted.

B. Primary Container Labeling Review

A separate primary container labeling review will be performed by Jibril Abdus Samad and/or Vicky Borders-Hemphill and reviewed by Marjorie Shapiro

V. Review Of Common Technical Document-Quality Module 3.2

The review of module 3.2 is provided below.

VI. Review of Immunogenicity Assays – Module 5.3.1.4

A review of the product immunogenicity assays is included at the end of the document.

Rituximab: The anti-drug antibody immunogenicity assay for rituximab has sufficient sensitivity (1.42 ng/ml) and demonstrates sufficient drug tolerance (detects 10 ng/mL ADA in the presence of up to 10 µg/ml rituximab and 100 ng/ml ADA in the presence of up to 200 mg/mL rituximab). However there are some concerns by the OSIS reviewer regarding the low positive control sample used in the assays for the clinical studies. There is no neutralizing assay.

Hyaluronidase: The anti-drug antibody immunogenicity assay for rHuPH20 has sufficient sensitivity (0.977 ng/ml plasma). The tolerance of the assay is not clear, however, the rHuPH20 concentration in the DP is at most (b) (4) µg/mL, therefore high levels of rHuPH20should not be present at the time blood samples are taken for immunogenicity.

The neutralizing ADA method is based on the based on the USP method, which uses tubes and not plates. Therefore only a limited number of samples and controls can be run at a time. The assay validation was performed in discrete units as several different reports describe different aspects of the validation. However, the assay itself appears to be acceptable. The OSIS reviewer found that the cut-point was not determined using drug naïve subjects

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TABLE OF CONTENTS

DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

Reviewer comments are show in italicized Arial font throughout the review. Unless otherwise noted, all figures and tables are copied directly from the submission.

S. DRUG SUBSTANCE

Reviewer comment: *Note that rituximab SC has the same active ingredient as Rituxan. This BLA cross references BLA 103705. The rituximab SC DS manufacturing process is the same as the current rituximab v1.2 DS manufacturing process, which is described in 103705.5236 and was approved in 2006. More recently, the manufacture of v1.2 rituximab a(b) (4) was approved in 2015 in 103705.5444. Therefore the DS review is specific to information for the SC manufacturing process and any modifications to both the v1.2 and SC processes.*

(b) (4)

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(b) (4)

P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

There are two strengths for Rituxan SC:

- 1400 mg rituximab and 23,400 U (2000 U/mL) hyaluronidase per 11.7 mL
- 1600 mg rituximab and 26,800 U (2000 U/mL) hyaluronidase per 13.4 mL

Reviewer comment: *Note that GNE uses the term "Rituxan SC" to refer to both DP strengths for brevity. For the purposes of this review, the same terminology will be used.*

Rituxan SC is a sterile, colorless to yellowish, clear to opalescent solution. The 1400 mg presentation is in (b) (4) single (b) (4) vials, with an extractable volume of 11.7 mL (1400 mg/11.7 mL) and the 1600 mg presentation is in (b) (4) single (b) (4) vials, with an extractable volume of 13.4 mL (1600 mg/13.4 mL). The compositions for each are shown in Table P.1.3.

Table P.1-3 Composition of Rituxan 1400 mg and 1600 mg Solution for SC Injection

Ingredient	Nominal Amount per Vial[a]		Concentration	Function	Specifications
	Rituxan SC 1400 mg (Ro 045-2294/F04)	Rituxan SC 1600 mg (Ro 045-2294/F05)			
RO 045-2294 (rituximab)	(b) (4)	(b) (4)	120 mg/mL	Active ingredient	Internal specification (see Section S.4.1 *Specification [rituximab]*)
Recombinant human hyaluronidase (rHuPH20)	23,400 U	26,800 U	2000 U/mL[b]	Active ingredient	Internal specification (see Section S.4.1 *Specification [vorhyaluronidase alfa]*)
L-Histidine	(b) (4)		(b) (4)	(b) (4)	Ph. Eur./USP-NF
L-Histidine hydrochloride monohydrate					Ph. Eur.
α,α-Trehalose dihydrate					Ph. Eur./USP-NF
L-Methionine					Ph. Eur./USP-NF
Polysorbate 80			0.06% (w/v)		Ph. Eur./USP-NF
Total volume adjusted with water for injection (WFI)	q.s.[c] to 11.7 mL	q.s.[c] to 13.4 mL	—		Ph. Eur./USP-NF

[a] Calculated figures based on nominal amount per vial.

