CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761103Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

BLA Number: 761103
Review Number: First round
Review Date: April 15, 2019

Drug Name/Dosage Form	Ruxience (rituximab-xxxx[1]) injection, for intravenous use
Strength/Potency	100 mg/10 mL, 500 mg/50 mL (10 mg/mL concentration)
Route of Administration	Intravenous
Rx/OTC dispensed	Rx
Indications	For the following indications approved for Rituxan: Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's Granulomatosis) and microscopic polyangiitis
Applicant/Sponsor	Pfizer Ireland Pharmaceuticals/U.S. Agent: Pfizer, Inc.

Product Overview

Rituximab-xxxx (PF-05280586) is a chimeric monoclonal IgG1 antibody, and the rituximab-xxxx drug product, Ruxience, has been developed as a proposed biosimilar to U.S.-licensed Rituxan. Rituximab-xxxx binds to CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes, and malignant B cells. Upon binding to CD20, rituximab-xxxx mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC), and antibody dependent cellular phagocytosis (ADCP), which are applicable to mechanisms of action of rituximab in B cell malignancies and in autoimmune diseases.

The rituximab-xxxx molecule is constructed as a chimera of mouse variable regions binding human CD20 on framework and constant regions of human IgG1, and has one N-linked glycosylation site on each heavy chain CH2 domain. The Fc regions of the heavy chains retain Fc effector functions important in the mechanism of action of rituximab.

Rituximab-xxxx is produced in genetically engineered CHO (b) (4) cells. Rituximab-xxxx drug product, Ruxience, is manufactured to the same concentration and presentation, but different formulation excipients, as U.S.-licensed Rituxan. Ruxience is a sterile, preservative-free, clear to slightly opalescent, colorless to pale brownish-yellow solution for intravenous infusion and supplied in single-dose vials containing PF-05280586 at 100 mg/10 mL or 500 mg/50 mL.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Rukman De Silva	OPQ/OBP/DBRR IV
Drug Product	Ksenija Grgac	OPQ/OBP/DBRR IV
Drug Substance Microbiology Drug Product Microbiology	Aimee Cunningham Scott Nichols	OPQ/OPF/DMA IV OPQ/OPF/DMA IV
Facility	Michael Shanks	OPQ/OPF/DIA
Immunogenicity assay	Rukman De Silva	OPQ/OBP/DBRR IV
Analytical Similarity	Rukman De Silva	OPQ/OBP/DBRR IV
Labeling	Scott Dallas	OPQ/OBP
Product quality Team Lead Microbiology QAL Facility Branch Chief	Bazarragchaa Damdinsuren Reyes Candau-Chacon Peter Qiu	OPQ/OBP/DBRR IV OPQ/OPF/DMA IV OPQ/OPF/DIA

[1] Suffixes are proposed, pending FDA review

Immunogenicity assay Team Lead	Haoheng Yan	OPQ/OBP/DBRR IV
CMC RPBM	Kelly Ballard	OPQ/OPRO
Application Team Lead	Bazarragchaa Damdinsuren	OPQ/OBP/DBRR IV

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
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Cross-Disciplinary Team Lead DPARP Team Lead	Angelo de Claro Nikolay Nikolov	OHOP/DHP ODEII/DPARP
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Clinical Pharmacology	Shalini Wickramaratne Senarath Yapa, Salah Hamed	OTS/OCP/DCP II
CMC Statistics Clinical Statistics	Chao Wang Kate Dwyer Ginto Pottackal	OB/DB VI OB/DB V OB/DB II

Names:

- Proprietary Name: Ruxience
- Non-Proprietary/USAN/INN: Rituximab-xxxx/rituximab
- CAS Registry number: 174722-31-7
- Company/Laboratory code: PF-05280586
- OBP systematic name: MAB CHIMERIC (IGG1) ANTI P11836 (CD20_HUMAN) [PF-05280586]
- Other Names: None

Submissions Reviewed:

Submission(s) Reviewed /sequence number	**Document Date**
STN 761103 /0001 (BLA submission)	7/25/2018
/0003 (response to IR #1)	8/22/2018
/0005 (response to IR #1)	9/7/2018
/0006 (response to IR #2)	9/10/2018
/0016 (response to IR #3)	12/10/2018
/0020 (response to IR #4)	1/7/2019
/0022 (response to IR #5)	1/8/2019
/0027 (response to IR #5)	1/30/2019
/0029 (response to IR #6)	2/19/2019
/0032 (response to IR #7)	3/11/2019
/0033 (response to IR #8)	3/13/2019
/0035 (response to IR #9)	3/27/2019
/0037 (response to IR #10)	4/10/2019

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	II	(b) (4)		3	N/A	N/A	Not reviewed. Sufficient information related to control of materials is in the BLA.
	III			3	N/A	N/A	Not reviewed. Sufficient information related to compatibility with the product is in the BLA.
	III			3	N/A	N/A	
	III			3	N/A	N/A	
7105	V	Pfizer Manufacturing Belgium NV	Drug Product Manufacturing Facilities and Equipment	3	N/A	N/A	Not reviewed. Sufficient information related to validation sterilization process is in the BLA.

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 is enough data in the application; therefore, the DMF did not need to be reviewed.)

B. Other documents: IND 110426

3. Consults: None

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

OPQ, CDER, recommends approval of BLA 761103 for Ruxience manufactured by Pfizer, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Ruxience is well-controlled and leads to a product that is pure and potent. The analytical similarity assessment as presented in the BLA supports that:

- The biological product, rituximab-xxxx, is highly similar to U.S.-licensed Rituxan notwithstanding minor differences in clinically inactive components,
- A sufficient scientific bridge was established to support the use of E.U.-approved MabThera as a comparator in clinical trials supporting this application.

As summarized in the following sections of this review, OBP, OPF/DMA and OPF/DIA reviewers have all concluded that this BLA should be approved. Therefore, I recommend that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance: (b) (4)
  - Drug Product: Pfizer Manufacturing Belgium NV, Puurs, Belgium
- Fill size and dosage forms:
  - 100 mg/10 mL (10 mg/mL concentration), single-dose vial, injection
  - 500 mg/50 mL (10 mg/mL concentration), single-dose vial, injection
- Dating period:
  - 100 mg/10 mL Drug Product: 24 months when stored at 2-8 °C
  - 500 mg/50 mL Drug Product: 24 months when stored at 2-8 °C
  - Drug Substance in (b) (4): (b) (4) months when stored at (b) (4) °C
  - For packaged products: Not packaged
- Exempt from lot release:
  - Yes. Ruxience is a specified product exempted according to 21 CFR 601.2a.

C. Benefit/Risk Considerations:

Ruxience (rituximab-xxxx, PF-05280586) is a proposed biosimilar to U.S.-licensed Rituxan and proposed for use in all indications approved for Rituxan: non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's Granulomatosis), microscopic polyangiitis and pemphigus vulgaris. Ruxience is manufactured to the same concentration and presentation, but different formulation excipients as U.S.-licensed Rituxan.

To support a determination that PF-05280586 is highly similar to U.S.-licensed Rituxan, and to establish a 3-way scientific bridge to justify the use of clinical data generated from use of E.U.-approved MabThera, Pfizer performed an analytical similarity assessment using a sufficient number of PF-05280586 drug substance and drug product lots, U.S.-licensed Rituxan, and E.U.-approved MabThera drug product lots. The product quality attributes evaluated covered biological activities, primary and higher order structure, post-translational modifications, glycosylation profile, product size and charge variants, protein concentration, and the stability profile of the product. The attributes are each assigned to scientifically justified risk categories,

and the attribute similarity data package was generated and evaluated using appropriate analytical and statistical methods. The data provided in the BLA support a determination that PF-05280586 is highly similar to U.S.-licensed Rituxan. In addition, the data support the adequacy of the analytical component of scientific 3-way bridge to justify the use of clinical data generated using E.U.-approved MabThera.

The OPQ review of manufacturing has determined that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing as submitted in the BLA submission are sufficient to assure a consistent and safe product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents.

The immunogenicity assay review identified that the anti-drug antibodies (ADA) assays have insufficient drug tolerance to assure sensitive detection of ADA in clinical samples collected during dosing period and that the neutralizing antibody (NAb) assays have insufficient assay sensitivity to assure detection of neutralizing antibodies that may be present in clinical samples. The multidisciplinary BLA review team will consider the totality of the evidence in combination with immunogenicity risk of rituximab to reach a regulatory decision.

The technical assessments for OBP drug substance and drug product quality and immunogenicity assay, DMA microbiological drug substance and drug product, DIA facility, OBP labeling and OBP analytical similarity are located as separate documents in the Panorama informatics platform (see list in the end of this review).

D. Recommendation on Phase 4 (Post-Marketing) Commitments (draft language)**:**

1. (b) (4)

II. Summary of Quality Assessments:

A. Analytical Similarity Assessment

I. Analytical Assessment Overview

To support a demonstration that Ruxience (PF-05280586) is highly similar to the U.S.-licensed Rituxan reference product, and to establish a 3-way scientific bridge, Pfizer performed an analytical similarity assessment using up to 15 independent drug substance and drug product lots of PF-05280586, up to 55 lots of U.S.-licensed Rituxan, and up to 65 lots of E.U.-approved MabThera. Rituximab molecular attributes are each assigned to risk categories based on potential impact to safety, efficacy, PK/PD, and immunogenicity, and attribute similarity was evaluated using appropriate statistical methods (Table 1). CDC, ADCC, apoptosis, and binding to CD20 activities reflect the mechanism of action for rituximab and therefore were evaluated for analytical similarity using statistical equivalence testing. The similarity data package (analytical data provided in the original submission and in response to information requests) was generated using methods that are appropriately validated or qualified for their intended purpose.

The strength of U.S.-licensed Rituxan is labeled in mass per unit volume (mg/mL). U.S.-licensed Rituxan is filled into vials with volumes of 100 mg in 10 mL and 500 mg in 50 mL[2].

[2] U.S. Prescribing Information, U.S.-licensed Rituxan. Accessed from https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103705s5450lbl.pdf.

Ruxience is seeking approval for the same strength as U.S.-licensed Rituxan. Comparative protein concentration (mg/mL), reviewed as part of the analytical similarity assessment, and extractable volume and fill weight data (b) (4) were used to inform the assessment of whether the proposed presentation of Ruxience has the same strength as the presentation of U.S.-licensed Rituxan. Based on the similarity and manufacturing data, the 100 mg/10 mL and 500 mg/50 mL of Ruxience vial presentations have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as the respective presentations of U.S.-licensed Rituxan. These presentations meet the statutory "same strength" requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.

II. Analytical Studies Used to Assess Similarity

Table 1: Quality Attributes Analyzed to Assess Similarity

Characteris-tics	Quality Attribute	Risk category[1]	Assay	Supports a Determination of Highly Similar
Biological activity	CDC activity	1	CDC bioassay using Ramos cells	Yes
	ADCC activity	1	ADCC assay using primary NK cells	Yes
	Apoptosis	1	Apoptosis of Ramos cells	Yes
	Binding to CD20	1	CD20 binding by flow cytometry	Yes
	FcγRIIIa binding	2	Surface plasmon resonance (SPR)	Yes*
	FcγRIIIa binding	3	Reporter gene assay	Yes*
	FcγRIIIb binding	3	SPR	Yes[$]
	FcγRIIa binding	2 (131H) 3 (131R)		Yes Yes[$]
	FcγRIIb binding	3		Yes[$]
	FcγRI binding	3		Yes
	Complement (C1q) binding	2	ELISA	Yes
	FcRn binding	2	SPR	Yes
Drug Product Attribute	Protein concentration	2	UV spectroscopy	Yes
Glycosylation	Total Afucosylation	2	HILIC	Yes
	Man5	2		Yes*
	G0 glycan	2		Yes*
	G1 glycan	2		Yes
	G2 glycan	2		Yes
	N-linked glycan profile	3		Yes*
	Terminal galactosylation	2		Yes*
	Sialic acid	3	ESI-QTOF MS	Yes
Charge Variants	Acidic species	2	CEX-HPLC	Yes
	Main species	2		Yes*
	Basic species	3		Yes*
Size variants	Monomer	2	SE-HPLC	Yes[#]
	HMMS	2		Yes[#]
		3	SEC-MALS, AUC-SV	Yes
	Fragments	3	CGE (reducing)	Yes

	Heavy and Light Chain	3		Yes
	Intact IgG	2	CGE (non-reducing)	Yes[#]
Primary Structure	Amino acid sequence	3	LC/MS, Edman Sequencing	Yes
	Molar mass	3	LC/MS	Yes
	N- and C- terminal sequencing	3	LC/MS	Yes
Secondary structure	Protein structural integrity	3	Far-UV CD	Yes
		3	FTIR spectroscopy	Yes
Tertiary structure	Protein structural integrity	3	Near-UV CD spectroscopy	Yes
		3	Intrinsic Fluorescence Emission spectroscopy	Yes
	Thermal stability	3	DSC	Yes
	Disulfide bonds	3	LC/MS Peptide mapping/VIS spectroscopy	Yes
Post Translational Modifications	Deamidation	3	LC/MS/MS-peptide mapping	Yes
	Oxidation	3		Yes
	Glycation	3	SEC/ESI MS	Yes
Stability Profile	Multiple attributes degradation profiles under different conditions	3	Multiple methods	Yes

[1] - Equivalence testing for the high risk category (1) attributes: Equivalence margin was determined as 1.5σR of US-Rituxan data and results were determined as 90% CI of mean difference between two products.

- Quality range (QR) testing for moderate risk category (2) attributes: The QR limits were set based on the range of the values obtained for US-Rituxan variation, expressed as 3 times SD. High similarity was considered to have been demonstrated if 90% of data points were within the QR.
- Visual similarity for low risk category or qualitative nature attributes (3).

* Analytical differences are noted, see discussion in section IV.

[$] Similar low binding affinities by SPR.

[#] Attributes where PF-05280586 lots have slightly higher purity compared to U.S.-licensed Rituxan and E.U.-approved MabThera lots, thus differences do not suggest increased risk (immunogenicity, safety and potency).

III. Scientific Justification and Bridge to U.S.-licensed Reference Product

To establish a 3-way scientific bridge to justify the relevance of clinical data obtained with E.U.-approved MabThera to a demonstration of biosimilarity of PF-05280586 to the U.S.-licensed Rituxan, Pfizer performed pairwise comparison of analytical data obtained from PF-05280586, U.S.-licensed Rituxan, and E.U.-approved MabThera. The data as presented in the BLA submission support the adequacy of the analytical component of scientific 3-way bridge to justify the use of clinical data generated using E.U.-approved MabThera.

IV. Analytical Differences Identified and Resolution/Residual Uncertainties

Each of the attributes described in Table 1 met the pre-determined similarity criteria for the pairwise comparison between PF-05280586, U.S.-licensed Rituxan, and E.U.-approved MabThera, with the exceptions of the analytical differences for the following quality attributes (denoted with * in Table 1):

- FcγRIIIa 158F allotype binding (tested by SPR, risk ranking 2): Tighter binding affinity to the FcγRIIIa 158F allotype (the allotype known for a weaker binding by rituximab) was observed for PF-05280586, while binding to the higher-affinity FcγRIIIa 158V allotype were similar for all

three products. Overall, the results from primary NK cell ADCC assay (as a main function of the FcγRIIIa binding) and FcγRIIIa 158V binding SPR assay support that PF-05280586, Rituxan and MabThera are similar in their ability to bind FcγRIIIa. The NK cell assay directly probes cell killing and therefore more closely reflects the mechanism of action. Potentially slightly tighter binding of PF-05280586 to the low affinity FcγRIIIa allotype compared to U.S.-licensed Rituxan does not suggest a significant risk of impacting safety or efficacy.

- FcγRIIIa binding (by reporter gene assay, risk ranking 3): Differences in dose response curve maxima between the PF-05280586, Rituxan and MabThera lots, as well as intra-product lot-to-lot variability, were observed. The applicant reasoned that this assay is sensitive to G0 (afucosylated) glycan content (see below). The results of primary NK cell ADCC assay and FcγRIIIa 158V binding SPR assay support that PF-05280586, Rituxan and MabThera are similar in their ability to bind FcγRIIIa and induce ADCC effector function.
- G0 glycan (by HILIC, risk ranking 2): The applicant's data showed that differences in the level of G0 glycans that are below 7.6% do not have significant impact on ADCC, which is the attribute most likely to be impacted by G0 differences). The applicant also provided data demonstrating that the observed difference (approximately 1.5%) in G0 between the products does not have an impact on ADCC activity.
- Man5 (by HILIC, risk ranking 2): The actual values and the difference are small (0.4% vs 1.2% average content in PF-05280586 and in Rituxan lots, respectively), and such levels will not affect the antibody product clearance and PK (Goetze AM, et al. Glycobiology, 2011;21:949-59). This assessment is also supported by the comparative PK study results reviewed by the clinical pharmacology team.
- N-linked glycan profile (by HILIC, risk ranking 3): The visual similarity did not meet due to differences in G0 and Man5.
- Terminal galactosylation (by HILIC, risk ranking 2): Eighty seven percent of PF-05280586 batches fall within the U.S.-licensed Rituxan quality range (just outside of 90% acceptance criterion). The worst-case PF-05280586 batch with 37% terminal galactosylation showed similar CDC activity (the biological activity impacted by terminal galactosylation) to the U.S.-licensed Rituxan lots and other PF-05280586 lots.
- Basic species and consequently main-peak species (by CEX-HPLC, risk ranking 3 and 2, respectively): The applicant showed that this difference is due to C-terminal lysine and amidated proline content. Numerous publications have shown that the C-terminal lysine is cleaved from antibody products in vivo within a short period after intravenous administration; additionally these modifications have no effect on antibody structure, antigen binding and Fc-mediated functions.

The differences described above would not impact the activity of the product and do not preclude a determination that PF-05280586 is highly similar to U.S.-licensed Rituxan.
The totality of analytical data as presented in the BLA support that PF-05280586 is highly similar to U.S.-licensed Rituxan.

B. CQA Identification, Risk and Lifecycle Knowledge Management

Table 2: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA type	CQA	Risk	Origin and process linkage	Control Strategy
Identity	Identity	Bioactivity, Safety	Intrinsic to the molecule	(b) (4)
Potency	Potency - CDC	Bioactivity, Safety	Intrinsic to the molecule	
	Potency - ADCC	Bioactivity, Safety	Intrinsic to the molecule	
N-linked glycans	Afucosylated species (G0+G1a+G1b+G2+ Man5)	ADCC, PK	Cell culture process (b) (4)	
	Other common glycans G0, G0F, G1F (a+b), G2F	ADCC, CDC, PK	Cell culture process (b) (4)	
Size-Related Variants	Intact IgG/Heavy Chain and Light Chain/Monomer	Bioactivity, PK	Manufacturing process	
	HMMS	Bioactivity, PK, Immunogenicity, Safety	Manufacturing process	
	Fragmentation	Bioactivity, PK	Manufacturing process	
Post Translational Modifications	* Methionine Oxidation	PK	Manufacturing process. (b) (4)	
	** Asparagine deamidation (in CDR)	Bioactivity (has potential to affect binding to CD20)	Manufacturing process. (b) (4)	
Charge Heterogeneity	* Acidic, main and basic species	Bioactivity, Immunogenicity, Safety	Cell culture at (b) (4)	

DS - drug substance, DP - drug product
* Applicant considers these attributes as non-CQA, however these are tested as part of (b) (4) DS and DP release or shown in the existing levels do not affect purity, potency and safety.
** Applicant did not name this as a QA, however these are shown in the existing levels do not affect purity, potency and safety.

C. Drug Substance, rituximab-xxxx, Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 3: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management. (Additional to API CQAs shown in Table 2)

CQA type	CQA	Risk	Origin and process	Control Strategy

			linkage	
DS Composition	Appearance (coloration, clarity)	Bioactivity, Safety	Product and formulation	(b) (4)
	pH	Bioactivity	Formulation (b) (4)	
	* Protein Concentration	Bioactivity	Manufacturing process (b) (4)	
	(b) (4)	Bioactivity, stability	(b) (4) Manufacturing process (b) (4)	
Process-related impurities	Residual Host Cell Proteins (HCP)	Safety, Immunogenicity	Cell culture (b) (4)	
	Residual Host Cell DNA	Safety (gene transfer)	Cell culture, (b) (4)	
	* (b) (4)	Immunogenicity, Safety	(b) (4)	
	** Raw Materials (process impurities), Leachables	Immunogenicity, Safety	Raw materials, manufacturing process	
Bioburden	Bioburden	Safety, Purity, and Efficacy (degradation or modification of the product by contamina-ting microorganisms)	Raw materials and manufacturing process	
Endotoxin	Endotoxin	Safety, Purity	Raw materials and manufacturing process	
Viral Adventitious Agents	Viral Safety	Safety	Raw materials and manufacturing process	
	Mycoplasma	Safety	Raw materials and manufacturing process	

DS - drug substance, DP - drug product, IPC – in-process control
* Applicant considers these attributes as non-CQA, however these are tested as part of (b) (4) DS and DP release or shown in the existing levels do not affect purity, potency and safety.
** Applicant did not name this as QA, however these are shown in the existing levels do not affect purity, potency and safety.

- **Description:** Rituximab-xxxx (PF-05280586) is a monoclonal antibody constructed as a chimera of mouse variable regions binding human CD20 on framework and constant regions of human IgG1. The Fc regions of the heavy chains retain Fc effector functions important in mechanism of action of the molecule, and each have one N-linked glycosylation site in the CH2 region. Rituximab-xxxx contains 32 cysteine residues and they are predicted to form 16 disulfide bonds. Each heavy chain consists of 451 amino acids with 11 cysteine residues and each light chain consists of 213 amino acids with 5 cysteine residues. The theoretical molecular mass varies from 147076.2 – 147400.5 Da due to predominant N-linked glycoforms,

and the specific absorption coefficient at 280 nm is 1.67 mL/mg/cm. Rituximab-xxxx is produced in engineered CHO (b) (4) cells.

- **Mechanisms of Action (MoA):** Rituximab-xxxx targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes and malignant B cells. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include CDC, ADCC and ADCP, which are applicable to MoAs of rituximab in B cell malignancy indications; in addition, it can induce apoptosis in human B cell lymphoma cells.
  In RA and associated chronic synovitis settings, B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor and other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine production. Thus, it is believed that rituximab works in the autoimmune diseases by disrupting of these activities by depleting B cells.
  Potency Assays: 1. CDC assay is a cell-based cytotoxicity assay used as an in vitro measure of PF-05280586 CDC activity. This assay is used in DS and DP release and stability testing.
  2. FcγRIIIa Reporter Gene Assay is a cell line-based reporter gene assay to measure an attribute which modulates ADCC. This assay is used in DP release and stability testing.

- **Reference Materials (RM):** A two-tiered approach is applied (b) (4)

- **Critical starting materials or intermediates:** (b) (4)

- **Manufacturing process summary:** (b) (4)

(b) (4)

- **Container closure:** PF-05280586 drug substance is stored in (b) (4) manufactured by (b) (4)
- **Dating period and storage conditions:** A shelf-life of (b) (4) months when stored at (b) (4) °C (long term) is acceptable based on available stability data from the process validation and clinical lots.

D. Drug Product, Ruxience, Quality Summary:

Table 4 provides a summary of the identification, risk, and lifecycle knowledge management for drug product-specific CQAs that derive from the drug product manufacturing process and general drug product attributes. Active pharmaceutical ingredient and drug substance CQAs apply to drug product (see Tables 2 and 3).

Table 4: Drug Product-specific CQA Identification, Risk, and Lifecycle Management (Additional to API CQAs shown in Table 2)

CQA type	CQA	Risk	Origin	Control Strategy
DP Composition and Strength	Appearance (coloration, clarity)	Bioactivity, Safety	Product, formulation	(b) (4)
	Protein Concentration	Bioactivity	Manufacturing process (DS and DP formulation)	
	* Osmolality	Bioactivity	Formulation	
	pH	Bioactivity	Formulation	
	* Polysorbate 80	Bioactivity, stability	Raw material control, Manufacturing process (formulation)	
Particles	Visible Particles	Safety	DP manufacturing process, CCS	
	Subvisible Particles	Safety, Immunogenicity	DP manufacturing process, CCS and product	
Content	* Extractable Volume	Efficacy	DP manufacturing process (fill)	
Sterility	Sterility	Safety (infection),	Contamination may be	

(contaminant)		purity, and efficacy via degradation or modification of the product by microbial contamination	introduced throughout the DP manufacturing process or failure of container closure integrity
Endotoxin	Endotoxin	Safety (pyrogenic fever, increased immunogenicity risk) and purity	Raw materials, manufacturing process, or failure of container closure integrity
Container closure integrity	Container closure integrity	Safety (maintenance of sterility during shelf life)	Container closure breaches during storage

(b) (4)

DS - drug substance, DP - drug product, IPC – in-process control
* Applicant considers these attributes as non-CQA, however these are tested as part of (b) (4) DS and DP release.

- **Potency and Strength:** 500 mg/50 mL, 100 mg/10 mL (10 mg/mL concentration)
- **Summary of Product Design:** A sterile, clear to slightly opalescent, colorless to pale brownish-yellow solution for intravenous administration and contains no preservatives. Presented in single-dose vials.
- **List of Excipients:** Histidine, sucrose, edetate disodium dihydrate (EDTA), polysorbate 80.
- **Reference Materials:** Same as the PF-05280586 drug substance RMs.
- **Manufacturing process summary:** (b) (4)
- **Container closure:** 50 mL or 15 mL (b) (4) glass vial (b) (4) with a (b) (4) stoppers (b) (4) and crimp seals with flip-off caps (b) (4) (b) (4)

- **Dating period and storage conditions:** A shelf-life of 24 months when stored at 5 ± 3 °C is acceptable for 100 mg/10 mL and 500 mg/50 mL Ruxience based on available stability data from the process validation and clinical lots.

E. Novel Approaches/Precedents: None

F. **Any Special Product Quality Labeling Recommendations:** The following conditions regarding storage are recommended to be deleted from the USPI Section 2.8:
- The in-use microbial hold study provided does not support holding the solution for infusion for (b) (4)
- The compatibility study is incomplete to support use of (b) (4) with the diluted Ruxience solutions.

G. Establishment Information:

Overall Recommendation:				
DRUG SUBSTANCE				
Function	**Site Information**	**DUNS/FEI Number**	**Preliminary Assessment**	**Final Recommendation**
DS manufacturing, IPC testing, release and stability testing, DS storage, MCB and WCB storage	(b) (4)		Approve – VAI according to PLI*	Approve based on PLI
DS and DP release and stability testing, MCB and WCB storage	Pfizer Ireland Pharmaceuticals Grange Castle Business Park Dublin, Clondalkin, Ireland	3004145594	n/a	Approve based on facility profile
DS and DP release testing and stability testing (potency testing only)	(b) (4)		n/a	Approve based on facility profile
DS and DP release testing and stability testing (potency testing only)			n/a	Approve based on facility profile
Production of the MCB and WCB	Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC One Burtt Road, Andover, MA	1222181	n/a Similarity data inspection*	No Further Evaluation
DRUG PRODUCT (inclusive of the DP testing sites shown for Drug Substance)				
Function	**Site Information**	**DUNS/FEI Number**	**Preliminary Assessment**	**Final Recommendation**
DP manufacturing, release and stability testing, DS storage	Pfizer Manufacturing Belgium NV Rijksweg 12, Puurs, Belgium	1000654629	Approve - based on previous history and waiver granted by OBP/OPF.	Approve based on facility profile

DS - drug substance, DP - drug product, MCB - Master Cell Bank, WCB - Working Cell Bank, PLI - Pre-License Inspection
* See section H. Facilities.

H. Facilities:

During the review cycle, a Pre-License Inspection (PLI) of (b) (4) was conducted from (b) (4) by OPQ/OFP/DIA and OPQ/OBP. This inspection covered the drug substance manufacturing and the

testing laboratories. A FDA 483 with four observations was issued at the completion of the inspection. The observations cited in the FDA Form 483 were: (b) (4) The inspection was classified as voluntary action indicated (VAI). In the firm's written response, the firm has committed to taking appropriate corrective actions to address the deficiencies, and FDA found the response to be adequate. OPF/DIA recommends an approval of the (b) (4) drug substance facility regarding BLA 761103.
Analytical similarity data of this BLA was inspected as part of inspection of Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC (Andover, MA) which was conducted from January 14 to 18, 2019 by ORA and OPQ/OBP. There was a two-item FDA Form 483 issued at the conclusion of the inspection and the inspection was classified as VAI. In the firm's written response, the firm has committed to taking appropriate corrective actions to address the deficiencies, and the responses are adequate.

I. Lifecycle Knowledge Management:

I. Drug Substance:

i. Protocols approved (section):

1. Monitoring of Cell Bank Stability (3.2.S.2.3)
2. Preparation, Qualification and Storage of Renewal Working Cell Banks (3.2.S.2.3)
3. (b) (4) Lifetime and Storage Validation (3.2.S.2.5)
4. (b) (4) Lifetime and Storage Validation (3.2.S.2.5)
5. (b) (4) Lifetime and Storage Validation (3.2.S.2.5)
6. (b) (4) Lifetime and Storage (3.2.S.2.5)
7. (b) (4) Performance (3.2.S.2.5)
8. Stability Program for Primary and Working Reference Material (3.2.S.5)
9. Post-approval Stability Protocol and Stability Commitment (b) (4) (3.2.S.7.2, at recommended storage conditions of (b) (4) °C and accelerated condition of (b) (4) °C)

ii. Outstanding review issues/residual risk: None.

iii. Future inspection points to consider: None.

II. Drug Product

i. Protocols approved (section):

1. Post-approval Stability Protocol and Stability Commitment (100 mg/10 mL) (3.2.P.8.2)
2. Post-approval Stability Protocol and Stability Commitment (500 mg/50 mL) (3.2.P.8.2)

ii. Outstanding review issues/residual risk: None.

iii. Future inspection points to consider: None.

Review documents related to this Executive Summary (in Panorama)**:**

- Drug substance quality review by Rukman De Silva, PhD (OPQ/OBP/DBRR IV)
- Drug product quality review by Ksenija Grgac, PhD (OPQ/OBP/DBRR IV)
- Drug substance microbiology review by Aimee Cunningham, PhD (OPQ/OPF/DMA IV)
- Drug product microbiology review by Scott Nichols, PhD (OPQ/OPF/DMA IV)
- Analytical similarity review by Rukman De Silva, PhD (OPQ/OBP/DBRR IV)
- Facility review by Michael Shanks (OPQ/OPF/DIA)
- Immunogenicity assay review by Rukman De Silva, PhD (OPQ/OBP/DBRR IV)
- Labeling review by Scott Dallas, PhD (OPQ/OBP)

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 source			X	
9.	Transgenic Plant source			X	
10.	New Molecular Entity			X	
11.	PEPFAR drug			X	
12.	PET drug			X	
13.	Sterile Drug Product		X		
14.	Other: Proposed biosimilar		X		
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			X	
16.	Comparability Protocol(s)			X	
17.	End of Phase II/Pre-BLA Agreements			X	
18.	SPOTS (special products on-line tracking system)			X	
19.	USAN assigned name		X		
20.	Other			X	
	Quality Considerations				
21.	Drug Substance Overage			X	
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			X	
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			X	

Bazarragchaa Damdinsuren

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Reyes Candau-Chacon

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Zhihao Peter Qiu

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Christopher Downey

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Drug Product Quality Assessment

BLA STN 761103

Ruxience, a proposed biosimilar to US-licensed Rituxan

Manufacturer: Pfizer, Inc.

Quality Reviewer: Ksenija Grgac, Ph.D.
ATL: Bazarragchaa Damdinsuren, M.D., Ph.D.
Review Chief: Christopher Downey, Ph.D.

Division of Biotechnology Review and Research IV

OBP CMC Review Data Sheet

1. BLA#: STN 761103

2. Review Date: April 30, 2019

3. Primary Review Team:
    a. Product Quality Team:
        Rukman De Silva (DS, Immunogenicity assay, Analytical similarity)
        Ksenija Grgac (DP)
        Haoheng Yan (secondary for immunogenicity assay review)
        Aimee Cunningham (DS micro, OPF/DMA IV),
        Scott Nichols (DP micro, OPF/DMA IV)
        Reyes Candau-Chacon (QAL micro, OPF/DMA IV)
        Michael Shanks (facility, OPF/DIA)
        Peter Qiu (facility, OPF/DIA)
        Scott Dallas (OBP Labeling)
        Kelly Ballard (RBPM, OPRO)
        Bazarragchaa Damdinsuren (ATL, OBP)
    b. Medical Officers: Yvette Kasamon (DHP), Suzette Peng (DPARP)
    c. Pharm/Tox: Shalini Wickramaratne Senarath Yapa, Salah Hamed
    d. Clinical Pharmacology
    e. Statistics: Chao Wang
    f. RPM: Jennifer Lee (OND)

4. Major GRMP Deadlines:
    a. Filing Meeting: 9/14/2019
    b. Mid-cycle meeting: 12/17/2018
    c. Wrap-up meeting: 4/10/2019
    d. Primary review due: 4/05/2019
    e. Secondary review due: 6/21/2019
    f. BSUFA action date: 7/25/2019

5. Communications with Applicant:

Communication/Document:	Date:
IR #1	8/17/2018
IR #2	9/6/2018
IR #3	11/27/2018
IR #4	12/17/2018
IR #5	12/21/2018
IR #6	2/5/2019
IR #7	3/4/2019
IR #8	3/8/2019
IR #9	3/20/2019
IR #10	4/3/2019

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
STN 761103 /0001 (BLA submission)	7/25/2018	Yes
/0003 (response to IR #1)	8/22/2018	Yes
/0005 (response to IR #1)	9/7/2018	Yes
/0006 (response to IR #2)	9/10/2018	Yes
/0016 (response to IR #3)	12/10/2018	Yes
/0020 (response to IR #4)	1/7/2019	Yes
/0022 (response to IR #5)	1/8/2019	Yes
/0027 (response to IR #5)	1/30/2019	Yes
/0029 (response to IR #6)	2/19/2019	Yes
/0032 (response to IR #7)	3/11/2019	Yes
/0033 (response to IR #8)	3/13/2019	Yes
/0035 (response to IR #9)	3/27/2019	Yes
/0037 (response to IR #10)	4/10/2019	Yes
/0040 (response to LCM comment)	4/22/2019	Yes

7. Drug Product Name/Code/Type:
   a. Proprietary Name: Ruxience
   b. Trade Name: Ruxience
   c. Non-Proprietary Name/USAN/INN: Rituximab-xxxx/rituximab
   d. CAS Name: 174722-31-7
   e. Company/Laboratory code: PF-05280586/PF-7
   f. OBP systematic name: MAB CHIMERIC (IGG1) ANTI P11836 (CD20_HUMAN) [PF-05280586]
   g. Other names: none

8. Pharmacological Category: Recombinant chimeric monoclonal IgG1 antibody directed against human CD20

9. Dosage Form: Concentrate for solution for infusion (liquid in single-use vial)

10. Strength/Potency:
   (i): The concentration/strength of the Drug Product: 100 mg/10 mL, 500 mg/50 mL (10 mg/mL concentration)
   (ii): Type of potency assay(s): 1. Complement Dependent Cytotoxicity (CDC) assay is a cell-based cytotoxicity assay used as an in vitro measure of PF-05280586 CDC activity. 2. FcγRIIIa Reporter Gene Assay is a cell line-based reporter gene assay to measure an attribute which modulates antibody dependent cell-mediated cytotoxicity (ADCC).

11. Route of Administration: Intravenous infusion

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
		(b) (4)	Yes	Not reviewed.

	Scientific			Sufficient information related to control of materials is in the BLA.
[redacted] (b) (4)			Yes	Not reviewed. Sufficient information related to compatibility with the product is in the BLA.
			Yes	
			Yes	
7105	Pfizer Manufacturing Belgium NV	Drug Product Manufacturing Facilities and Equipment	Yes	Validation sterilization process, defer to DMA reviewer.

13. Inspectional Activities:
During the review cycle, a Pre-License Inspection (PLI) of DS manufacturing site, [redacted] (b) (4), was conducted from [redacted] (b) (4) by OPQ/OFP/DIA and OPQ/OBP. This inspection covered the drug substance manufacturing and the testing laboratories. A FDA 483 with four observations was issued at the completion of the inspection. The observations cited in the FDA Form 483 were: [redacted] (b) (4). The inspection was classified as VAI. In the firm's written response, the firm has committed to taking appropriate corrective actions to address the deficiencies and was considered adequate. OPF/DIA recommends an approval of the [redacted] (b) (4) drug substance facility regarding BLA 761103.

Analytical similarity data of this BLA was inspected as part of inspection of Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC (Andover, MA) which was conducted from January 14 to 18, 2019 by ORA and OPQ/OBP. There was a two-item FDA Form 483 issued at the conclusion of the inspection and the inspection was classified as VAI. In the firm's written response, the firm has committed to taking appropriate corrective actions to address the deficiencies and was considered adequate.
A PLI for DP manufacturing site, Pfizer Manufacturing Belgium NV (Puurs, Belgium) is waived based on previous history.

14. Consults Requested by OBP: none

15. Quality by Design Elements:
The following was submitted in the identification of QbD elements (check any that apply):

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

16. Precedents: none

17. Administrative:

A. Signature Block

Name and Title	Signature and Date
Christopher Downey, Ph.D. Review Chief Division of Biotechnology Review and Research IV (DBRR IV) Office of Biotechnology Products (OBP) Office of Pharmaceutical Quality (OPQ)	See attached
Bazarragchaa Damdinsuren, M.D., Ph.D. Team Leader DBRR IV, OBP, OPQ	See attached
Ksenija Grgac, Ph.D. Product Quality Reviewer DBRR IV, OBP, OPQ	See attached

B. CC Block

Recipient
Jennifer Lee, Clinical Division BLA RPM
OBP/DBRR IV File/BLA STN 761103

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

I recommend approval of BLA 761103 for Ruxience (rituximab-xxxx) manufactured by Pfizer Inc. The data submitted in this BLA adequately support the conclusion that the manufacture of Ruxience (rituximab-xxxx) is well controlled and leads to a product that is pure and potent.
I recommend approval of the proposed lot release and stability specifications and stability protocols for rituximab-xxxx drug substance and drug product. I recommend an expiry period of (b) (4) months for rituximab-xxxx drug substance when stored at (b) (4) °C. I recommend expiry periods of 24 months for Ruxience 500 mg/50 mL drug product and 100 mg/10 mL drug product when stored at 5 ± 3 °C.
Pfizer has employed an array of orthogonal, sensitive methods to characterize structural and functional similarities between the proposed biosimilar Ruxience and its reference product, US-licensed Rituxan. The data in the analytical similarity assessment adequately support the demonstration that Ruxience (rituximab-xxxx) is highly similar to US-licensed Rituxan.
It is recommended that Ruxience (rituximab-xxxx) be approved for human use and under conditions specified in the package insert.

II. List Of Deficiencies To Be Communicated

There are no CMC-related deficiencies precluding approval of this BLA.

III. List Of Post-Marketing Commitments/Requirement (draft)

(b) (4)

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

Pfizer claims a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria per 21 CFR Part 25.31(c). Pfizer Inc claims that to their knowledge, no extraordinary circumstances exist. The request for categorical exclusion is acceptable.

V. Primary Container Labeling Review

The CMC labeling review was performed by Dr. Scott Dallas, CDER/OPQ/OBP. The review memo is uploaded to Panorama separately.