[b] Corresponding to (b) (4) µg/mL; the rHuPH20 units are of the same nominal value as the USP units derived from the USP monograph for hyaluronidase of animal origin.

[c] q.s. = *quantum satis* (as much as may suffice).

Reviewer comment: *Note that GNE considers the hyaluronidase to be an active ingredient. Although the categorization was discussed during the review period, ultimately the Agency also made a decision to consider the hyaluronidase an active ingredient.*

Both container closures are colorless type (b) (4) glass vials with (b) (4) rubber stoppers and aluminum overseals with a plastic flip-off cap.

3.2.P.2 Pharmaceutical Development

(b) (4)

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(b) (4)

IMMUNOGENICITY

2.5 Clinical Overview

The clinical development program for rituximab SC was based on PK-bridging to the approved rituximab IV doses and dosing intervals for NHL and CLL, and clinical bridging to exclude major differences in efficacy and safety associated with the SC route of administration. Immunogenicity of rituximab and rHuPH20 was evaluated in all three rituximab SC PK studies, BP22333/SparkThera, BO22334/SABRINA, and BO25341/SAWYER.

Anti-Rituximab ADA:

- In the SparkThera study, the post-baseline incidence of ADA was 4% in the IV group and 1% in the SC group, including after 9 months of follow-up post the last dose.
- In the SABRINA study, the post-baseline incidence of ADA was 1% in the IV group and 2% in the SC group, with currently available data. The treatment period is complete, but the 2-year follow-up is ongoing. Three patients in the SC arm developed HACA after the initial IV dose and prior to receiving the SC doses.
- In the SAWYER study, the post-baseline incidence of ADA was 7% in the IV group (6/89) and 2% in the SC group (2/85). The treatment period is complete, but the 4-year follow-up is ongoing. Two patients in the SC arm developed HACA after the initial IV dose and prior to receiving the SC doses.

Overall, the SC route of administration does not result in greater immunogenicity relative to the IV route of administration.

Anti-rHuPH20 ADA:

- Baseline ADA in the three studies ranged from 6-11%. For the majority of patients with positive ADA at baseline, ADA was not enhanced after treatment and were considered ADA negative post-baseline (treatment unaffected.)
- The post-baseline incidence of rHuPH20 ADA (treatment-induced and treatment-enhanced responses) ranged between 5% and 13% across the three studies.
- In the SABRINA study, the post-baseline incidence of ADA was 13% in the SC arm, but 13% in the IV arm, which did not receive rHuPH20. Therefore the SC arm incidence was considered to be 5%.
- None of the ADA+ patients among the three studies had neutralizing ADA.
- The rHuPH20 ADA prevalence among patients treated with rituximab SC is consistent with prevalence rates ranging from 3-11% in studies of rHuPH20 used in combination with other products for the treatment of primary immunodeficiency (IVIg), breast cancer (trastuzumab), or diabetes mellitus (insulin). None of the ADA were neutralizing. See Rosengren et al. 2015. Clinical Immunogenicity of rHuPH20, a Hyaluronidase Enabling Subcutaneous Drug Administration. The AAPS J. 17:5.

2.7 Clinical Summary

A new immunogenicity assay was developed for rituximab SC that has higher sensitivity and improved drug tolerance compared with the assay used for the rituximab IV clinical trials.

In the SparkThera study, samples were collected at the first cycle of rituximab on study and pre-dose at the second cycle of rituximab, and then at 3 months and 9 months following the last dose of rituximab. Samples for anti-rHuPH20 antibodies were collected at the same time points only from patients randomized to receive rituximab SC.

In the SABRINA study anti-rituximab antibodies were assessed at each visit immediately pre-dose rituximab and every 12 weeks at each follow-up visit until 96 weeks after the last dose. Anti-rHuPH20 antibodies were to be assessed according to the same schedule; however, after protocol Amendment B, the assessment of anti-rHuPH20 antibodies was only performed in patients receiving rituximab SC. Data for the rituximab IV arm are hence limited to Stage 1 induction.