VI. Review Of Common Technical Document – Quality Module 3.2

3.2.S. Drug Substance, 3.2.A Adventitious Agents Safety Evaluation and 3.2.R Regional information (method validation reports): reviewed by Dr. Rukman De Silva, a separate review is uploaded in Panorama.
3.2.P. Drug Product: is included in this document.
3.2.R Regional Information (analytical similarity): reviewed by Dr. Rukman De Silva, a separate review is uploaded in Panorama.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

Refer to review by Dr. Rukman De Silva, a separate review is uploaded in Panorama.

Contents:

P: Drug Product

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

The PF-05280586 drug product (DP) for infusion is presented in liquid forms of 100 mg/10 mL and 500 mg/50 mL, at concentrations of 10 mg/mL in formulation buffer containing 20 mM histidine, 85 mg/mL sucrose, 0.15 mM edetate disodium dihydrate (EDTA), and 0.2 mg/mL PS80 at pH 5.8 (Table 3.2.P.1-1). The 100 mg/10 mL presentation is provided in 15 mL vial with an overfill of (b) (4) mL, and the 500 mg/50 mL presentation in 50 mL vial with an overfill of (b) (4) mL. Both presentations are supplied in the clear, glass vials sealed with a stopper and aluminum seal with flip-off plastic cap with no overage.

Table 3.2.P.1-1. Composition of PF-05280586 Drug Product, 100 mg/10 mL and 500 mg/50 mL

Ingredient	Reference to Standard	Function	Unit Formula (mg/mL)
PF-05280586	In-house specification	Active ingredient	10
L-histidine	Ph.Eur., USP, JP	(b) (4)	1.20
L-histidine hydrochloride monohydrate	Ph.Eur., JP		2.57
Edetate disodium dihydrate	Ph.Eur., USP, JP		0.056
Polysorbate 80	Ph.Eur., NF, JP		0.2
Sucrose	Ph.Eur., NF, JP		85
Water for Injection	Ph.Eur., USP, JP		q.s. to 1 mL

The PF-05280586 DP is to be diluted with 0.9% sodium chloride solution or 5% dextrose solution for one-time intravenous administration.

Reviewer comment: *The description of the DP is adequate. The overfills meet USP <1151> recommendations.*

3.2.P.2 Pharmaceutical Development - Introduction

The DP development aimed to produce the product that is both pharmaceutically acceptable and highly similar to licensed rituximab. The Quality Target Product Profile (QTPP) was developed based on the target quality characteristics to be achieved at the end of the manufacturing process. Quality attributes (QA) relevant to the DP were risk assessed for criticality of the DP quality and for relevance to similarity. The QA's are the following: identity, potency/biological activity, protein concentration, extractable volume, appearance (visible particulates, clarity and coloration), pH, subvisible particles, osmolality, PS80, charge heterogeneity, purity and product-related impurities, safety (endotoxin, sterility and container closure integrity). The QTPP for PF-05280586 with associated CQAs is listed in Table 3.2.P.2-3.

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Bazarragchaa Damdinsuren

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Christopher Downey

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Drug Substance Quality Assessment

BLA STN 761103

Ruxience, a proposed biosimilar to US-licensed Rituxan

Manufacturer: Pfizer, Inc.

Quality Reviewer: Rukman De Silva, Ph.D.
ATL: Bazarragchaa Damdinsuren, M.D., Ph.D.
Review Chief: Christopher Downey, Ph.D.

Division of Biotechnology Review and Research IV

OBP CMC Review Data Sheet

1. BLA#: STN 761103

2. Review Date: April 24, 2019

3. Primary Review Team:
    a. Product Quality Team:
        Rukman De Silva (DS, Immunogenicity assay, Analytical similarity)
        Haoheng Yan (secondary for immunogenicity assay review)
        Ksenija Grgac (DP)
        Aimee Cunningham (DS micro, OPF/DMA IV),
        Scott Nichols (DP micro, OPF/DMA IV)
        Reyes Candau-Chacon (QAL micro, OPF/DMA IV)
        Michael Shanks (facility, OPF/DIA)
        Peter Qiu (facility, OPF/DIA)
        Scott Dallas (OBP Labeling)
        Kelly Ballard (RBPM, OPRO)
        Bazarragchaa Damdinsuren (ATL, OBP)
    b. Medical Officers: Yvette Kasamon (DHP), Suzette Peng (DPARP)
    c. Pharm/Tox: Shalini Wickramaratne Senarath Yapa, Salah Hamed
    d. Clinical Pharmacology
    e. Statistics: Chao Wang
    f. RPM: Jennifer Lee (OND)

4. Major GRMP Deadlines:
    a. Filing Meeting: 9/14/2019
    b. Mid-cycle meeting: 12/17/2018
    c. Wrap-up meeting: 4/10/2019
    d. Primary review due: 4/05/2019
    e. Secondary review due: 6/21/2019
    f. BSUFA action date: 7/25/2019

5. Communications with Applicant:

Communication/Document:	Date:
IR #1	8/17/2018
IR #2	9/6/2018
IR #3	11/27/2018
IR #4	12/17/2018
IR #5	12/21/2018
IR #6	2/5/2019
IR #7	3/4/2019
IR #8	3/8/2019
IR #9	3/20/2019
IR #10	4/3/2019

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
STN 761103 /0001 (BLA submission)	7/25/2018	Yes
/0003 (response to IR #1)	8/22/2018	Yes
/0005 (response to IR #1)	9/7/2018	Yes
/0006 (response to IR #2)	9/10/2018	Yes
/0016 (response to IR #3)	12/10/2018	Yes
/0020 (response to IR #4)	1/7/2019	Yes
/0022 (response to IR #5)	1/8/2019	Yes
/0027 (response to IR #5)	1/30/2019	Yes
/0029 (response to IR #6)	2/19/2019	Yes
/0032 (response to IR #7)	3/11/2019	Yes
/0033 (response to IR #8)	3/13/2019	Yes
/0035 (response to IR #9)	3/27/2019	Yes
/0037 (response to IR #10)	4/10/2019	Yes
/0040 (response to LCM comment)	4/22/2019	Yes

7. Drug Product Name/Code/Type:
   a. Proprietary Name: Ruxience
   b. Trade Name: Ruxience
   c. Non-Proprietary Name/USAN/INN: Rituximab-xxxx/rituximab
   d. CAS Name: 174722-31-7
   e. Company/Laboratory code: PF-05280586/PF-7
   f. OBP systematic name: MAB CHIMERIC (IGG1) ANTI P11836 (CD20_HUMAN) [PF-05280586]
   g. Other names: none

8. Pharmacological Category: Recombinant chimeric monoclonal IgG1 antibody directed against human CD20

9. Dosage Form: Concentrate for solution for infusion (liquid in single-use vial)

10. Strength/Potency:
   (i): The concentration/strength of the Drug Product: 100 mg/10 mL, 500 mg/50 mL (10 mg/mL concentration)
   (ii): Type of potency assay(s): 1. Complement Dependent Cytotoxicity (CDC) assay is a cell-based cytotoxicity assay used as an in vitro measure of PF-05280586 CDC activity. 2. FcγRIIIa Reporter Gene Assay is a cell line-based reporter gene assay to measure an attribute which modulates antibody dependent cell-mediated cytotoxicity (ADCC).

11. Route of Administration: Intravenous infusion

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
[redacted] (b) (4)			Yes	Not reviewed. Sufficient information related to control of materials is in the BLA.
			Yes	Not reviewed. Sufficient information related to compatibility with the product is in the BLA.
			Yes	
			Yes	
7105	Pfizer Manufacturing Belgium NV	Drug Product Manufacturing Facilities and Equipment	Yes	Validation sterilization process, defer to DMA reviewer.

13. Inspectional Activities:
During the review cycle, a Pre-License Inspection (PLI) of DS manufacturing site, [redacted] (b) (4), was conducted from [redacted] (b) (4) by OPQ/OFP/DIA and OPQ/OBP. This inspection covered the drug substance manufacturing and the testing laboratories. A FDA 483 with four observations was issued at the completion of the inspection. The observations cited in the FDA Form 483 were: [redacted] (b) (4) The inspection was classified as VAI. In the firm's written response, the firm has committed to taking appropriate corrective actions to address the deficiencies and was considered adequate. OPF/DIA recommends an approval of the [redacted] (b) (4) drug substance facility regarding BLA 761103.
Analytical similarity data of this BLA was inspected as part of inspection of Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC (Andover, MA) which was conducted from January 14 to 18, 2019 by ORA and OPQ/OBP. There was a two-item FDA Form 483 issued at the conclusion of the inspection and the inspection was classified as VAI. In the firm's written response, the firm has committed to taking appropriate corrective actions to address the deficiencies and was considered adequate.
A PLI for DP manufacturing site, Pfizer Manufacturing Belgium NV (Puurs, Belgium) is waived based on previous history.

14. Consults Requested by OBP: none

15. Quality by Design Elements:
The following was submitted in the identification of QbD elements (check any that apply):

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

16. Precedents: none

17. Administrative:

A. Signature Block

Name and Title	Signature and Date
Christopher Downey, Ph.D. Review Chief Division of Biotechnology Review and Research IV (DBRR IV) Office of Biotechnology Products (OBP) Office of Pharmaceutical Quality (OPQ)	See attached
Bazarragchaa Damdinsuren, M.D., Ph.D. Team Leader DBRR IV, OBP, OPQ	See attached
Rukman De Silva, Ph.D. Product Quality Reviewer DBRR IV, OBP, OPQ	See attached

B. CC Block

Recipient
Jennifer Lee, Clinical Division BLA RPM
OBP/DBRR IV File/BLA STN 761103

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

I recommend approval of BLA 761103 for Ruxience (rituximab-xxxx) manufactured by Pfizer Inc. The data submitted in this BLA adequately support the conclusion that the manufacture of Ruxience (rituximab-xxxx) is well controlled and leads to a product that is pure and potent.
I recommend approval of the proposed lot release and stability specifications and stability protocols for rituximab-xxxx drug substance and drug product. I recommend an expiry period of (b) (4) months for rituximab-xxxx drug substance when stored at (b) (4) °C. I recommend expiry periods of 24 months for Ruxience 500 mg/50 mL drug product and 100 mg/10 mL drug product when stored at 5 ± 3 °C.
Pfizer has employed an array of orthogonal, sensitive methods to characterize structural and functional similarities between the proposed biosimilar Ruxience and its reference product, US-licensed Rituxan. The data in the analytical similarity assessment adequately support the demonstration that Ruxience (rituximab-xxxx) is highly similar to US-licensed Rituxan.
It is recommended that Ruxience (rituximab-xxxx) be approved for human use and under conditions specified in the package insert.

II. List Of Deficiencies To Be Communicated

There are no CMC-related deficiencies precluding approval of this BLA.

III. List Of Post-Marketing Commitments/Requirement (draft)

(b) (4)

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

Pfizer claims a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria per 21 CFR Part 25.31(c). Pfizer Inc claims that to their knowledge, no extraordinary circumstances exist. The request for categorical exclusion is acceptable.

V. Primary Container Labeling Review

The CMC labeling review was performed by Dr. Scott Dallas, CDER/OPQ/OBP. The review memo is uploaded to Panorama separately.

VI. Review Of Common Technical Document – Quality Module 3.2

3.2.S. Drug Substance, 3.2.A Adventitious Agents Safety Evaluation and 3.2.R Regional information (method validation reports): are included in this document.
3.2.P. Drug Product: reviewed by Dr. Ksenija Grgac, a separate review is uploaded in Panorama
3.2.R Regional Information (analytical similarity): reviewed by Dr. Rukman De Silva, a separate review is uploaded in Panorama.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

Refer to review by Dr. Rukman De Silva, a separate review is uploaded in Panorama.

Table of Contents

Unless otherwise noted, figures and tables in the review are adapted or copied directly from the submission. Some of the figures and tables in the submission were updated during the review cycle, the review contains only the updated final versions. The reviewer's comments are distinguished by use of italic font.

DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

PF-05280586 is a chimeric immunoglobulin G1 (IgG1) kappa monoclonal antibody (mAb) directed against the CD20 antigen. CD20 is a non-glycosylated transmembrane phosphoprotein, found on the surface of normal precursor B-cells, mature B-lymphocytes and malignant B-cells. PF-05280586 has been developed as a biosimilar to US-licensed Rituxan® (rituximab).

S. DRUG SUBSTANCE

3.2.S.1 General information

Nomenclature of PF-05280586 DS is presented in Table 3.2.S.1.1-1.

Table 3.2.S.1.1-1: Nomenclature of PF-05280586 drug substance

Name/code	Description
International Nonproprietary Name (INN) for licensed product	rituximab
INN name for Pfizer Biosimilar	To be determined
Chemical Name (IUPAC)	Not applicable
Internal Company or Laboratory Code (Pfizer)	PF-05280586 or rituximab-Pfizer or PF7
Rituximab CAS Registry Number	174722-31-7

3.2.S.1.2 Structure

3.2.S.1.3 General Properties

The complementary-determining regions (CDRs) of PF-05280586 derived from mouse anti-human B-lymphocyte antigen CD20 and the framework and constant regions derived from human IgG1. PF-05280586 consists of two identical heavy (H) chains and two identical light (L) chains, covalently linked with four inter-chain disulfide bonds. The N terminus of H and L chain contains mainly pyroglutamic acid due to the presence of N-terminal glutamine residue. The N-linked glycosylation consensus sequence in the CH2 region is occupied with mainly asialo-, core-fucosylated, complex-type biantennary N-linked glycans with zero or one terminal galactose residues (G0F and G1F). Both C-terminal lysine and amidated proline were observed at minor levels in PF-05280586 structure.

PF-05280586 contains 32 cysteine residues and they are predicted to form 16 disulfide bonds, including both intra-chain and inter-chain. The theoretical pI of PF-05280586 is 8.9 and the specific absorption coefficient at 280 nm is 1.67 $(mg/mL)^{-1}$ cm^{-1}. The theoretical molecular mass of PF-05280586 varies from 147076.2 – 147400.5 Da due to predominant N-linked glycoforms. The primary sequence of the L and H chains are shown below.

Figure 3.2.S.1.2-1. PF-05280586 amino acid sequence

The predicted intra- and inter-chain disulfide bonds are highlighted with connecting lines. The putative CDRs are underlined, the N-linked glycosylation consensus sequence is in bold italics and the C-terminal lysine is shown in parenthesis.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

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Rukman De Silva

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Bazarragchaa Damdinsuren

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Date: 4/24/2019 02:12:28PM
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Christopher Downey

Digitally signed by Christopher Downey
Date: 4/24/2019 02:56:44PM
GUID: 508da6d9000264ed71c49d80cfe4e31a

Memorandum of Review

STN:	BLA 761103
Subject:	Analytical Similarity Review
Review Date:	4/11/2019
Primary Reviewer:	Rukman De Silva, PhD
Secondary Reviewer:	Bazarragchaa Damdinsuren, MD, PhD
Tertiary Reviewer:	Christopher Downey, PhD
Applicant:	Pfizer Inc.
Product:	Ruxience (rituximab-xxxx; PF-05280586), proposed biosimilar to US-licensed Rituxan
Indications:	The following indications approved for US-licensed Rituxan: rheumatoid arthritis, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)
Action Due Date:	7/25/2019

Review sections in this memorandum are organized to facilitate the assessment of analytical similarity with the section titles remaining the same as those in the BLA submission for ease of reference.

3.2.R.3. Analytical Similarity

General Information and Overview

PF-05280586 is developed as a biosimilar to US-licensed Rituxan (the applicant referred as rituximab-US) and the EU-approved MabThera (the applicant referred as rituximab-EU). *Herein, US-licensed Rituxan is referred to as "Rituxan" and EU-approved MabThera as "MabThera*." The criteria (qualitative and quantitative) for assessing similarity for PF-05280586 were developed based on the licensed rituximab product information. PF-05280586 analytical similarity development strategy includes assessment of the licensed rituximab product lots, including those used as comparator lots for nonclinical and clinical studies, to maximize the understanding of the comparator product profile. Rituxan and MabThera lots were acquired on the open market.

As part of clinical development, the applicant conducted three clinical studies; 1) Study B3281001: a controlled, multicenter, multinational, randomized, double-blind, a three- way single dose PK/PD study in subjects with active rheumatoid arthritis (RA) comparing PF-05280586 to Rituxan and MabThera; 2) Study B3281004: a subsequent extension study of B3281001 and 3) Study B3281006: a comparative, randomized, double-blind study in patients with CD20-positive, low tumor burden-follicular lymphoma using PF-05280586 and MabThera to evaluate the safety and efficacy and immunogenicity of PF-05280586 in comparison to MabThera.

Reviewer's comment: *The clinical program used only the 500 mg presentations of PF-05280586 and MabThera or Rituxan. The analytical similarity assessment includes both the 100 mg and 500 mg presentations.*

3.2.R.3.8 Analytical Method Qualification

Information regarding methods used in the analytical similarity assessment can be found in 3.2.S.4.2 (Analytical Procedures) and 3.2.R.3.1.3 (Description of Characterization Methods). The QC release methods were all validated (see Section S.4.3), and other characterization methods were shown to be suitable for their intended use. Additional technical reports for the assays used for the comparative characterization of PF-05280586 for biological activity (for attributes assessed by statistical equivalence and by quality range analysis and FcγRIIIa RGA) were provided in 3.2.R.3.8 Technical Reports. The method qualification data for the non-release test biological activity assays is summarized in the following reviewer-generated table.

Reviewer's Table R.3.1: Analytical Method Qualification Summary

Method	Quality Attribute	Qualification Data
Apoptosis in Ramos cell Assay	Apoptosis	Qualified for accuracy (94-104%), precision, range and linearity (R^2=0.9867). Precision and accuracy range 50-150% EC50 ratio
Cell based binding in Ramos cells by FACS	CD20 binding	Qualified for precision (7.4% RDS at 100 target), linearity (R^2=0.9993), accuracy and range. Precision and accuracy range 50-150% EC50 ratio
C1q Binding	C1q Binding	Qualified for precision (3.6% RDS at 100% target), linearity (R^2=0.9993), accuracy (100% at 100% target) and range (50-120% RP).
Primary NK Cell ADCC Assay	ADCC	Qualified for precision (7.2%, n=8), linearity (R^2=0.9989), accuracy and range. Precision and accuracy range 50-130% EC50 ratio
FcγRIIIa RGA	ADCC	Qualified for specificity (typical dose-response observed for PF-05280586), precision (target 100% RSD 2.9%), linearity (R^2=0.997), and accuracy (target 100%: 101%).
FcγR binding by SPR	FcγRI, FcγRIIa (131H, 131R), FcγRIIb, FcγRIIIb, FcγRIIIa (158F, 158V)	Qualified for specificity, accuracy and precision
FcRn binding by SPR	FcRn binding	Qualified for specificity, accuracy (100% at 100% target) and precision (8.5% RDS for n=9).

Reviewer's comment: *The biological activity methods used in analytical similarity testing are qualified for their intended purpose. During the analytical similarity inspection, we reviewed the FcγRIIIa RGA assay, FcγR SPR binding assay and primary NK ADCC assay protocols and qualification results, and these were deemed acceptable. However, the method qualification information of physiochemical assays (FTIR, CD, Far-UV spectroscopy, near-UV spectroscopy, SEC-MALS, AUC-SV, and DSC) are not provided. These are well established biophysical methods that are used for non-product specific characterization. SEC-MALS, and AUC-SV are orthogonal methods to SE-HPLC for monomer and HMMS analysis. The applicant provided representative spectra/thermograms of PF-05280586 in comparison with MabThera and Rituxan by these methods. The results show high degree of similarity between PF-05280586 and Rituxan and MabThera samples. In addition, the assessment of method capabilities demonstrates the method is sensitive for the detection of as low as 2% unfolded proteins. Therefore, FTIR, CD, Far-UV spectroscopy, near-UV spectroscopy, SEC-MALS, AUC-SV, and DSC assays are suitable for intended use.*

3.2.R.3.1.1 Risk Ranking and Statistical Analysis of Quality Attributes

Quality attributes (QAs) related to similarity were ranked into 3 tiers for analysis according to their potential impact on activity, PK/PD, safety and immunogenicity, and guided by scientific literature on the reference product. Attributes that have the highest level of risk (assays for clinically relevant mechanism(s) of action of rituximab) are assigned to analysis Tier 1. Attributes having moderate risk are assigned to analysis Tier 2 and the lowest risk to analysis Tier 3.

The statistical analysis of the QAs applies varying statistical rigor depending on the assigned tier level.

- Equivalence testing was applied to results of QAs with Tier 1 ranking. The equivalence test is a hypothesis test where the null hypothesis (H0) is that the two groups are not equivalent and the alternative hypothesis (H1) is that the two groups are equivalent. The decision rule is to reject the null hypothesis of non-equivalence and claim analytical similarity for the QA if the (1 - 2 α)100% two-sided confidence interval of the mean difference between the biosimilar and reference product is within ($-1.5\sigma_R$, $1.5\sigma_R$), where α is the preset significance level of the test. Unless otherwise specified, α is set at 0.05. *Note: The assessment of statistical analysis for Tier 1 QAs was performed by CMC Statistics reviewer Dr. Chao Wang.*
- A quality range approach was used to evaluate attributes assigned to Tier 2. The statistical quality range is defined as ($\mu_R - X\sigma_R$, $\mu_R + X\sigma_R$), where μ_R and σ_R are the estimated mean and standard deviation, respectively, of the US-licensed Rituxan (or EU-approved MabThera) and X is the standard deviation multiplier (X=3, the justifications for each multiplier can be found within the relevant 3.2.R.3 sections). The applicant noted that the resulting quality range will be further evaluated, and adjusted if necessary, as to its scientific relevance. The QA is deemed as meeting the quality range similarity criteria if 90% or greater of test lot values fall within the quality range. A further assessment is performed for any quality attribute having < 90% of test lots within the quality range.
- Attributes assigned to Tier 3 were evaluated in tabular or graphical format for visual comparisons. Details of statistical methods used in the equivalence test and quality range analysis were provided in Section 3.2.R.5.

The assessment tiers applied to PF-05280586 QAs are summarized in the following reviewer-generated table.

Reviewer's Table R.3.2: Statistical Tier rankings for PF-05280586 quality attributes

Quality Attribute	Analytical Method(s)	Statistical Assessment Tier	Rationale
Potency	Apoptosis Assay, CDC Bioassay, Binding to CD20 target antigen by flow cytometry, Primary NK Cell ADCC Assay	1	Known mechanisms of action of rituximab: - Binding to CD20 assay assesses binding of rituximab to target antigen CD20 on B cell surface, - Apoptosis assay assesses the target cell apoptosis via caspase activation pathway, - CDC assay measures cell lysis via complement cascade activation by rituximab bound to target cells,

			- ADCC assay is assesses target cell lysis by human NK cells activated by target cell bound rituximab.
Potency	FcγRIIIa binding (SPR), FcγRIIa 131H binding (SPR), C1q binding (ELISA), FcRn Binding (SPR),	2	FcγRIIIa receptor is relevant for ADCC, FcγRIIa receptor is relevant to ADCP, C1q binding corelates to CDC activity, FcRn binding is relevant to clearance of mAbs in vivo
Potency	FcγRIIIa reporter gene assay, FcγRI, FcγRIIa 131R, FcγRIIb, FcγRIIIb binding (SPR)	3	FcγRIIIa receptor is relevant for ADCC, Binding to FcγRI, FcγRIIa 131R, FcγRIIb, and FcγRIIIb is involved in Fc-mediated functions
Protein Concentration	UV Spectroscopy	2	Protein concentration is relevant to clinical dose
Total Afucosylation	Hydrophilic Interaction Liquid Chromatography (HILIC)	2	Afucosylated N-linked glycan content is relevant to ADCC activity
Man5*	HILIC	2	The levels of high mannose forms may impact PK
G0 glycan*	HILIC	2	G0 glycans can impact ADCC and CDC activity
G1 glycan*	HILIC	2	G1 glycans can impact ADCC and CDC activity
G2 glycan*	HILIC	2	G2 glycans can impact ADCC and CDC activity
Terminal Galactosylation	HILIC	2	Terminal galactosylation of N-linked glycan can impact CDC activity
Acidic species	CEX-HPLC	2	Deamidation may lead to generation of acidic species could affect the biological activity
Main species*	CEX-HPLC	2	Main species can impact structure, stability and function
Monomer	SE-HPLC	2	Monomer is the primary active species
HMMS	SE-HPLC	2	The levels of HMMS may impact immunogenicity
Intact IgG	CGE (Non-reducing)	2	intact IgG could indicate fragmentation due to disulfide bond breakage or scrambling and would be, potentially, relevant to immunogenicity and activity
Primary Structure	Mass Spectrometry (LC/MS, LC/MSMS), Edman Sequencing	3	To confirm the identical primary sequence
N-linked Glycan Profile	HILIC	3	The N-linked glycan species can impact immunogenicity
Basic species	CEX-HPLC	3	C-terminal lysine and/or C-terminal amidated proline elute as basic species
Fragments	CGE (Reducing)	3	IgG fragments may theoretically expose a new epitope, causing increased immunogenicity
HMMS*	SEC-MALS, AUC-SV	3	To characterize the HMMS using orthogonal methods
Heavy and Light Chain (HC +LC)	CGE (Reducing)	3	heavy chain and light chain would be, potentially, relevant to immunogenicity
Secondary structure	Far-UV CD and FTIR spectroscopy	3	Secondary structure contributes to antibody folding, function and properties including stability.
Tertiary structure	Near-UV CD spectroscopy - Intrinsic Fluorescence	3	Tertiary structure contributes to antibody function and properties including stability

	Emission spectroscopy		
Thermal stability	DSC	3	Thermal stability is an overall integrity of HOS
Deamidation*	LC/MS/MS-peptide mapping	3	Can alter structure, stability or function and may lead to degradation
Oxidation*	LC/MS/MS-peptide mapping	3	Can alter structure, stability or function
Glycation*	SEC/ESI MS	3	Can alter structure and function
Sialic Acid content*	HILIC	3	Can impact CDC and ADCC activity

* - QAs assessed per the Agency's request

Reviewer's comment: *Note that the risk ranking and assessment of the amounts of individual post-translational modifications, charge variant (main species), HMMS (characterization using orthogonal methods) and sialic acid content were not included in the initial submission and were added per our request during review cycle (these attributes denoted as * in the Table). Overall, the risk ranking and assessment tiers of the QAs are in agreement respectively with the Agency's recommendation provided to the applicant and the OBP's internally recommended QA risk ranking for proposed rituximab biosimilar products. More details are discussed in relevant sections below.*

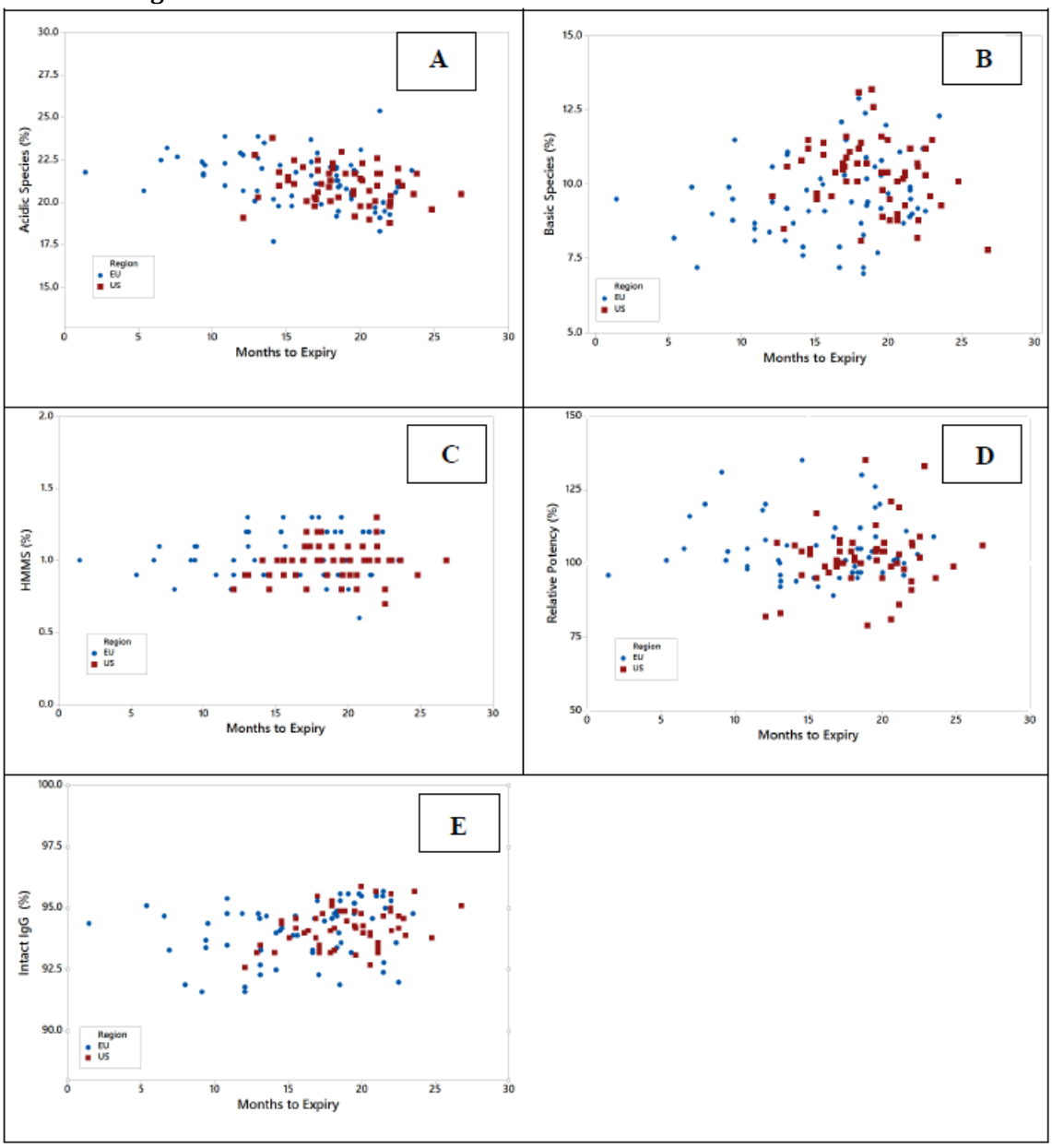
3.2.R.3.1.2 Lots Enrolled in Similarity Assessment

- US-Rituxan and EU-MabThera Lots

Rituxan and MabThera DP lots were purchased from the open market without a predetermined criterion. A total of 55 Rituxan DP lots and 65 MabThera DP lots (from both 100 and 500 mg presentations) were used for the analytical similarity exercise. These Rituxan and MabThera lots' remaining times to expiry ranged from approximately 12-27 and 1-23 months, respectively (see plots in Figure 3.2.R.3.1.2-1). Each DP lot contains a unique lot number, but it does not mean that each DP lot is derived from a unique DS batch. The applicant stated that the licensed DP lots were enrolled (received, recorded and prepared for analysis) in the similarity assessment within the manufacturer's assigned expiry date, were stored under the manufactured recommended storage conditions of 2-8 °C or aliquoted within manufacturer's labeled expiry, frozen, and stored at -60°C to -90°C (*see Sample Handling section below for supporting data for sample frozen storage*). Each frozen aliquot was intended for single use only.

The applicant evaluated frozen Rituxan and MabThera DP lots to assess whether lot age impacts QAs (plotted in Figure 3.2.R.3.1.2-1)). The applicant used these QAs because they were shown to be stability-indicating.

Figure 3.2.R.3.1.2-1: Assessment of quality attributes against Rituxan and MabThera Lot age at time of testing



Reviewer's comment: *The tested attributes did not show appreciable trends over the shelf life, although no trend analysis was performed (based on the provided graphs, the acidic and basic variants might have minor trending). Therefore, the results for a given attribute were used for the analytical similarity assessment, regardless of the Rituxan or MabThera lot age at the time of testing within the use period.*

The numbers of Rituxan and MabThera DP lots enrolled in similarity assessment are adequate. The data show that the majority of these DP lots were within 12-24 months to expiry (i.e., age ranges) at their enrollment into the assessment/testing, which is a reasonable distribution range. As shown in Figure 3.2.R.3.1.2-1 above, Rituximab and MabThera DP lots are relatively stable

and show no significant degradation trends over the shelf life under normal storage conditions. Thus, the applicant's approach of using data for each of Rituxan and MabThera regardless of lot age in the similarity assessment is acceptable.

The following comment was sent to the applicant in IR (dated 12/21/2018) "17. Provide a basis (i.e., selection criteria) for the selection of the number of lots used and the specific lots evaluated for those assays where only a subset of the total lots manufactured or purchased were assessed in analytical similarity studies. For example, 13 out of 55 US Rituxan lots and 14 out of 65 EU-MabThera lots were used in the ADCC activity similarity assessment, but no justification was provided for why these lots were selected for testing".
In the response (1/08/2019), the applicant stated that originator product lots were purchased from the open market at regular intervals without pre-selected purchasing criteria under the reasonable assumption that every originator product lot is fully representative of the product. Pre-selected originator lots were used in an analytical similarity testing of ADCC activity in primary NK cell ADCC assay. This is to ensure the entire range of originator product afucosylation/G0 is represented in the ADCC study.
Because the impact of total afucosylation and G0 glycan on ADCC is well established, the proposed originator product lot pre-selection criteria are acceptable. See the review section below regarding the discussion related to total afucosylation and G0 glycan on ADCC activity.

PF-05280586 Lots

Ten PF-05280586 DS lots and 12 DP lots produced at the commercial scale and 5 development scale DS lots (including clinical reference material 124281pg3, derived from development DS lot 10P123K602) were included in the similarity assessment. The lot genealogy of all PF-05280586 DS and DP lots included in similarity assessment is summarized by the reviewer in the following table.

Reviewer's Table R.3.3: Lot genealogy of all PF-05280586 DS/DP lots used in similarity assessment

DS Lot #	Manufacturing Scale (L)	DP Presentation (mg)	DP Lot #	DS/DP Lot Use
10P123K602	(b) (4)	N/A	N/A	Development, clinical reference material
10P123K603		N/A	N/A	Development
11P123L001		N/A	N/A	Development
11P123L002		N/A	N/A	Development
11P123L003		N/A	N/A	Development
87200		N/A	N/A	Development
87201		N/A	N/A[a]	Nonclinical
87000		N/A	N/A	Development
87001		N/A	N/A	Development
87002		100	Z01758	Clinical inventory, Primary stability
		500	**Y07950**[b]	
87003		100	Z02284	Clinical inventory, Primary stability
		500	**Y09480**[b]	
		500	A10440[b]	Clinical inventory
87004		100	L47502	Clinical inventory, Primary stability, Process validation
		500	**B04148**[b]	Clinical inventory, Primary stability, Process validation
87005		100	**B05692**	Clinical inventory, supportive stability, Process validation
87006		100	R91910	Supportive stability, Process validation
		500	B04147	Clinical inventory, Primary stability, Process validation
		100	**B04146**	
87007		N/A	N/A	Clinical inventory, supportive stability, Process validation
87004, 87005		500	L57104	Clinical inventory, supportive stability, Process validation

Bold: DS batches and DP lots were selected as independent lots for statistical analyses
[b] Lot used in comparative clinical study

Reviewer's comment: *As identified in the Reviewer's Table R.3.3, 15 independent PF-05280586 DS and DP lots were used for the similarity assessment. However, not all PF-05280586 lots were included for each QA assessment, the details of independent lots selected for equivalence (Tier 1) and quality range (Tier 2) analyses are provided in Table 3.2.R.3.1.2-2 in the submission. The DP lots include both 100 mg and 500 mg presentations. Overall, the number of PF-05280586 lots enrolled in similarity assessment is acceptable.*

The following clarification comment to confirm use of reference materials was sent to the applicant in IR dated 12/21/2018 "10. Section 3.2.R.3.1.2.1 notes that the reference material manufactured from DS batch 10P123K602 was used for the analytical similarity assessments. Please confirm that a single reference material lot was used in all analytical similarity studies." In the response (1/08/2019), the applicant confirmed that a single reference material, clinical reference material lot 124281pg3, was used throughout the PF-05280586 development, including analytical testing to support all similarity studies. The primary reference material has

been tested in some of the assays in the similarity assessment as a test sample, but not as reference material. The response is acceptable.

3.2.R.3.6 Appendix - Sample handling

As mentioned, the purchased Rituxan and MabThera DP vials were aliquoted prior the expiry and stored at -60°C to -90°C until further use in the similarity assessment. To support the suitability of such storage procedure, the applicant provided data from freeze thaw (F/T) and long-term storage studies.

- Freeze/Thaw Study:

Three originator product lots (Rituxan lots 3158170 and 3185087, MabThera lot N7095B17) were subjected to 3 cycles F/T, stored at 2-8°C and frozen at -80°C, and selected attributes were compared after each cycle (*I have summarized the results in the following table*).

Reviewer's Table R.3.4: Summary of freeze/thaw study

Quality Attribute	Analytical Procedure	Results
Protein concentration	UV Spectroscopy	Tested for information only to adjust the concentration for further test. Results were not provided.
Charge heterogeneity	CEX	No significant trends were observed for acidic, main, and basic species.
Purity - Monomer, HMMS and LMMS	SE-HPLC	Slight increase in HMMS observed at 3X F/T. No change to monomer and LMMS levels.
Purity - Intact IgG, fragment, and other	CGE (non-reducing)	No trends of intact IgG, fragment content, and other species were observed.
Purity - HC+LC, fragment, other	CGE (reducing)	No trends of HC+LC, fragment content, and other species observed.
N-linked glycan profile	HILIC	No changes for afucosylated glycans (G0+G1+G2), and for high Man species (Man5).
Methionine oxidation	Limited Lys-C Peptide mapping	No significant changes in levels of methionine oxidation was observed.
Potency / Biological Activity	Cell-based CDC assay	Results for non-frozen and after 3X F/T samples were provided, no obvious change was observed.
Primary structure and post-translational modifications	LC/MS-subunit analysis	Minor mass differences without new species were observed for isoforms of 3X F/T sample compared to non-frozen sample.
Higher order structure	Near-UV CD Spectroscopy	No significant difference in the spectra.

Reviewer's comment: *Note that only CDC activity was assessed in this study. The results support that no product quality changes are likely to occur due to freeze thaw, especially with a single freeze thaw (the aliquots are intended for single thaw only).*

- Long-term storage:

The applicant tested one lot each of Rituxan and MabThera under long-term (up to 68 months) storage at -60 to -90 °C for using multiple vials of Rituxan lot (Lot# 991945, lot expiry date: July 31, 2014) and MabThera lot (Lot# H0104B01, lot expiry date: December 31, 2012). The results over a 68-months period for MabThera lot and 45-months for Rituxan lot are provided in the submission.

Reviewer's comment: *The provided results show no significant change for the tested QAs for the durations of the storage, however, no data on potency was provided in the original BLA. The following IR was sent to the applicant on 3/04/2019"19. The long-term storage study for US-licensed Rituxan and EU-approved MabThera to support sample aliquoting and storage did not include testing for potency (refer to section 3.2.R.3.6.2. Impact of Long-Term Storage: Reference Product Stored at −60°C to −90 °C). Provide scientific justification and supporting data to demonstrate that long-term storage at −60 °C to −90 °C does not affect the potency of US-licensed Rituxan and EU approved MabThera samples".*
In the response (3/11/2019), the applicant did not provide potency results of Rituxan and MabThera samples, however concluded that structural stability is maintained over long-term storage, therefore, impact on potency would not be expected based on the following assessments. All test methods used in similarity assessment showed no change in the QAs for Rituxan (up to 45 months) or MabThera (up to 70 months) when stored at -60 C to -90 °C. In addition, no change in potency was observed after three cycles of F/T and stored at 2-8°C and frozen at -80°C. Furthermore, forced degradation studies demonstrated that when there is an impact on potency, changes are also observed in several stability indicating methods, such as CEX, SE-HPLC, and CGE (Reducing and Non-Reducing). Finally, no change was observed in either the quality attributes or potency in PF-05280586 reference material 124281pg3 stored at −70 °C for 94 months (data provided in the response).
Overall, these results support that long-term storage at -60 to -90 °C (for up to 68 months for MabThera and for up to 45 months for Rituxan) do not affect the rituximab product QAs (as compared to non-frozen samples).
In conclusion, the applicant's approach to aliquot and freeze store the originator product lots for further analysis is acceptable.