In the SAWYER study anti-rituximab antibodies were assessed pre-dose at Cycle 5 and Cycle 6 in Part 1 and pre-dose at each treatment cycle in Part 2. Anti-rHuPH20 antibodies (SC cohorts only) were assessed pre-dose Cycle 6 in Part 1 and pre-dose during Cycles 2-6 in Part 2. Additional samples were then taken at each follow-up visit until 9 months after the last dose of rituximab for anti-rHuPH20 antibodies and until 24 months after the last dose of rituximab for anti-rituximab antibodies.

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Marjorie Shapiro

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Kathleen Clouse Strebel

Digitally signed by Kathleen Clouse Strebel
Date: 5/09/2017 05:54:53PM
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First Approval for Subcutaneous Administration of Rituximab

Recommendation: Approval

BLA 761064
Executive Summary
Review Date: 5/8/2017

Drug Name/Dosage Form	Rituxan HYCELA, rituximab, injection, solution
Strength/Potency	1400 mg rituximab/23,400 U hyaluronidase/11.7 mL and 1600 mg rituximab/26,800 U hyaluronidase/13.4 mL
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
Indication	Treatment of patients with follicular lymphoma, diffuse large B-cell lymphoma and chronic lymphocytic leukemia
Applicant/Sponsor	Genentech

Product Overview

Rituxan HYCELA is a combination of Rituxan and recombinant human hyaluronidase for subcutaneous administration of rituximab for the treatment of NHL and CLL. Rituximab is a chimeric IgG1, kappa anti-CD20 mAb produced in Chinese hamster ovary (CHO) cells. It has multiple mechanisms of action including CDC, ADCC, ADCP and the induction of apoptosis. RHuPH20 is a recombinant human hyaluronidase produced in CHO cells. The purpose of adding the rHuPH20 to rituximab DP is to increase the dispersion and absorption of rituximab when administered subcutaneously, resulting in a significantly shorter infusion time for the patient.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance/Drug Product	Marjorie Shapiro	OBP/DBRR 1
Hyaluronidase	Shen Luo	OBP/DBRR 4
Facilities	Thuy Nguyen	OPF/DIA
Microbiology	Candace Gomez-Broughton Natalia Pripuzova	OPF/DMA
Labeling	Jibril Abdus-Samad	OBP
Business Regulatory Process Manager	Melinda Bauerlien	OPRO
Tam Lead Hyaluronidase	Serge Beaucage	OBP/DBRR 4
Team Lead Microbiology	Reyes Candau-Chacon	OPF/DMA
Team Lead Facilities	Peter Qiu	OPF/DMA
Application Technical Lead	Marjorie Shapiro	OBP/DBRR 1

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Laura Wall	OHOP/DHP
Cross-disciplinary Team Lead	Angelo de Claro	OHOP/DHP

Medical Officer	Alexandria Schwarsin	OHOP/DHP
Pharm/Tox	Natalie Simpson	OHOP/DHOT
Clinical Pharmacology	Olanrewaju Okusanya	OCP/DCPV
Statistics	Jingjing Ye	OB/DBV

a. Names
   i. Proprietary Name: RITUXAN HYCELA
   ii. Trade Name: RITUXAN HYCELA
   iii. Non-Proprietary/USAN: rituximab/hyaluronidase
   iv. CAS name: 174722-31-7
   v. Common name: C2B8, MabThera
   vi. INN Name: rituximab/ vorhyaluronidase alfa
   vii. OBP systematic name:
   MAB CHIMERIC (IGG1) ANTI P11836 (CD20_HUMAN) [2B8]
   RPROTFRAG P38567 (HYALP_HUMAN) HYALURONIDASE PH-20 [RHUPH20]

b. Pharmacologic category: Therapeutic recombinant chimeric monoclonal antibody (IgG1, kappa, anti-CD20) and recombinant human hyaluronidase as a dispersing agent.

Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
761064.1 (original submission)	8/26/2016
761064.2 manufacturing schedule	9/6/2016
761064.3 Response to IR #1	9/7/2016
761064.19 Response to IR #2	10/25/2016
761064.20 Response to IR #2	11/4/2016
761064.31 Response to IR #5	11/30/2016
761064.34 Response to IR #3	12/5/2016
761064.38 Inspection Waiver acknowledgement	12/9/2016
761064.45 Response to IR #5	12/22/2016
761064.46 Response to IR #5	1/5/2017
761064.61 Response to IR #7	1/30/2017
761064.62 Response to IR #7	2/6/2017
761064.67 Response to hyaluronidase inspection	2/10/2017
761064.69 Response to IR #8	2/23/2017
761064.70 Response to IR #7	3/1/2017
761064.71 Response to IR #9	3/13/2017
761064.73 Response to IR #6	3/31/2017
761064.74 Response to IR #10	4/7/2017
761064.75 Response to IR #10	4/14/2017
761064.77 Response to IR #11	4/26/2017

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	3	N/A	N/A	None
	Type V			3	N/A	N/A	None
	Type V			3	N/A	N/A	None

[1] Action codes for DMF Table: 1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows: 2 – Reviewed previously and no revision since last review; 3 – Sufficient information in application; 4 – Authority to reference not granted; 5 – DMF not available;6 – Other (explain under "Comments")

[2] Adequate, Adequate with Information Request, Deficient, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, Reference Listed Drug (RLD), or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Cross reference to other GNE applications	BLA 103705	BLA for rituximab v1.2, which is the same manufacturing process as rituximab sc DS (b) (4) (b) (4)

		(b) (4)
Cross reference to other GNE applications	IND 126650	IND for rituximab sc
LOA	NDA 21-859 Hylenex	Hylenex® recombinant (hyaluronidase human injection) is a component of rituximab SC DP

3. CONSULTS:

None

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation:
The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761064 for Rituxan HYCELA, manufactured by Genentech pending acceptable compliance checks. The data submitted in this application are adequate to support the conclusion that the manufacture of Rituxan HYCELA is well controlled and leads to a product that is pure and potent. We recommend that Rituxan HYCELA be approved for human use under the conditions specified in the package insert.

b. Summary of Complete Response issues
None

c. Action letter language
- Manufacturing location:
  - Drug substance
    Rituximab – Genentech, Inc. Vacaville, CA 95688
    Hyaluronidase – (b) (4)
  - Drug product – F. Hoffman-LaRoche Ltd. Kaiseraugst, Switzerland
- Fill size and dosage form
  1400 mg rituximab/23,400 Units hyaluronidase per vial
  1600 mg rituximab/26,800 Units hyaluronidase per vial
- Dating period:
  - Drug product – 30 months; 2-8ºC
  - Drug substance (rituximab) – (b) (4)
  - Drug substance (hyaluronidase - (b) (4)
  - Stability option (select one below):
    - Not applicable – data for both drug substances and drug product support the requested expiration dating periods with no further extensions
- Exempt from lot release
  - Yes - specified product per 601.2a

d. Benefit/Risk Considerations
Rituxan HYCELA (rituximab/hyaluronidase) is intended to deliver rituximab subcutaneously after the first dose of Rituxan is delivered intravenously. The benefit to patients is the reduced time at the infusion center. The higher concentration formulation does not result in higher levels of aggregates and the rates of immunogenicity between sc and iv delivery were comparable and low.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

Note: Details of the CMC information can be found in the following technical documents in Panorama under BLA 761064:

Rituximab DS and DP and Immunogenicity: Marjorie Shapiro "761064.CMC"
http://panorama.fda.gov/document/view?ID=5911b649004624294b40398d2270004e

Hyaluronidase DS and DP enzymatic activity assay method and validations: Shen Luo "BLA-761064 rHuPH20-CMC review_final"
http://panorama.fda.gov/document/view?ID=590c7d71004953f14f4c6a118f8c3fe6

Drug substance (rituximab and hyaluronidase) microbiology: Candace Gomez-Broughton "STN761064.ds.rev.mem.FINAL"
http://panorama.fda.gov/document/view?ID=59075747000cb384d429a6bdccb17641

Drug product microbiology: Natalia Pripuzova "761064 DP quality micro - March 2017"
http://panorama.fda.gov/document/view?ID=58c6fb320180dc594804900b3b21d5f1

Facilities: Thuy Thanh Nguyen "BLA 651064Final"
http://panorama.fda.gov/document/view?ID=58ee77950022e7caf2dabf7105a4b1a4

II. Summary of Quality Assessments

The control strategy for rituximab sc is based on the identification of critical quality attributes (CQAs), manufacturing and clinical experience, characterization data, analytical method understanding, process understanding, and stability data and the knowledge from the manufacture and clinical experience with rituximab iv.