3.2.R.3.1 Results and Discussion of Similarity Assessment

Note: The applicant provided raw values of the similarity assessment in section 3.2.R.3.5 Appendix – Raw Data of the submission.

Tier 1 Quality Attributes [from 3.2.R.3.2.2 Biological Activity]
The applicant used a statistical equivalence test for Tier 1 QAs to support the demonstration of similarity. These assays include those assessing clinically relevant mechanism(s) of action of the product for each indication for which approval is sought (described in 3.2.R.3.2.2 - Mechanisms of Action), and include the apoptosis assay, CDC bioassay, binding to CD20, and ADCC assay. For all these assays, relative EC50 ratios of each test sample were calculated by the comparison of the PF-05280586 reference material EC50 to the test sample EC50. *The assessment of statistical analysis for Tier 1 QAs is performed by CMC Statistics reviewer Dr. Chao Wang (refer to the CMC Statistics review for details).*

- Apoptosis Assay:

Cell based apoptosis assay probes target cell apoptosis via the caspase-dependent pathway triggered by rituximab binding to cell surface CD20. The assay is performed by adding serially diluted samples of PF-05280586, Rituxan or MabThera to Ramos cells to induce apoptosis detected by luminescence. The applicant noted that the expected EC50 of the method is 50-150%, with accuracy between 94-104% and %RSD of 3.9-15.9%.

Apoptosis assay similarity assessment included 18 PF-05280586 (DS and DP) lots (including 10 independent lot) to 23 Rituxan and 15 MabThera DP lots. 10 independent PF-05280586 (DS and DP) lots were used for the statistical analysis. (summaries of relative EC50 are shown in Tables 3.2.R.3.2.2-4 and -5, graphical presentation and statistical analysis are in Figures 3.2.R.3.2.2-5 and -6).

Table 3.2.R.3.2.2-4. Summary of Descriptive Statistics for Apoptosis Activity of Rituximab-EU, PF-05280586, and Rituximab-US

Relative EC50 (%)						
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	15	102	6.7	6.6	84	112
Pfizer	18	101	7.8	7.7	86	118
US	23	99	8.6	8.7	82	119

Table 3.2.R.3.2.2-5. Summary of Descriptive Statistics for Apoptosis Activity of PF-05280586 Independent Lots

Relative EC50 (%)					
N	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
10	100	7.9	7.9	86	113

Figure 3.2.R.3.2.2-5. Apoptosis Activity of PF-05280586, Rituxan and MabThera Lots

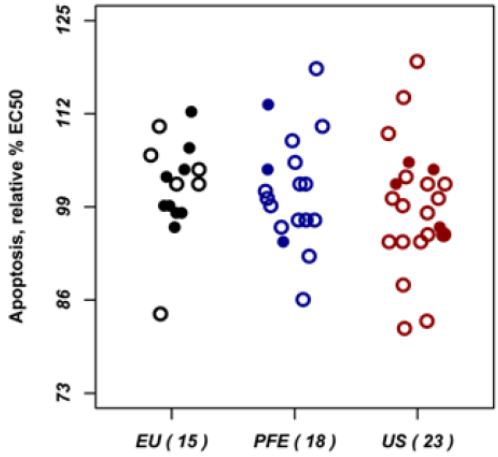


Figure 3.2.R.3.2.2-6. Statistical Analysis of Apoptosis Activity for PF-05280586, Rituxan and MabThera Lots

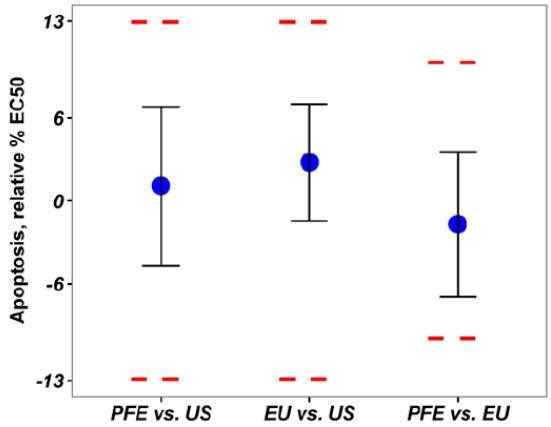


Fig. 3.2.R.3.2.2-5: The solid circles represent the PF-05280586, Rituxan and MabThera lots that were used in the clinical trials.
Fig. 3.2.R.3.2.2-6: The mean difference and 90% confidence interval of the mean difference in relative potency (%) for MabThera vs. Rituxan, PF-05280586 vs. MabThera and PF-05280586 vs. Rituxan. The solid circles represent

the mean difference. The confidence interval is represented by the error bars. The dashed lines represent the acceptance limits of $\pm 1.5\sigma_R$. PFE equals PF-05280586.

Reviewer's comment: *The apoptosis activities of Rituxan, PF-05280586, and MabThera as measured by this cell-based assay are similar with substantial overlap. PF-05280586 data meets Tier 1 similarity criteria for apoptosis activity, supporting a demonstration that PF-05280586 is highly similar to Rituxan and MabThera.*

- CDC Bioassay

CDC is one of the known mechanisms of action (MoA) for rituximab. PF-05280586 (using 27 DS and DP lots, including 15 independent lots), Rituxan (54 lots), and MabThera (61 lots) were evaluated for their ability to induce complement-mediated lysis of Ramos cells using the CDC assay. PF-05280586 is serially diluted and incubated with Ramos cells, and fixed concentration of human serum complement is added and incubated for 2 hours at 37°C. At the end of the incubation, bioluminescent generated by adenylate kinase release is measured.
The applicant provided representative dose response curves of the CDC assay profile. Summaries of relative EC50 are shown in Tables 3.2.R.3.2.2-1 and 3.2.R.3.2.2-2, graphical presentation and statistical analysis are in Figures 3.2.R.3.2.2-2 and 3.2.R.3.2.2-3.

Reviewer's comment: *CDC bioassay is a release method for PF-05280586 and its validation is reviewed in section 3.2.S.4.3. In general, the CDC bioassay range is 50-175% with accuracy of 96-102% across the ranges and an intermediate precision of ≤6%.*

Table 3.2.R.3.2.2-1: Summary of Descriptive Statistics for CDC Activity of Rituximab-EU, PF-05280586, and Rituximab-US

Relative Potency (%)						
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	61	104	10.4	9.9	89	135
Pfizer	27	98	10.6	10.8	78	114
US	54	102	10.5	10.3	79	135

N = sample size, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum

Table 3.2.R.3.2.2-2. Summary of Descriptive Statistics for CDC Activity of PF-05280586 Independent Lots

Relative Potency (%)					
N	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
15	98	11.6	11.9	79	114

N = sample size, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum

Figure 3.2.R.3.2.2-2. CDC Activity of Rituximab-EU, PF-05280586, and Rituximab-US Lots

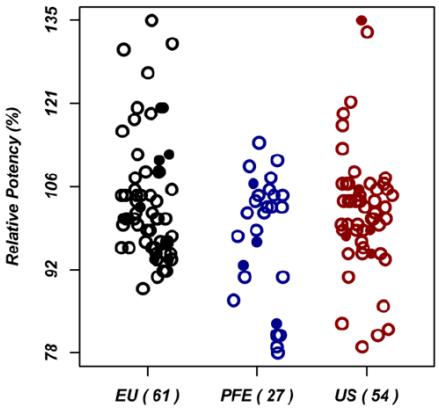
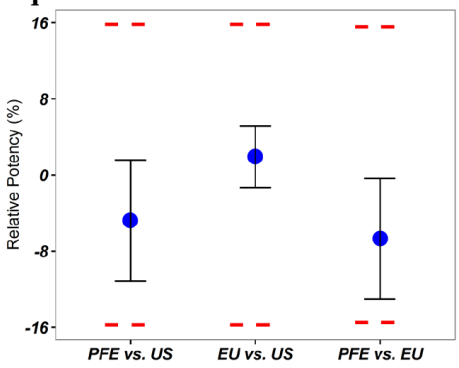


Figure 3.2.R.3.2.2-3. Statistical Analysis of CDC Activity for Rituximab-EU, PF-05280586, and Rituximab-US using an Equivalence Test



Reviewer's comment: *The CDC activity results of PF-05280586 ranged between 78-114% with a mean of 98%, which is slightly lower than those of Rituxan and MabThera but well within the assay variability. The CDC activities of PF-05280586, Rituxan and MabThera are similar with substantial overlap. PF-05280586 data meets statistical equivalence similarity criteria for CDC activity.*

- Binding to CD20 target antigen by flow cytometry

Cell-based binding assay by flow cytometry was used to assess the binding of PF-05280586 (18 DS and DP lots, including 10 independent lots), Rituxan (17 lots) and MabThera (11 lots) to CD20 expressed on Ramos cells. The assay was performed by adding dilutions of the analyte product to Ramos cells for binding to CD20 on Ramos cells, after adding the FTIC labeled secondary antibody, resulting fluorescent signal was measured using FACSCalibur system. The assay qualification in section 3.2.R.3.8 show that the range of the method is 50-150% with an accuracy of 105-108% and %RSD of 7.5-8.9%. The applicant provided representative dose response curves of CD20 binding profiles. Summaries of relative EC50 are shown in Tables 3.2.R.3.2.2-1 and 3.2.R.3.2.2-2 graphical presentation and statistical analysis are in Figures 3.2.R.3.2.2-2 and 3.2.R.3.2.2-3.

Table 3.2.R.3.2.2-1. Summary of Descriptive Statistics for CD20 Binding Activity of Rituximab-EU, PF-05280586, and Rituximab-US

Relative EC50 (%)						
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	11	97	4.5	4.6	90	102
Pfizer	18	99	7.9	8.0	85	110
US	17	96	6.7	7.0	86	110

N = sample size, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum

Table 3.2.R.3.2.2-2. Summary of Descriptive Statistics for CD20-binding Activity of PF-05280586 Independent Lots

Relative EC50 (%)					
N	**Mean**	**SD**	**CV**	**Min**	**Max**
10	95	7.2	7.5	85	104

N = sample size, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum

Figure 3.2.R.3.2.2-2. CD20 Binding Activity of Rituximab-EU, PF-05280586, and Rituximab-US Lots

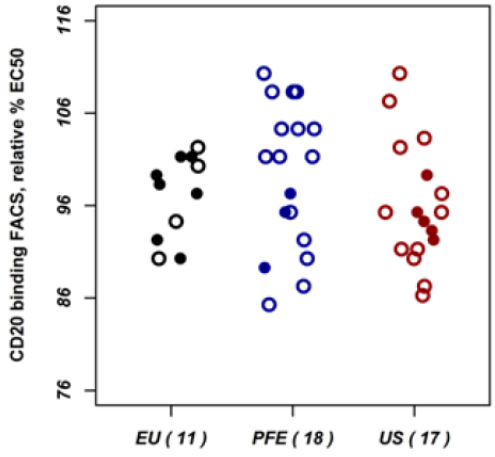
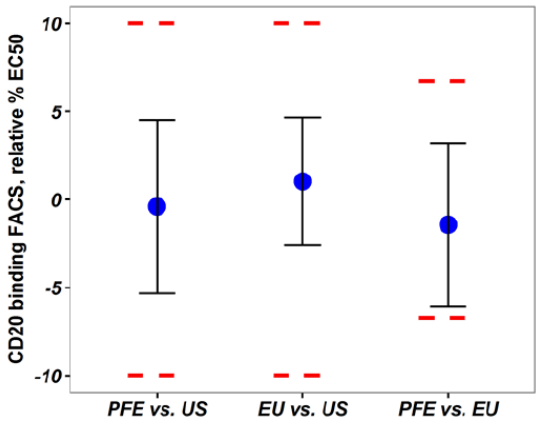


Figure 3.2.R.3.2.2-3. Statistical Analysis of Target Binding to CD20 for Rituximab-EU, PF-05280586, and Rituximab-US using an Equivalence Test



Reviewer's comment: *The CD20 binding activities of PF-05280586, Rituxan, and MabThera are similar with substantial overlap. The similarity data show that the PF-05280586 lots fall well within the equivalence margins derived from Rituxan and MabThera testing, respectively. PF-05280586 data meets statistical equivalence similarity criteria for CD20 binding.*

- Primary NK Cell ADCC Assay

Primary NK cell ADCC assay is assessed using Ramos cells as the target cells and NK cells are the effector cells. The ADCC assay measures the ADCC mechanism with target cell lysis as the readout. After adding the diluted drug samples in NK cells to the plated Ramos cells, the cell killing is measured by quantifying the release of fluorescence. The assay qualification results in section 3.2.R.3.8 show that the method range is 50-130% with accuracy 93-98% across the range and %RSD 1.7-13.8%.

The applicant also discussed that FcγRIIIa 158V/V polymorphism is associated with higher response rate to rituximab treatment (Mellor 2013), and during sample testing, NK cells isolated from healthy human donors with FcγRIIIa 158 V/V or 158 V/F were randomly used, which represent the more sensitive populations compared to those with the FcγRIIIa 158 F/F.

Reviewer's comment: *The earlier understanding that FcγRIIIa 158 (V/V) genotype connected to better clinical response to rituximab perhaps due to higher affinity of V/V FcγRIIIa for binding to IgG1 (Koene HR, et al., Blood 1997) is debated by more recent publications from prospective studies that do not find a role for differences in the polymorphisms (Kenkre VP, et al. Clin Cancer Res. 2016). Therefore, we do not consider the importance of one polymorphism over others in our assessment.*

Lot selection: The similarity assessment for ADCC included the comparison of a total of 18 lots of PF-05280586 (10 independent DS and DP lots) and 13 Rituxan and 14 MabThera DP lots.

Reviewer's comment: *Note that only subsets of the Rituxan and MabThera lots were tested in this ADCC assay. Because of the clear correlation between afucosylation (G0 glycan levels) and*

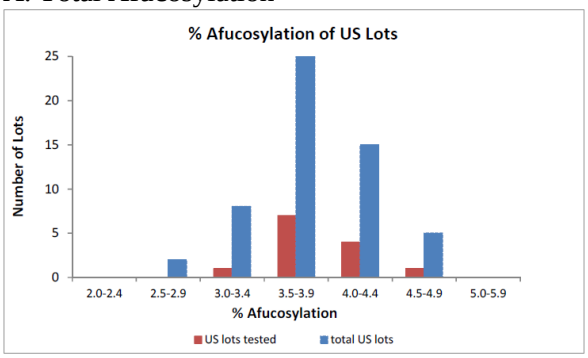
the ADCC activity, the applicant selected the originator lots for ADCC testing covering the distributing ranges observed in all originator lots and provided the following data. The originator product lots included in the similarity assessment contain different levels of total afucosylation (Rituxan 2.9-4.7%, MabThera 2.4-5.6%) and G0 glycans (Rituxan 0.5-1.6%, MabThera: 0.4-1.9%). In the following section, the applicant argues that the subset of Rituxan and MabThera lots tested in NK cell ADCC assay are representative of all originator product lots considering the distribution/content of afucosylated (and G0) glycans.

The impact of N-glycan structures of rituximab on ADCC activity and binding to FcγRIIIa is well documented in literature, e.g. Shields et al. (JBC.2002. 277:26733), Shinkawa et al. (JBC 2003. 288:3466), and Okazaki et al. (JMB 2004. 336:1239)). These published studies have been conducted with different fucosylation levels in rituximab that have affected the ADCC activity. For instance, rituximab samples with <50% fucose had enhanced ADCC activity. The afucosylated complex and hybrid and high mannose glycans had higher binding to both FcγRIIIa variants and higher ADCC activity relative to the fucosylated glycans. When increasing amounts of fucosylated complex and hybrid structure content were added to the sample with afucosylated complex structures, a decrease in ADCC activity was observed. (See the review section 3.2.S.3.1 for the characterization results of PF-05280586 on total afucosylation and ADCC activity.)

To understand the effect of total afucosylation and G0 N-glycan levels in rituximab products lots, the applicant provided data from PF-05280586, Rituxan and MabThera DP lots containing various amounts of these of these attributes, i.e., 4.3-5.1% total afucosylation, 2.4-2.7% G0; 2.9-4.7% total afucosylation, 0.5-1.6% G0; and 2.4-5.6% total afucosylation, 0.4-1.9% G0, respectively for each product (see dose response curves in Figure 3.2.R.3.2.2-11 of the submission). A shift in EC50 or upper asymptote in ADCC assay is observed in samples with very low total afucosylation or G0 glycan levels, and consistent with the findings in the above literature. *Details of N-glycan analysis and its correlation to the biological activity is discussed in section Glycosylation (and Associated Biological Activities) below. The applicant's comparison of distributions of afucosylation and G0 glycans in the lots included in the similarity assessment and in lots tested in the ADCC assay is shown here in Figures 3.2.R.3.2.2-8 and 3.2.R.3.2.2-9.*

Figure 3.2.R.3.2.2-8. Distribution of Total Afucosylation and G0 N-linked Glycan of Rituxan Lots Selected for the Primary NK Cell ADCC Assay

A. Total Afucosylation



B. G0 N-linked glycans

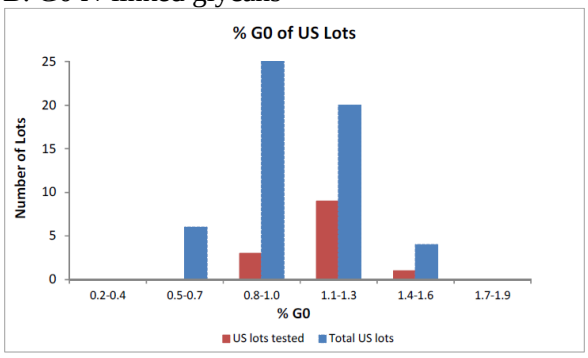
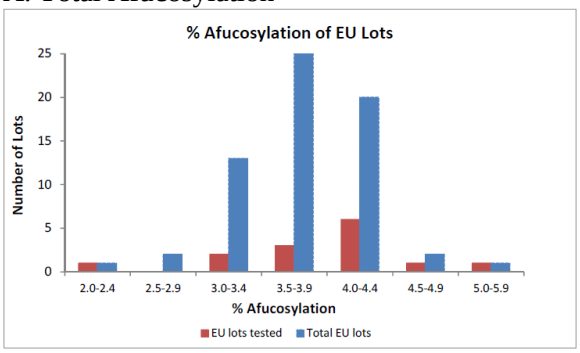
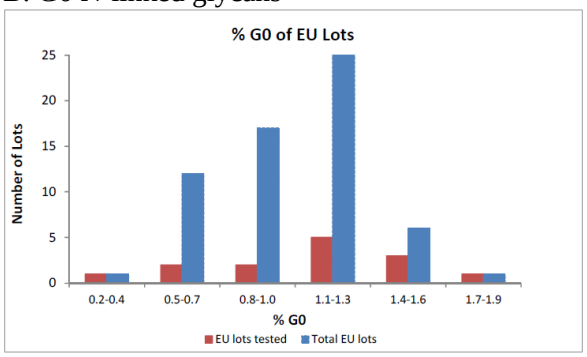


Figure 3.2.R.3.2.2-9. Distribution of Total Afucosylation and G0 N-linked Glycan of MabThera Lots Selected for the Primary NK Cell ADCC Assay

A. Total Afucosylation



B. G0 N-linked glycans



These figures show that the afucosylation and G0 glycan contents in Rituxan and MabThera lots tested in NK cell ADCC assay are representative of ranges observed in all originator product lots.