The control strategy for hyaluronidase is based on the identification of critical quality attributes (CQAs), manufacturing and clinical experience, characterization data, analytical method understanding, process understanding, and stability data.

The table in Section A provides a summary of CQA identification and risk management. For the purposes of this table, CQAs are limited to attributes intrinsic to the drug substance (active pharmaceutical ingredient).

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Drug Substance API CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Rituximab				
Aggregates (Product Variant)	Impact on biological activity, immunogenicity, PK/PD, and safety Process	(b) (4)		
Antigen Binding (Potency)	MOA - Impact on efficacy	Intrinsic to molecule		(b) (4)
CDC	MOA - Impact on efficacy	Intrinsic to molecule and		

(Potency)			(b) (4)
Afucosylation (Product Variant and Potency)	MOA - Impact on efficacy		
G0 (Product Variant and Potency)	MOA - Impact on efficacy		
Primary Sequence	Impact on efficacy, safety and immunogenicity		
Secondary and Tertiary Structure	Impact on efficacy, PK/PD and immunogenicity		
rHuPH20 recombinant hyaluronidase			
Enzymatic activity (Potency)	MOA – Impact on rituximab distribution, PK	Intrinsic to molecule	(b) (4)

		(b) (4)
Aggregates (Purity)	Impact on MOA and immunogenicity	
Oxidized Species (Purity)	MOA – impact on enzymatic activity when both Met residues are oxidized	
Hydrolyzed Species (Purity)	MOA – impact on enzymatic activity	
Primary Sequence	Impact on rituximab distribution, PK and immunogenicity	

		(b) (4)
Oligosaccharide Profile	MOA – impact on enzymatic activity	

B. Drug Substance Rituximab Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 2: Drug Substance (Rituximab) CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Visual Appearance: color and clarity (General)	Impact on safety and immunogenicity	(b) (4)		(b) (4)
Protein Quantity (General)	Impact on efficacy			
(b) (4)	Impact on safety and immunogenicity	(b) (4)	Data were provided in BLA 103705 and the current BLA	(b) (4)

(Process Impurity)		(b) (4)	(b) (4)	
(b) (4) (Process Impurity)	Impact on safety and immunogenicity		Data were provided in BLA 103705 and the current BLA (b) (4	(b) (4)
(b) (4) (Process Impurity)	Impact on safety and immunogenicity		Data were provided in BLA 103705 and the current BLA (b) (4	
(b) (4) (Process Impurity)	Impact on safety		Data were provided (b) (4	
(b) (4) (Process Impurity)	Impact on safety		Data were provided in BLA 103705 (b) (4) (b) (4)	
(b) (4)	Impact on safety		Data were provided (b) (4	

(Process Impurity)			(b) (4)
Endotoxin (Contaminant)	Impact on safety and purity	May be introduced at any step	
Bioburden (Contaminant)	Impact on safety, purity, and efficacy (degradation or modification of product by contaminating organism)	May be introduced at any step	

a. Description (rituximab)
Rituximab (2B8/Rituxan SC, MAB CHIMERIC (IGG1) ANTI P11836 (CD20_HUMAN) [2B8]) is a chimeric IgG1, kappa anti-CD20 monoclonal antibody produced in CHO cells. The molecular weight is ~145,000 Da. It has the typical structure of an IgG1 antibody with 4 interchain disulfide bonds, 12 intrachain disulfide bonds and glycosylation at Asn301 in the CH2 domain.

b. Mechanism of action
Rituximab binds to CD20 on the surface of B cell malignancies and normal B cells and predominantly kills cells via antibody effector functions such as antibody dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC) and antibody dependent cellular phagocytosis (ADCP). It can also induce apoptosis.

c. Potency Assay
Potency is assessed with a CDC assay where CD20+WIL2-S cells (human B-lymphoblastoid cells) are incubated with dilutions of rituximab and human complement. Live cells are quantitated by adding AlamarBlue with a fluorescent read-out.

d. Reference material(s)
The current reference standard, Batch C2B8809-3, is both a primary and working reference standard, qualified from a lot produced using the v1.2 production process. See ross referenced BLA 103705.

e. Critical starting materials or intermediates
Cell banks (MCB/WCB) are cross referenced in BLA 103705.

f. Manufacturing process summary
The commercial process for rituximab is the same as for rituximab v1.2 (b) (4)
(b) (4)
The rituximab drug substance manufacturing process is well controlled.

g. Container closure
(b) (4)

h. Dating period and storage conditions
(b) (4)

C. Drug Substance Hyaluronidase Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 3: Drug Substance (Hyaluronidase) CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Visual Appearance: color (General)	Impact on safety and immunogenicity	(b) (4)		
Protein Quantity (General)	Impact on efficacy			
(b) (4) (Process Impurity)	Impact on safety and immunogenicity			
(b) (4) (Process Impurity)	Impact on safety and immunogenicity			
(b) (4) (Process Impurity)	Impact on safety			

(b) (4) (Process Impurity)	Impact on safety, immunogenicity, and allergenicity	(b) (4)
(b) (4) (Process Impurity)	Impact on safety	
(b) (4) (Process Impurity)	Impact on safety	
(b) (4) (Process Impurity)	Impact on safety	
(b) (4) (Process Impurity)	Impact on safety	

		(b) (4)
(b) (4) (Process Impurity)	Impact on safety	
Endotoxin (Contaminant)	Impact on safety and purity	
Bioburden (Contaminant)	Impact on safety, purity and efficacy (degradation or modification of the product by contaminating organism)	

a. Description (hyaluronidase, recombinant human)
Recombinant human hyaluronidase (rHuPH20, RPROTFRAG P38567 (HYALP_HUMAN) HYALURONIDASE PH-20 [RHUPH20]) is a glycosylated single chain protein with 447 amino acids. The calculated molecular weight of the full length polypeptide is 51,106 Da. Glycosylation increases the molecular weight to 60,000-65,000 Da. There are 6 N-linked and one O-linked glycosylation sites.

Note that rHuPH20 is approved as HYLENEX as a 505(b)(2) NDA.

b. Mechanism of action
rHuPH20 depolymerizes hyaluronan under physiological conditions and acts as a spreading factor in vivo and facilitates the dispersion and absorption of rituximab by temporarily clearing a path through the connective tissue in the subcutaneous space.

c. Potency Assay
Enzymatic activity is measured with a turbidimetric assay (b) (4)

(b) (4)

d. Reference material(s)
There are two reference standards: The Assay Reference Standard (ARS) is used for quantitative measurements; the Purity and Characterization Reference Standard (PCRS) is used for qualitative measurements.

(b) (4)

(b) (4)

The protocol to qualify new primary and working ARS reference standards is adequate.

e. Critical starting materials or intermediates

(b) (4)

f. Manufacturing process summary

(b) (4)

The DS manufacturing process is well controlled for microbial quality. (b) (4)

(b) (4)

g. Container closure

(b) (4)

h. Dating period and storage conditions

(b) (4)

D. Drug Product [Rituximab/Hyaluronidase] Quality Summary

Table 4 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 4: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Protein Concentration (Rituximab)	Impact on efficacy	Bulk rituximab DP manufacture	Release and stability testing (b) (4)	
Protein Concentration (Hyaluronidase)	Impact on efficacy	Bulk hyaluronidase DP manufacture	Release and stability testing	Content determined based on activity of DS
Appearance (General)	Measure of purity, impact on product safety and immunogenicity	DP manufacture (b) (4)	DP Release and stability testing (b) (4)	
pH (General)	Impact on product stability and conformation	DS manufacture (b) (4)	DP Release and stability testing (b) (4)	Controlled via input materials and BDS
Osmolality	Impact on product stability and	DS manufacture (b) (4)	DP Release and stability testing	Controlled via input materials and BDS