Statistical analysis of ADCC data. Summaries of relative EC50 and equivalency testing for ADCC data are shown in Tables 3.2.R.3.2.2-7, -8 and -9, graphical presentation and statistical analysis are in Figures 3.2.R.3.2.2-12 and -13.

Table 3.2.R.3.2.2-7. Summary of Descriptive Statistics for ADCC Activity of Rituximab-EU, PF-05280586, and Rituximab-US

Relative EC50 (%)						
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	14	90	12.5	14.0	64	106
Pfizer	18	96	7.9	8.2	79	108
US	13	89	13.0	14.6	73	119

N = sample size, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum

Table 3.2.R.3.2.2-8. Summary of Descriptive Statistics for NK ADCC Activity of PF-05280586 Independent Lots

Relative EC50 (%)					
N	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
10	95	7.5	7.9	83	104

Table 3.2.R.3.2.2 -9. Summary of Equivalence Testing for Primary NK Cell ADCC Activity (% Relative EC50)

Comparison	Reference SD (%)	Mean Difference	90% Confidence Interval of the Mean Difference	Equivalence margin of $1.5\hat{\sigma}_R$	Pass or Fail Equivalence
PFE vs. US	12.97	6.26	(-1.18 , 13.7)	19.45[a]	Pass
EU vs. US	12.97	1.03	(-7.36 , 9.43)	19.45[a]	Pass
PFE vs. EU	12.51	5.23	(-1.83 , 12.28)	18.77[b]	Pass

SD = standard deviation; PFE = PF-05280586; EU = Rituximab-EU; US = Rituximab-US

a. $1.5\hat{\sigma}_R$ calculated using rituximab-US lots

b. $1.5\hat{\sigma}_R$ calculated using rituximab-EU lots

Figure 3.2.R.3.2.2-12. Primary NK Cell ADCC Activity of Rituximab-EU, PF-05280586, and Rituximab-US

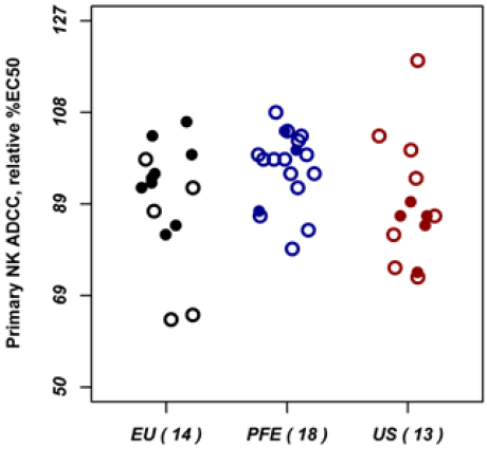
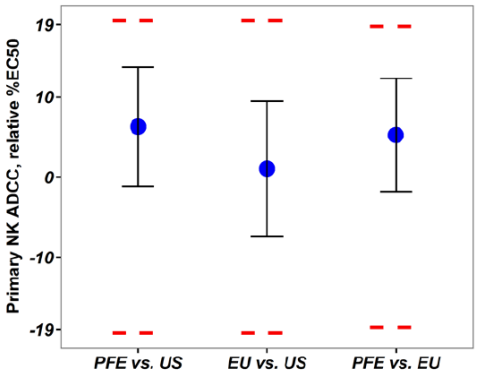


Figure 3.2.R.3.2.2-13. Statistical Analysis of Primary NK Cell ADCC Activity for PF-05280586, Rituximab-US and Rituximab-EU using an Equivalence Test



Reviewer's comment: *The ADCC activities of PF-05280586, Rituxan and MabThera as measured by NK cell-based assay have substantial overlap. Total afucosylated glycans and G0 species affects the analysis of ADCC. The evaluation of ADCC data showed statistical equivalence among PF-05280586, Rituxan and MabThera, which supports a demonstration of high similarity between PF-05280586 and Rituxan.*

Note that in section 3.2.R.3.5 Appendix – Raw data, Table 3.2.R.3.5-14, the applicant provided the apoptosis, CD20 binding, and CDC and ADCC activity results of PF-05280586, Rituxan and MabThera lots used in comparative clinical study. Clinical study lots were representative of the lots used in the similarity assessment, and support similarity conclusion between PF-05280586, Rituxan and MabThera lots.

Tier 2 Quality Attributes

The applicant used a statistical quality range test for quality attributes assigned to Tier 2 to support the demonstration of highly similar. The quality range is calculated as range of ± 3*SD around mean derived from the originator product batches.

Reviewer's comment: *In the original BLA submission, the applicant did not describe pairwise comparisons with EU-approved MabThera (i.e., the quality range assessments were provided only for PF-05280586 compared to US-licensed Rituxan batches). Therefore, the following comment was sent to the applicant (in IR dated 3/4/2019) "20. In order to support the analytical portion of the scientific bridge that justifies the relevance of comparative clinical data generated using EU-approved MabThera, Pfizer submitted comparative analytical data using EU-approved MabThera, US-licensed Rituxan and PF-05280586. You provided pairwise comparisons between three products for attributes evaluated by the equivalency method, however, for attributes analyzed by the quality range approach, you did not include pairwise comparisons between PF-05280586 and EU-approved MabThera or between US-licensed Rituxan and EU-approved MabThera. Provide the pairwise analyses for all comparisons between PF-05280586 and EU-*

approved MabThera and between US-licensed Rituxan and EU-approved MabThera analyzed by the quality range approach".

In response (3/11/2019), the applicant provided pairwise comparisons of statistical quality ranges between PF-05280586 and US-licensed Rituxan, and PF-05280586 and EU-approved MabThera lots. The assessments are discussed in each section for individual QAs below.

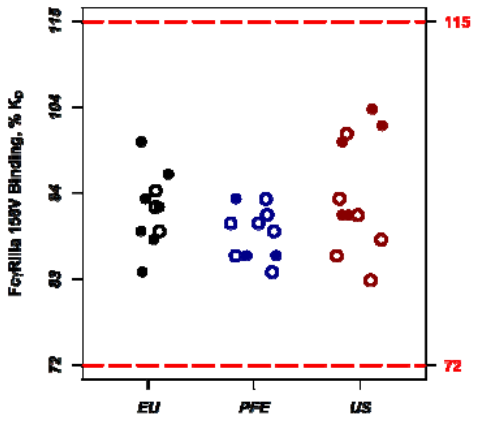
Note that figures show plotted results from individual lots of EU-approved MabThera (denoted as EU), US-licensed Rituximab (denoted as US) and PF-05280586 (PFE), identifying the lots used in the clinical trials as the solid circles. The red dashed lines represent quality range derived from Rituxan lots.

- FcγRIIIa binding (SPR) [from 3.2.R.3.2.2.2.4]:

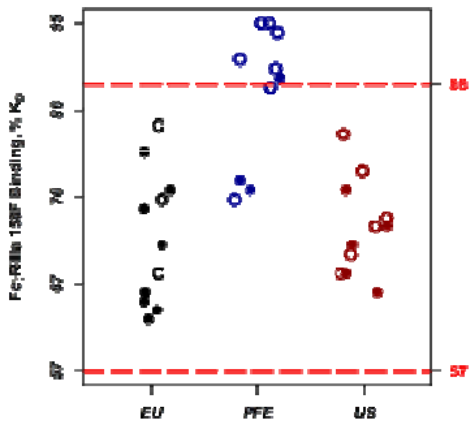
Fc receptor binding affects effector functions as well can affect the PK of mAb. Therefore, the applicant assessed binding to a variety of Fc receptors thought to be associated with effector function and PK. Binding to FcγRIIIa is linked to ADCC activity. To assess binding to FcγRIIIa, the applicant employed SPR binding assay to assess the binding affinity and kinetics of PF-05280586, Rituxan, and MabThera to FcγRIIIa 158V and 158F allotypes (representative sensorgrams of the reference material 124281pg3 and three product lots are shown in Figure 3.2.R.3.2.2-14 of the submission). Rituximab binding to FcγRIIIa 158F is weaker than binding to FcγRIIIa 158V, therefore showed more variability and difference in the binding sensorgrams. For SPR similarity assessment, the applicant used 10 independent (DS and DP) lots of PF-05280586 and 11 Rituxan and 11 MabThera DP lots that were previously tested in primary NK cell ADCC assay. The results are shown in Figure 3.2.R.3.2.2-17.

Figure 3.2.R.3.2.2-17. Statistical Quality Range for FcγRIIIa SPR Binding Activity Comparison of Rituximab-EU, PF-05280586, and Rituximab-US

FcγRIIIa 158V



FcγRIIIa 158F



Reviewer's comment: *Lower FcγRIIIa 158F allotype (previously assumed as prevalent in low responders to rituximab therapy) binding was observed for PF-05280586 (relative K_D mean 87% compared to the Rituxan and MabThera means respectively, 73% and 72%), as six PF-05280586 lots were outside of the Rituxan quality range limits, while FcγRIIIa 158V binding were comparable for all three products.*

All PF-05280586 and the licensed product lots tested in the FcγRIIIa SPR assays were tested in the primary NK cell ADCC assay. The NK cell ADCC results using human donor cells with both FcγRIIIa 158V/V and 158V/F genotypes passed the statistical equivalence test. It is also relevant that the primary NK cell ADCC assay measures the avidity effect because of the FcγRIIIa clustering that results from the target cell-rituximab immune complex binding, while FcγRIIIa SPR binding assay measures the monomeric binding between rituximab and FcγRIIIa. Overall, the results from NK cell ADCC assay and FcγRIIIa SPR binding support that PF-05280586, Rituxan and MabThera are similar in their ability to bind FcγRIIIa.

- FcγRIIa 131H binding (SPR) [from 3.2.R.3.2.2.3.]

FcγRIIa (131H and 131R) binding was evaluated by SPR. Binding to this receptor is thought to be a step inducing antibody-dependent cellular phagocytosis (ADCP). The applicant states that FcγRIIa binding assay was used as a surrogate for assessing ADCP, and that measuring the binding of rituximab to FcγRIIa provides a more meaningful similarity assessment than a cell-based ADCP activity.

Reviewer's comment: *Note that ADCP is a plausible MoA of rituximab, and no assessment directly measuring and comparing the ADCP activity was performed. Overall, the ADCP assays have high baseline activity and may not be that informative, in addition phagocytosis depends on many receptors and in vitro is more promiscuous than ADCC. Therefore, it is acceptable that the applicant did not verify a correlation between FcγRIIa and ADCP in its own hands.*

As published previously (Bruhns et al., 2009) low affinity binding of rituximab licensed products to FcγRIIa 131H (KD >2000 nM) and 131R (KD >2500 nM) were observed. The applicant included representative sensorgrams in Figure 3.2.R.3.2.2-20 of the submission. The applicant stated that low binding of PF-05280586 and the licensed products to FcγRIIa 131R did not achieve binding saturation at the highest concentration. Therefore, the binding to FcγRIIa 131H only was assessed by a quality range similarity assessment (and the binding to FcγRIIa 131R by qualitative comparison). The assessment included the comparison of a total of 11 lots of PF-05280586 (10 independent DS and DP lots) and 11 Rituxan and 11 MabThera DP lots. Summaries of FcγRIIa 131H binding activities and statistical testing are shown in Tables 3.2.R.3.2.2-16, and -17, graphical presentation of statistical quality rangers are in Figures 3.2.R.3.2.2-22.

Table 3.2.R.3.2.2-16. Summary of Descriptive Statistics for FcγRIIa 131H SPR Binding Activity of Rituximab-EU, PF-05280586, and Rituximab-US

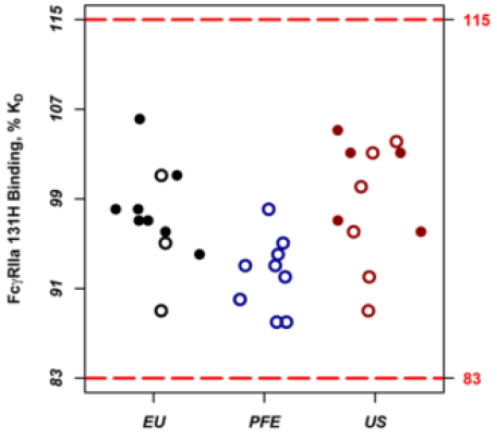
Relative K_D (%)						
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	11	97	4.4	4.5	89	106
PFE	11	91	3.9	4.2	84	98
US	11	99	5.3	5.4	89	105

Table 3.2.R.3.2.2-17. Summary of Descriptive Statistics for FcγRIIa 131H SPR Binding Activity of PF-05280586 Independent Lots

Relative K_D (%)					
N	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
10	92	3.2	3.5	88	98

N = sample size, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum

Figure 3.2.R.3.2.2-22. Statistical Quality Range for FcγRIIa 131H SPR Binding Activity Comparison of Rituximab-EU, PF-05280586, and Rituximab-US



Reviewer's comment: *The FcγRIIa 131H binding results (% K_D) show that PF-05280586 (range 84-98%), and EU-approved MabThera (89-106%) are within the US-licensed Rituxan (89-105%) quality range of 83-115%. Therefore, the results support a demonstration that PF-05280586 and Rituxan (and MabThera) are highly similar.*

- C1q binding (ELISA) [from 3.2.R.3.2.2.1.2]

Binding of human C1q to rituximab products (a key aspect of the CDC mechanism) was assessed by an ELISA binding assay (incubation of diluted rituximab samples with human C1q and quantitation of absorbance 650/450 nm from a detection antibody). The relative C1q binding affinities of samples were determined from comparison of the EC50 value with the PF-05280586 reference standard. The C1q similarity assessment included the comparison of 19 lots (11 independent) of PF-05280586 (DS and DP) and 11 Rituxan and 11 MabThera DP lots (representative dose-response curves are shown in Figure 3.2.R.3.2.2-4 of the submission). Summaries of C1q binding activities and statistical testing are shown in Tables 3.2.R.3.2.2-4, and -5, graphical presentation of statistical quality rangers are in Figure 3.2.R.3.2.2-6.

Table 3.2.R.3.2.2-4. Summary of Descriptive Statistics for C1q Binding Activity of Rituximab-EU, PF-05280586, and Rituximab-US

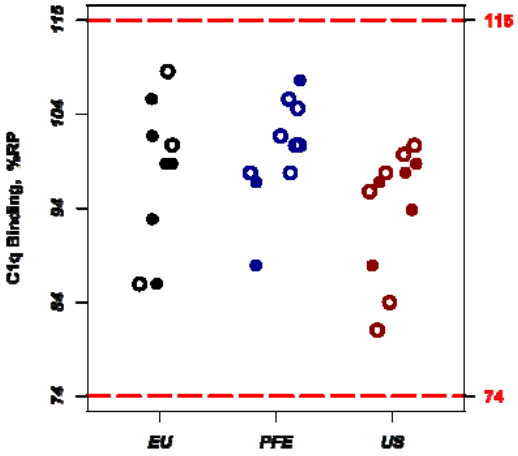
	Relative Potency (%)					
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	11	100	8.2	8.3	86	109
Pfizer	19	101	5.6	5.5	88	111
US	11	94	6.8	7.2	81	101

Table 3.2.R.3.2.2-5. Summary of Descriptive Statistics for C1q Binding Activity of PF-05280586 Independent Lots

Relative Potency (%)					
N	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
11	100	5.4	5.4	88	108

N = sample size, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum

Figure 3.2.R.3.2.2-6. Statistical Quality Range for C1q Binding Comparison of PF-05280586, Rituximab-US, Rituximab-EU



Reviewer's comment: *The relative C1q binding values overlap between the three product lots. The results show that C1q bindings to rituximab products are similar between PF-05280586, Rituxan and MabThera and support 3-way similarity.*

- FcRn Binding (SPR) [from 3.2.R.3.2.2.5]

The neonatal Fc receptor, FcRn, plays an important role in IgG homeostasis, by binding the Fc region and protecting the molecule from lysosomal degradation, thus prolonging the half-life of the antibody. The applicant evaluated binding to human FcRn by SPR analysis. The similarity assessment includes assessment of 11 (10 independent) lots of PF-05280586 and 11 Rituxan and 11 MabThera DP lots. Summaries of FcRn binding activities and statistical testing are shown in Tables 3.2.R.3.2.2-19, and -20, graphical presentation of statistical quality rangers are in Figures 3.2.R.3.2.2-27.

Table 3.2.R.3.2.2-19. Summary of Descriptive Statistics for FcRn SPR Binding Activity of Rituximab-EU, PF-05280586, and Rituximab-US

Relative K_D (%)						
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	11	92	5.8	6.3	84	98
Pfizer	11	99	8.8	8.9	82	114
US	11	92	7.1	7.6	78	101

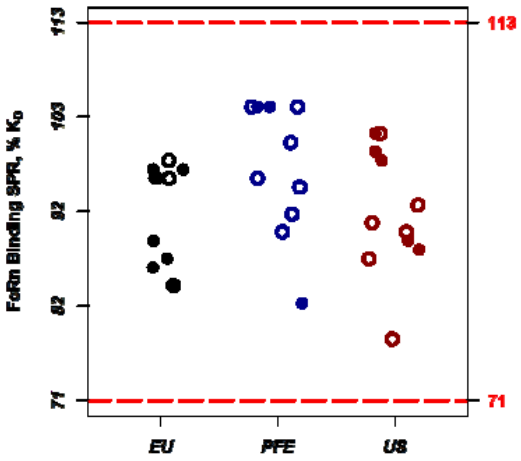
N = sample size, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum

Table 3.2.R.3.2.2-20. Summary of Descriptive Statistics for FcRn SPR Binding Activity of PF-05280586 Independent Lots

Relative K_D (%)					
N	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
10	97	7.5	7.7	82	104

N = sample size, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum

Figure 3.2.R.3.2.2-27. Statistical Quality Range for FcRn SPR Binding Activity of Rituximab-EU, PF-05280586, and Rituximab-US

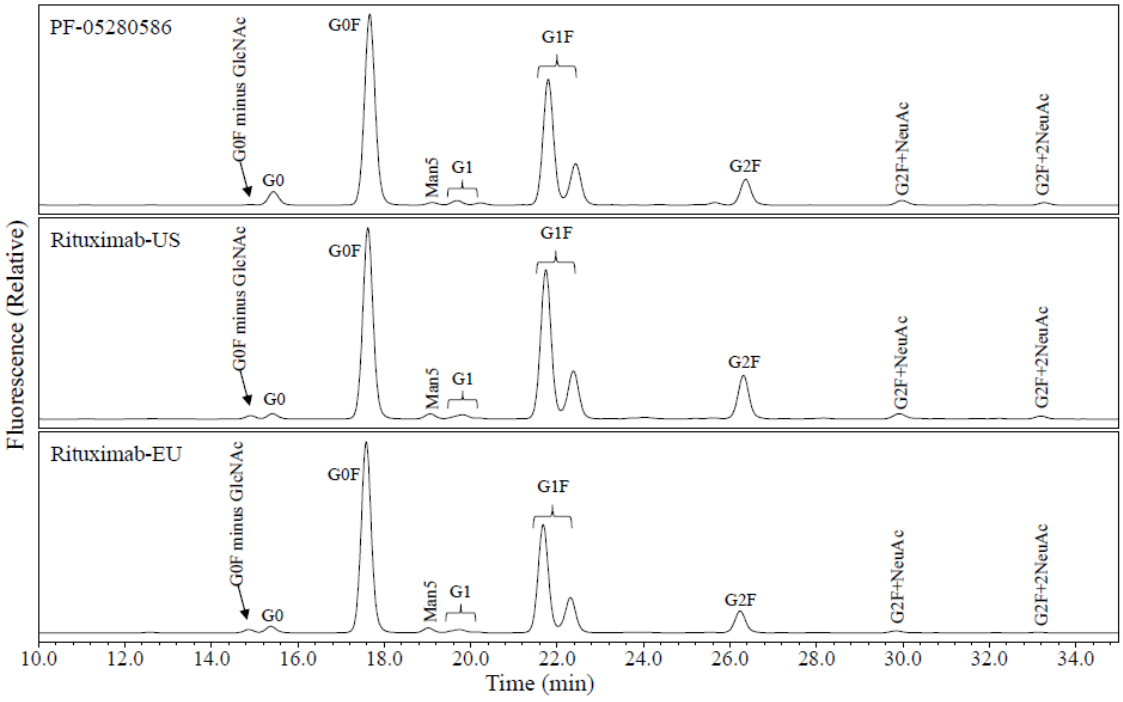


Reviewer's Comment: *The results from the FcRn binding assay showed the three products have similar means, and the ranges overlap. The results support PF-05280586, Rituxan, and MabThera are similar with respect to FcRn binding.*

- Glycosylation (and Associated Biological Activities)

For the similarity assessment, the applicant assessed the N-linked glycan QAs of terminal galactosylation, G0F species, G1F(a+b) species, G2F species, total afucosylation and G0 species, as these are important contributors for PF-05280586 effector function and PK. This includes a combination of quality range (Tier 2) statistical assessments for total afucosylation and terminal galactosylation and more qualitative (Tier 3) comparison of the overall N-linked glycan profile. *(Analytical similarity assessment of terminal galactosylation is discussed below under Tier 3 QAs.)* N-linked glycan mapping of rituximab involved enzymatic release of N-linked glycans by peptide-N-glycosidase F (PNGaseF) followed by labeling with 2-aminobenzamide (2-AB) and analysis by hydrophilic interaction liquid chromatography (HILIC) with fluorescence detection (representative profiles are shown in Figure 3.2.R.3.2.3-1).

Figure 3.2.R.3.2.3-1. Representative 2-AB HILIC N-Linked Glycan Mapping Profiles of PF-05280586, Rituximab-US, and Rituximab-EU



Quantitative values of the glycan species from 15 independent PF-05280586 lots, 55 Rituxan and 65 MabThera lots were provided in Table 3.5.R.3.5-20 in 3.2.R.3.5 Appendix, and the ranges are summarized in Table 3.2.R.3.2.3-1.

Table 3.2.R.3.2.3-1. Summary of Ranges for Total Afucosylation and Terminal Galactosylation and Individual N-linked Glycoforms in Rituximab-US, PF-05280586 and Rituximab-EU by HILIC

Glycan Species (%)	PF-05280586 (n=15)	Rituximab-US (n=55)	Rituximab-EU (n=65)
Total Afucosylated Species	4.3 – 5.1	2.9 – 4.7	2.4 – 5.6
Terminal Galactosylated Species	37.0 – 49.0	45.8 – 58.3	43.2 – 57.2
G0F minus GlcNAc	0.1 – 0.2	0.5 – 1.1	0.5 – 1.1
G0	2.4 – 2.7	0.5 – 1.6	0.4 – 1.9
G0F	43.5 – 55.4	33.6 – 48.3	35.3 – 51.1
Man5	0.3 – 0.6	0.9 – 1.6	0.9 – 1.7
G1(a+b)*	1.1 – 1.6	1.0 – 1.6	0.0 – 1.8
G1Fa	22.8 – 29.8	28.0 – 34.0	26.9 – 33.7
G1Fb	8.7 – 10.9	9.8 – 11.1	9.1 – 11.0
G2	0.1 – 0.3	0.2 – 0.6	0.2 – 0.7
G1F + NeuAc	0.5 – 1.3	0.1 – 0.3	0.1 – 0.5
G2F	4.3 – 7.0	6.1 – 11.8	5.9 – 11.6
G2F + NeuAc	1.1 – 2.0	0.7 – 2.0	0.7 – 1.8
G2F + 2NeuAc	0.6 – 1.4	0.2 – 1.1	0.2 – 0.9

* In rituximab-EU lot H0542B04, the G1(a+b) glycoforms were not detected in the chromatographic profile.

Reviewer's comment: *The N-glycan profile of Rituxan and MabThera lots are consistent with the published data in Schiestl et al. (Nat Biotechnol. 2011;29(4):310-2). However, differences*

were observed for number of glycan species ranges in PF-05280586 lots vs Rituxan and MabThera lots.

In the assessment initially submitted in the BLA, the applicant performed a similarity assessment of the total afucosylated species [G0, G1(a+b), Man5 and G2] only. The afucosylated and high mannosylated glycoforms have potentially distinct effects in PK and CDC activity, and therefore these glycoforms should be assessed individually. Therefore, the following comment was sent to the applicant (in IR dated 12/21/2018) "15. In the analytical similarity assessment, you measured the individual glycan species and performed a 3-way similarity assessment of the total afucosylated species [G0, G1(a+b), Man5 and G2] between PF-05280586, US-Rituxan and EU-MabThera. There are potentially distinct activities of afucosylated and high mannosylated glycoforms; for example, high mannose forms are relevant to PK via clearance by mannose receptors and G0 glycoforms, with and without fucose, impact CDC activity. Therefore, update the analytical similarity assessment to include separate evaluations of the major afucosylated glycoforms (e.g., sum of G0, G1, G2) and high mannose forms by quality range comparisons." In the response (1/08/2019), the applicant updated the analytical similarity assessment to include evaluations for each of the major afucosylated N-linked glycans, G0, G1, G2, and Man5. I have summarized the results in reviewer-generated Table R.3.15.

Reviewer's Table R.3.5: Summary of afucosylated N-linked glycans (G0, G1, G2, and Man5)

Product	N	G0%		G1%		G2%		Man5	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
MabThera	65	1.1	0.29	1.2	0.25	0.4	0.11	1.2	0.19
PF-05280586	15	2.6	0.10	1.4	0.12	0.2	0.08	0.4	0.09
Rituxan	55	1.0	0.23	1.3	0.17	0.4	0.10	1.2	0.18

As shown in Figures 3.2.R.3.2.3-7 and 3.2.R.3.2.3-8, G1 and G2 content in PF-05280586 lots fall within the quality range derived from Rituxan lots, thus supporting the similarity of PF-05280586 to Rituxan.

Figure 3.2.R.3.2.3-7. Individual Results and Statistical Quality Range for G1(a+b) in Rituximab-EU, PF-05280586 and Rituximab-US Lots by HILIC

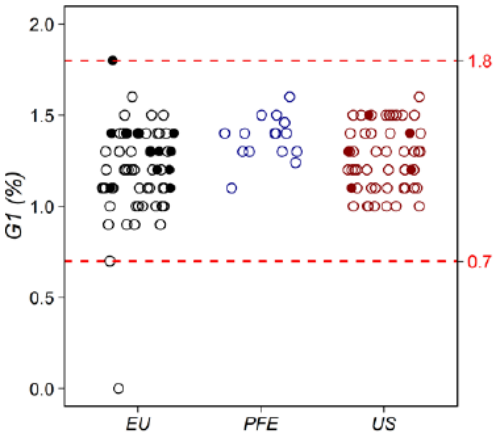
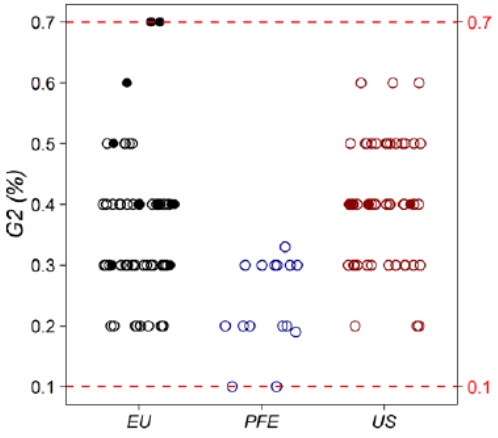


Figure 3.2.R.3.2.3-8. Individual Results and Statistical Quality Range for G2 in Rituximab-EU, PF-05280586 and Rituximab-US Lots by HILIC



However, as shown in Figure 3.2.R.3.2.3-6 below, none of the PF-05280586 lots fall within the quality ranges derived from Rituxan lots for G0. The applicant discusses that the maximum levels of G0 found in PF-05280586 are 2.7% while the maximum found in Rituxan is 1.6%. This difference in levels of G0 (1.5% from the reviewer's table R.3.15) did not have an impact on ADCC activity as presented in section 3.2.R.3.2.2 Biological Activity – Characterization of the Fc Domain. Furthermore, the applicant's data and published literature showed that at levels below 7.6% G0, differences in the levels of Fc afucosylation and G0 glycans do not have a significant impact on ADCC (Section 3.2.R.3.2.3 N-linked Glycan Structure - Structure Function Analysis, and Chung et al., mAbs,4:326, 2012). Therefore, considering also the assessment of afucosylated N-linked glycans (see below), the observed differences of G0 in PF-05280586 and in Rituxan are not clinically meaningful and do not preclude a conclusion that the products are highly similar.

Figure 3.2.R.3.2.3-6. Individual Results and Statistical Quality Range for G0 in Rituximab-EU, PF-05280586 and Rituximab-US Lots by HILIC

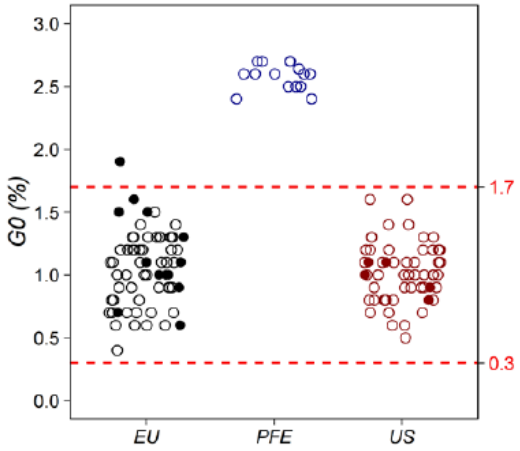
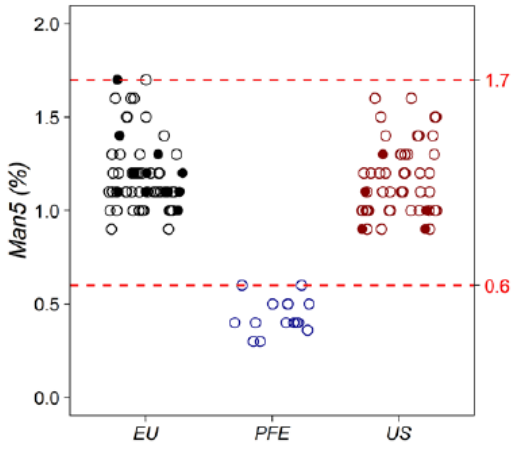


Figure 3.2.R.3.2.3-9. Individual Results and Statistical Quality Range for Man5 in Rituximab-EU, PF-05280586 and Rituximab-US Lots by HILIC



As shown in Figure 3.2.R.3.2.3-9 above, only 2 out of 15 PF-05280586 lots fall within the quality range derived from Rituxan lots for percent Man5, however, the actual values and the difference are small. In theory, high mannose species affect the antibody product clearance/PK through binding to mannose receptor. The very minor difference of Man5 in PF-05280586 and in Rituxan lots (0.4% vs 1.2% in average respectively) is unlikely to result in any difference in serum clearance (Goetze AM, et al., High-mannose glycans on the Fc region of therapeutic IgG antibodies increase serum clearance in humans. Glycobiology, 2011;21:949-59). Therefore, the minor difference in the relative abundance of high mannose does not preclude a finding that PF-05280586 is highly similar to Rituxan.

Total afucosylation:

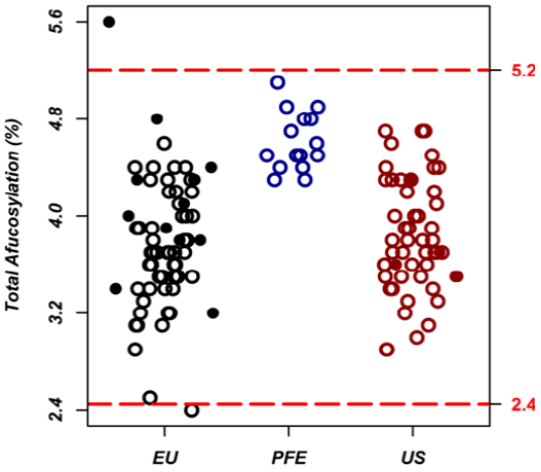
The statistical analysis of total afucosylation (G0 + G1(a+b) + G2 + Man5) for PF-05280586, Rituxan and MabThera are shown in Table 3.2.R.3.2.3-3, and Figure 3.2.R.3.2.3-4 shows all data with quality range derived from Rituxan lots. All PF-05280586 lots are within the quality range of Rituxan.

Table 3.2.R.3.2.3-3. Summary of Descriptive Statistics for Total Afucosylation in PF-05280586, Rituxan and MabThera

Total Afucosylation (%)						
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	65	3.8	0.53	14.1	2.4	5.6
Pfizer	15	4.6	0.24	5.2	4.3	5.1
US	55	3.8	0.46	12.0	2.9	4.7

N = Sample size, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum

Figure 3.2.R.3.2.3-4: Total Afucosylation in PF-05280586, Rituxan and MabThera

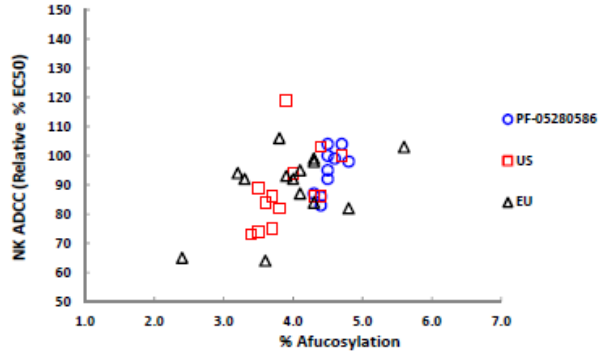


Reviewer's comment: *The plots show higher total afucosylated species in PF-05280586 than in the licensed products which is due to the higher G0 glycan levels in PF-05280586. The similarity assessment show that afucosylated species content in PF-05280586 lots fall within the quality range derived from Rituxan lots thus supporting the similarity of PF-05280586 to Rituxan. The results also support 3-way similarity between the products.*

Because the ADCC activity of rituximab is influenced by the levels of total afucosylation and G0 glycans (Schiestl et al., Nat Biotechnol. 2011;29(4):310-2), the applicant studied this correlation in PF-05280586, Rituxan and MabThera lots (Figure 3.2.R.3.2.3-4).

Figure 3.2.R.3.2.3-4: Impact of total afucosylated N-glycans and G0 glycans on NK cell ADCC activity

A.



B.

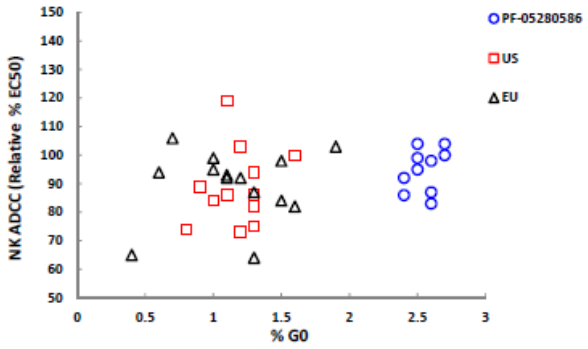


Figure 3.2.R.3.2.3-4. NK cell ADCC activities from PF-05280586 independent lots, Rituxan, and MabThera lots were plotted against their corresponding levels of afucosylation (Panel A) and G0 glycan (Panel B).

Reviewer's comment: *The above data hint at a small correlation between total afucosylation content and ADCC activity (no trend analysis was provided). The data presented in section 3.2.S.3.1 shows that Fc afucosylation below 13% and G0 glycans below 8% do not have a significant impact on ADCC activity (in Figure 3.2.S.3.1-22 above). Therefore, no impact on Fc related activities is expected due to G0 and total afucosylation differences observed in PF-05280586 and Rituxan lots. The statistical and functional assessments of total afucosylated N-linked glycans support a demonstration that PF-05280586 is highly similar to Rituxan.*

Terminal galactosylation:

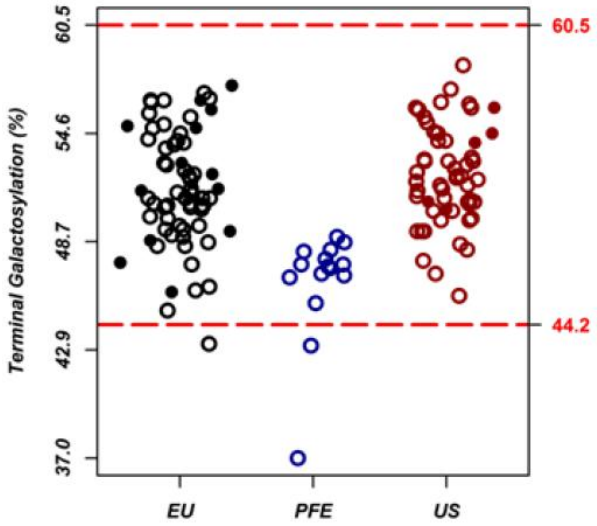
The statistical analysis of terminal galactosylation (G1F + G1(a+b) + G2F + G2) in PF-05280586, Rituxan and MabThera are shown in Table 3.2.R.3.2.3-4, and Figure 3.2.R.3.2.3-5 shows all data with quality range derived from Rituxan lots. Thirteen of 15 PF-05280586 lots are within the quality range of Rituxan.

Table 3.2.R.3.2.3-4: Summary of statistical assessment for PF-05280586, Rituxan and MabThera Galactosylation

Terminal Galactosylation (%)						
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	65	51.7	3.16	6.1	43.2	57.2
Pfizer	15	46.5	3.00	6.4	37.0	49.0
US	55	52.4	2.71	5.2	45.8	58.3

N = Sample size, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum

Figure 3.2.R.3.2.3-5: Statistical quality range of terminal galactosylation for PF-05280586, Rituxan and MabThera lots

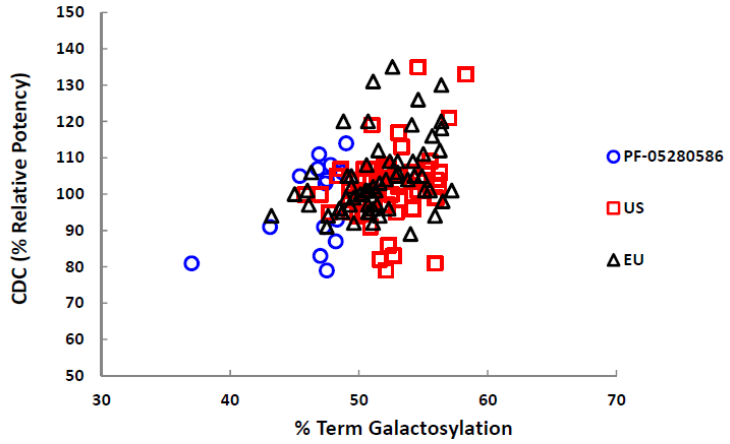


Reviewer's comment: *The quality range of terminal galactosylation from Rituxan lots is 44.2-60.5%, and 87% of PF-05280586 batches fall within this range (slightly outside of the 90% acceptance criterion). The terminal galactosylation content of 37.0% and 43.1% in PF-05280586 lots 10P123K603 and 11P123L001, respectively were outside of the quality range. It has been reported in scientific literature that the level of terminal β-galactose on Fc glycans can*

increase CDC activity through C1q binding (Brady et al., mAbs,7(3), 2015). In addition, Boyd et. al (Mol Imm., 1311, 1995) showed that ADCC activity of alemtuzumab (a mAb with β-galactosylated glycans) did not change after treatment of β-galactosidase.