(General)	conformation	(b) (4)	(b) (4)	
Particulate matter (visible and sub-visible) (General)	Impact on product safety and efficacy	DP manufacture (b) (4)	DP Release and stability testing Ph. Eur.2.9.19 Light obscuration	
Endotoxin (Contaminant)	Impact on safety and purity	Contamination could be introduced throughout DP manufacturing	The control strategies described for sterility assurance also limit the introduction of endotoxin. The DP is tested for endotoxin at release. DP endotoxin specification (b) (4) EU/mL.	
Sterility (Contaminant)	Impact on safety; (b) (4)	Contamination could be introduced (b) (4)	(b) (4) Adequate validation data supporting sterility assurance of the finished drug product. Sterility testing of the DP at release	

Container Closure Integrity (Contaminant)	Impact on safety	DP manufacture (b) (4)	Container closure integrity testing is included in the DP stability specification. Container closure integrity testing is performed using a validated test.	

a. Potency and Strength
RITUXAN HYCELA is supplied as rituximab/hyaluronidase Injection at either 1400 mg rituximab and 23,400 U hyaluronidase or 1600 mg rituximab and 26,800 U hyaluronidase

b. Summary of Product Design
Quality Target Product Profile
- The 1400 mg rituximab vial contains a withdrawable volume of 11.7 mL and the 1600 mg rituximab vial contains a withdrawable volume of 13.4 mL.
- The 1400 mg dose is intended for CLL patients and the 1600 mg dose is intended for FL and DLCBL patients.
- Binds to CD20 on B cells and effects depletion via ADCC and CDC, apoptosis and synergism with chemotherapeutic agents
- Sterile, preservative-free liquid for injections, 120 mg/mL
- Once transferred from vial into a syringe, the solution is physically and chemically stable for 48 hours at 2-8°C and 8 hours at 30°C in diffused daylight. It is compatible with (b) (4) syringe (b) (4) and injection needles.
- It meets pharmacopeial requirements for parental dosage forms
- There is an acceptable risk/benefit ratio to patients due to process- or product-related impurities.

c. List of Excipients
L-Histidine and L-Histidine hydrochloride monohydrate – (b) (4)
α, α Trehalose dihydrate – (b) (4)
L-Methionine – (b) (4)
Polysorbate 80 – 0.06% (w/v)

The amount of each excipient per vial is dependent whether it is a 1400 mg or 1600 mg vial.

d. Reference material(s)
The rituximab reference standard is the same as used for drug substance, cross referenced in BLA 103705

The rHuPH20 reference standard used to assess enzymatic activity is the same as used for rHuPH20

e. Manufacturing Process
(b) (4)

(b) (4)

f. Container Closure
USP/Ph. Eur. (b) (4) vials with (b) (4) rubber stoppers (b) (4). The 1400 mg strength uses a (b) (4) and the 1600 mg strength uses a (b) (4).

g. Expiration Date & Storage Conditions
The shelf life for drug product in both strengths is 30 months at 2-8°C.

E. Novel Approaches/Precedents

RITUXAN HYCELA is considered a combination product with two active ingredients, rituximab as the API with activity against B cell malignancies, and rHuPH20, recombinant human hyaluronidase, to increase the dispersion and absorption of rituximab when administered subcutaneously.

F. Any Special Product Quality Labeling Recommendations

None

G. Establishment Information

OVERALL RECOMMENDATION:					
DRUG SUBSTANCE					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
Manufacture of rituximab Drug Substance (b) (4) QC, Release and Stability Testing Storage of DS	Genentech, Inc. 1000 New Horizons Way Vacaville, CA 95688 USA	004074162/ 3002902534	Inspection waived due to a recent inspection of BLA 761053 covering the manufacturing area. Site acceptable	NA	Approve based on inspection and compliance history
(b) (4)	Roche Singapore Technical Operations Pte. Ltd. 10 Science Park Road Floor #4, Room #29 Singapore 117684	937189173/ 3007164129	Inspection waived	NA	Approve based on inspection and compliance history
	Genentech, Inc.	146373191/	Inspection	NA	Approve based on based on

(b) (4)	1 Antibody Way Oceanside, CA 92056-5802 USA	3006129086	waived		inspection and compliance history
	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 USA	080129000 /2917293	Inspection waived	NA	Approve based on inspection and compliance history
	Roche Diagnostics GmbH Nonnenwald 2 82377 Penzberg Germany	323105205/ 3002806560	Inspection waived	NA	Approve based on inspection and compliance history
Storage of rituximab and rHuPH20	F. Hoffmann-La Roche Ltd. Grenzacherstrasse 124 4070 Basel Switzerland	3002807200	Inspection waived	NA	Approve based on inspection and compliance history
(b) (4)			Acceptable	No FDA 483	Approve
					No Further Evaluation

(b) (4)					
			Inspection waived	NA	Approve based on inspection and compliance history
			Inspection waived	NA	Approve based on inspection and compliance history
			Inspection waived	NA	Approve based on inspection and compliance history
			Inspection waived	NA	Acceptable

DRUG PRODUCT					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
Drug Product: Manufacture, Quality Control	F. Hoffmann-La Roche, Ltd Wurmisweg	485244961/ 3003973536	Acceptable	4-item 483	Acceptable - VAI

Testing, Release, Labelling, Secondary Packaging	Kaiseraugst, Switzerland CH-4303				

H. Facilities

Prior Inspection History

Drug Substance

Rituximab

A Pre-license inspection (PLI) of Genentech Inc. Vacaville, CA was completed by CDER/OPF and CDER/OBP (b) (4) (b) (4). The inspection was conducted in accordance with CPGM 7346.832 and ICH Q7. A comprehensive review of the facilities, utilities, equipment, processes and procedures was conducted to evaluate product quality, compliance to commitments in the BLA and compliance to cGMPs. A 2-item Form FDA-483, Inspectional Observations was issued at the conclusion of this inspection. The inspection was classified as VAI. This inspection covered the facility CCP1. An inspection waiver for BLA 761064 was completed and signed by the review team.

rHuPH20

Facility is recommended for approval based on PLI conducted by CDER/OPF and CDER/OBP (b) (4) in support of BLA 761064 for Hyaluronidase DS with the final classification of NAI. No FDA 483 was issued. The inspection was conducted in accordance with CPGM 7346.832M and ICH Q7. A comprehensive review of the facilities, utilities, equipment, processes and procedures was conducted to evaluate product quality, compliance to commitments in the BLA and compliance to cGMPs.

Drug Product

The inspection was conducted by ORA. This was a surveillance inspection (b) (4) (b) (4). ORA investigators also included coverage for the manufacturing operations of Rituximab/Hyaluronidase DP for BLA 761064 with (b) (4) profile. The inspection covered profiles (b) (4). The inspection resulted in a 4-item FDA-483, Inspectional Observations (b) (4) (b) (4) (b) (4) The firm's response to the FDA-483 appeared adequate. The inspection was classified as VAI.

I. Lifecycle Knowledge Management

a. Drug Substance

i. Protocols approved

- Annual GMP stability for rituximab and rHuPh20. No extension of shelf life needed.

- Protocols for qualification of new working cell banks and reference

(b) (4)

reference standards is included.

ii. Outstanding review issues/residual risk - none

iii. Future inspection points to consider

1. Rituximab - (b) (4) (b) (4)
2. rHuPH20 – none

b. **Drug Product**

i. Protocols approved - Annual GMP stability. No extension of shelf life needed.

ii. Outstanding review issues/residual risk – none

iii. Future inspection points to consider – follow up on 483 items.

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
	Product Type			
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity		X	
11.	PEPFAR Drug		X	
12.	PET Drug		X	
13.	Sterile Drug Product	X		
14.	Other_____			
	Regulatory Considerations			
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#_____)			X
16.	Comparability Protocol(s)		X	
17.	End of Phase II/Pre-NDA Agreements tem)		X	
18.	SPOTS (Special Products On-line Tracking System			X
19.	USAN Name Assigned	X		

20.	Other_____				
Quality Considerations					
21.	Drug Substance Overage				
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements		X		
27.	Real Time Release Testing (RTRT)			X	
28.	Parametric Release in lieu of Sterility Testing			X	
29.	Alternative Microbiological Test Methods				
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial Analytical Procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other _____				

Marjorie Shapiro

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