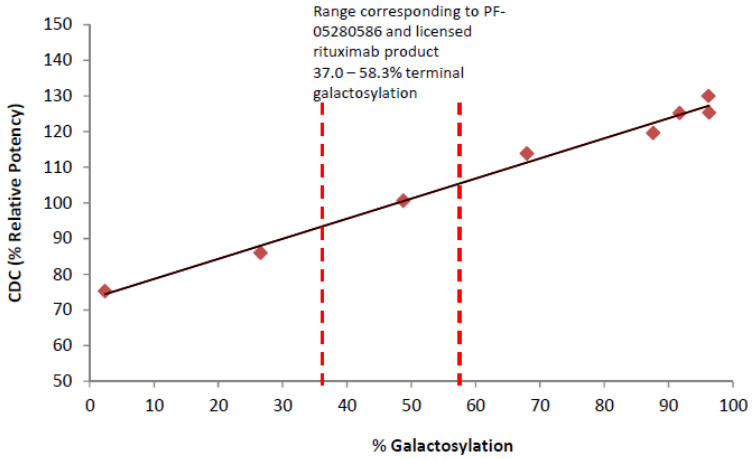
The applicant assessed the correlation between terminal galactosylation and CDC activity in the PF-05280586, Rituxan and MabThera lots (plots shown in Figure 3.2.R.3.2.3-2).

Figure 3.2.R.3.2.3-2: Terminal galactosylation levels in PF-05280586, Rituxan and MabThera lots and their CDC activities



Of note: To understand the potential impact of terminal galactosylation on CDC activity, the applicant treated PF-05280586 samples with β-1, 4- galactosidase or β-1, 4-galactosyltransferase to generate samples with terminal galactosylation ranging between 2 and 96%, and tested in the CDC assay (in 3.2.R.3.2.3. 3.2.R.3.2.3 - Structure-Function Analysis of N-Linked Glycovariants). The results show a strong correlation between these two parameters while galactosylation ranged between approximately 2% - 96% and the CDC activity between ~75% - ~130% (see Figure 3.2.S.3.1-20 copied from section 3.2.S.3.1).

Figure 3.2.S.3.1-20. CDC activities for PF-05280586 with different levels of terminal galactosylation



Red highlighted area indicates the terminal galactosylation levels that correspond to the levels observed in PF-05280586 and rituximab licensed products.

Reviewer's comment: *The plotted results in Figure 3.2.R.3.2.3-2 apparently show trending correlation between terminal galactosylation and CDC activity in rituximab products. Despite 37% terminal galactosylation in PF-05280586 batch 10P123K603 (outside of the Rituxan quality range), the batch showed similar CDC activity to the Rituxan and other PF-05280586 lots. Further, the equivalence evaluation of the CDC activity data included batch 10P123K603 and demonstrated that PF-05280586 is similar to Rituxan with respect to CDC activity. Therefore, the differences in terminal galactosylation between PF-05280586 and Rituxan does not preclude conclusion that PF-05280586 is highly similar to Rituxan.*

- Charge Heterogeneity:

The charge variants of PF-05280586, Rituxan and MabThera lots were evaluated by CEX-HPLC. Individual charge species from the acidic, main and basic peaks were identified in the characterization report (3.2.R.3.2.4. Charge Heterogeneity - Characterization). Representative expanded views of CEX-HPLC profiles for each product are shown in Figure 3.2.R.3.2.4-1. The applicant applied a quality range assessment for acidic peaks (peaks A1-A3) because the deamidated species contained in these peaks have "moderate" criticality. Other charge variants (main peak and basic peaks B1-B3, the latter containing N- and C-terminal variants) have "very low" criticality score, therefore graphical comparison similarity criteria are applied.

Figure 3.2.R.3.2.4-1: Representative expanded view of CEX-HPLC Individual Charge Fraction Assignment for PF-05280586, Rituxan and MabThera

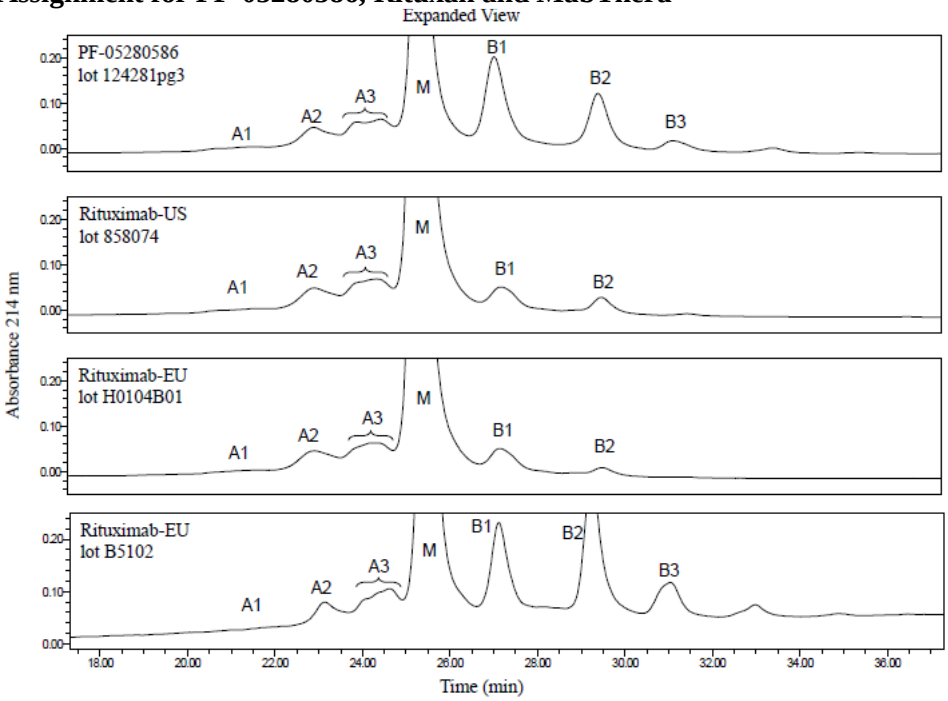


Figure 3.2.R.3.2.4-1. Acidic (A), main (M), and basic (B) individual fractions isolated from CEX-HPLC

Schiestl et al. (Nat Biotechnol. 2011;29(4):310-2) reported two distinct clusters of CEX-HPLC profiles various lots of licensed rituximab products, where the lots manufactured prior to a hypothesized manufacturing change have a higher level of basic species. The CEX-HPLC profile of the MabThera lot B5102 (*shown in Figure 3.2.R.3.2.4-5*), which is one of the earlier lots with the expiry date of May 31, 2010, is consistent with pre-change materials identified in the article.

As shown in the representative profiles, the additional peak B3 was observed in PF-05280586 and MabThera lot B5102. The applicant notes that the B3 fraction of PF-05280586 and MabThera lot B5102 contains 1 HC with N-terminal pyroglutamic acid (N-terminal Q), 1 HC with C-terminal lysine and 1 LC with N-terminal Q, and 1 H chain terminated with amidated proline in PF-05280586 (*see more details on characterization in Tables 3.2.R.3.2.4-1 and 3.2.R.3.2.4-2 in the submission*).

***Reviewer's comment**: It is well known that most charge variants are related to levels of N-terminal Q and C-terminal lysine for the approved rituximab products. Therefore, it is acceptable to evaluate the basic species in Tier 3 (see discussion below). Other variants are due to deamidated Asn or oxidized Met residues common among IgG1 mAbs.*

The similarity assessment for charged species included the comparison of a total of 24 lots PF-05280586 DS and DP lots, 55 Rituxan and 65 MabThera lots. I have summarized the charge heterogeneity data in Table R.3.16.

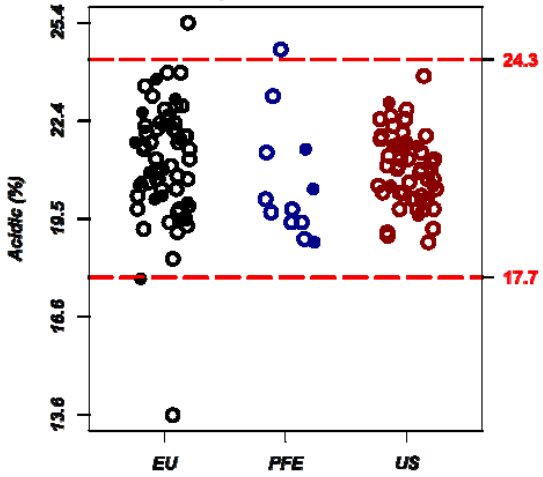
Reviewer's Table R.3.6: Summary of PF-05280586, Rituxan and MabThera lots charge heterogeneity

Product	N	Acidic Species %		Basic species %		Main species %	
		Mean	SD	Mean	SD	Mean	SD
MabThera	65	21.2	1.74	10.0	3.96	68.8	3.46
PF-05280586	24 (12*)	20.6 (20.6*)	1.37 (1.79*)	29.1 (29.2*)	2.27 (2.37*)	50.4 (50.1*)	1.65 (1.72*)
Rituxan	55	21.0	1.09	10.3	1.16	68.7	1.84

* data from PF-05280586 independent lots

As shown in Figure 3.2.R.3.2.4-5 (and submission Tables 3.2.R.3.2.4-1 and 3.2.R.3.2.4-4 in the submission), the acidic species in PF-05280586, Rituxan (the quality range is shown) and MabThera met the quality range similarity criteria.

Figure 3.2.R.3.2.4-5. Statistical Quality Ranges for Acidic Species for PF-05280586, Rituxan and MabThera Lots by CEX-HPLC



However, the basic species in PF-05280586 were higher than those of the originator product and did not meet the tier 3 statistical similarity, graphical comparison is shown in Figure

3.2.R.3.2.4-3. In addition, no assessment for main species was provided in the initial submission. Therefore, the following comment was sent to the applicant (in IR dated 12/21/2018) "In the analytical similarity assessment of charge heterogeneity (in Table 3.2.R.3.2.4-2), you state that for main peak species "criteria for similarity [were] not met, due to differences in the levels of basic species, which directly impact the levels of main species and are not expected to have any clinical impact" however, no data of main species were provided. Submit a complete similarity assessment for the main species in each product using an appropriate method of evaluation." In response (1/08/2019), the applicant provided analysis for the main species with a quality range assessment (Figure 1 below), which shows that the basic species level directly affects the level of main species.

Figure 3.2.R.3.2.4-3. Basic Species Results for MabThera, PF-05280586, and Rituxan Lots by CEX-HPLC

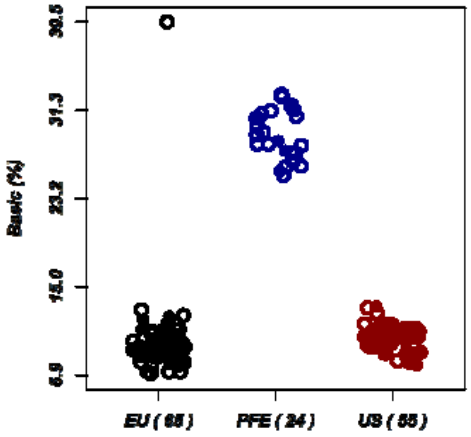


Figure 1. Statistical quality range for Main Species Results for MabThera, PF-05280586, and Rituxan Lots by CEX-HPLC

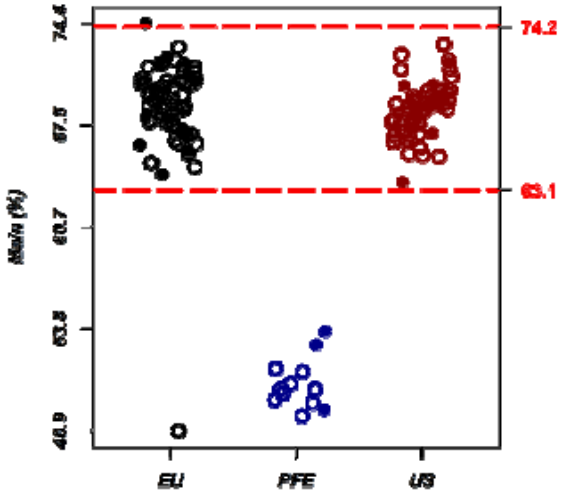


Figure 3.2.R.3.2.4-3 A single rituximab-EU lot, B5102, with 39.5% basic species may represent an earlier manufacturing process (Schiestl et al, 2011).

The applicant performed a characterization study to assess the contribution of basic species containing C-terminal lysine on the overall charge profile. This was done by treating the representative PF-05280586, Rituxan and MabThera lots with carboxypeptidase B digest (specifically targets basic amino acids (lysine and arginine) present at the C terminus) and analyzed with CEX-HPLC. With carboxypeptidase B digest the basic species content was dropped from 24.7-31.4% in to range of 12.1-15.6% for PF-05280586 lots, and from 7.8-11.2% to 6.0-10.0% for Rituxan and MabThera lots. However, these differences observed in the level of C-terminal lysine and amidated proline did not impact the relative potency (*CDC activity*) as shown in Table 3.2.R.3.2.4-7.

Table 3.2.R.3.2.4-7 Relative potency in untreated and Carboxypeptidase B treated PF-05280586, Rituxan and MabThera lots

	PF-05280586 Lot 128926-85		Rituximab-US Lot 991945		Rituximab-EU Lot H0104B01	
	Untreated	Treated	Untreated	Treated	Untreated	Treated
Relative Potency (%)	87	85	110	103	92	105

***Reviewer's comment**: As shown in Table 3.2.R.3.2.4-7, despite the difference in C-terminal lysine and amidated proline content, no differences were observed in CDC activity among PF-05280586, Rituxan and MabThera. Numerous publications have shown that the C-terminal lysine is cleaved from antibody products in vivo within a short period after administration, as well these modifications have no effect on antibody structure, antigen binding and Fc-mediated functions (Liu, H., et al., In vitro and in vivo modifications of recombinant and human IgG antibodies. MAbs, 2014. 6(5): p. 1145-54). In addition, analytical similarity was demonstrated for rituximab biological activities (apoptosis, CDC, binding to CD20, and ADCC) between PF-05280586, Rituxan and MabThera. Overall, the difference observed in charge variants would not impact the activity of the product and do not preclude a demonstration that PF-05280586 is highly similar to Rituxan.*

- Size variants:

Monomer and HMMS content by SE-HPLC:

Monomer is an active species of PF-05280586. A decrease of monomer content in PF-05280586 have a potential to impact efficacy due to the loss of biological activity and have an impact on PK/PD and increased risk of immunogenicity. Higher molecular mass species (HMMS) in PF-05280586 can increase the risk of immunogenicity. Therefore, the applicant assigned monomer and HMMS content as a Tier 2 attribute and evaluated the data using a quality range approach. The similarity assessment for monomer and HMMS included 24 PF-05280586 lots (12 independent lots), 55 Rituxan and 65 MabThera DP lots. These data are summarized in Tables 3.2.R.3.2.5-1 3.2.R.3.2.5-2 and 3.2.R.3.2.5-3, while dot plots with quality ranges derived from Rituxan lots are displayed respectively in Figures 3.2.R.3.2.5-4 and 3.2.R.3.2.5-5.

Table 3.2.R.3.2.5-1: Statistical summary of PF-05280586, Rituxan and MabThera monomer by SE-HPLC

Monomer (%)						
Region	N	Mean	SD	CV (%)	Min	Max
EU	65	98.9	0.18	0.2	98.3	99.3
Pfizer	24	99.3	0.10	0.1	99.1	99.5
US	55	99.0	0.11	0.1	98.7	99.2

Table 3.2.R.3.2.5-2: Statistical summary of PF-05280586, Rituxan and MabThera HMMS by SE-HPLC

HMMS (%)						
Region	N	Mean	SD	CV (%)	Min	Max
EU	65	1.0	0.18	17.0	0.6	1.6
Pfizer	24	0.6	0.07	11.2	0.5	0.8
US	55	1.0	0.12	12.6	0.7	1.3

Table 3.2.R.3.2.5-3: Statistical summary of Monomer and HMMS of PF-05280586 independent lots

Attribute	N	Mean (%)	SD (%)	CV (%)	Min (%)	Max (%)
Monomer	12	99.3	0.11	0.1	99.1	99.5
HMMS	12	0.6	0.09	14.0	0.5	0.8

N = Sample size, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum

Figure 3.2.R.3.2.5-4. Statistical Quality Range for Monomer Levels Determined for MabThera, PF-05280586 and Rituxan Lots by SE-HPLC

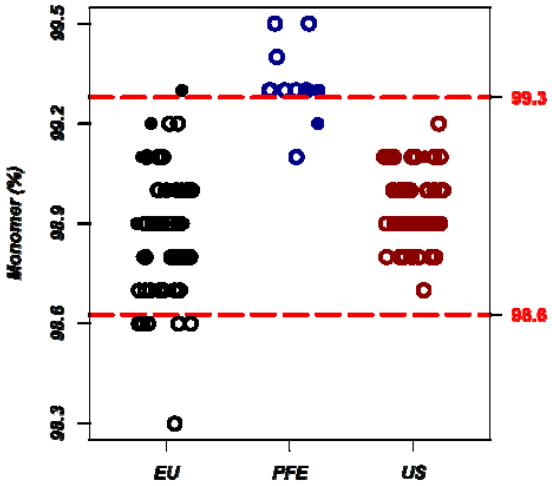
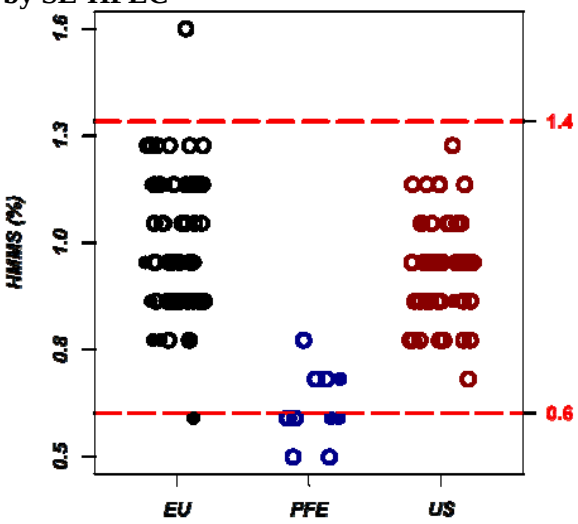


Figure 3.2.R.3.2.5-5. Statistical Quality Range for HMMS Levels Determined for MabThera, PF-05280586 and Rituxan Lots by SE-HPLC



Reviewer's comment: *The data show a higher percent of monomeric species and correspondingly lower percent of HMMS product-related impurities compared to Rituxan and MabThera. The quality range assessment yields 17% (2/12) of the PF-05280586 lots within the Rituxan quality range for monomer and 42% (4/12) within range for HMMS. PF-05280586 lots have better purity (and lower level of HMMS), thus do not impose increased risk (immunogenicity, safety and potency) compared to the approved rituximab products. Therefore, these data do not preclude a demonstration that PF-05280586 is highly similar to Rituxan.*

The original submission did not include assessment of aggregates using an orthogonal method(s). Therefore, the following comment was sent to the applicant (in IR dated 12/21/2018) "14. We note that HMMS by SE-HPLC were assessed as part of the analytical similarity assessment, however, except for HMMS characterization by SEC-MALS in representative product lots, no other orthogonal methods were used to further assess the aggregates (in Figure 3.2.R.3.2.5-2). Submit your comparative assessment of the aggregates (e.g., dimers and oligomers) in multiple product lots of PF-05280586, US-Rituxan and EU-MabThera using orthogonal methods, such as AUC, DLS and AF4 methods."
In the response (1/08/2019), the applicant provided HMMS results evaluated by SEC-MALS and AUC-SV. These results include an assessment of single lot from PF-05280586, MabThera and Rituxan. The applicant assessed the size variants using multiple methods; SE-HPLC, SDS-PAGE followed by Western blotting, SEC-MALS and AUC-SV. All lots tested in orthogonal methods confirmed a well-resolved monomer peak and a HMMS peak consistent with that of an IgG

dimer. Overall, the results show that the size variants in PF-05280586 are similar to the reference product.

The applicant did not provide similarity assessment results for subvisible particulates. In general, we do not expect subvisible particulate data to be included in analytical similarity assessments, although visible and subvisible particulates should be included as part of characterization of the product and addressed as part of the control strategy. However, as part of its forced degradation studies at elevated temperatures, the applicant assessed subvisible particulates of PF-05280586 (12 DP lots), Rituxan (6 lots) and MabThera (6 lots) using HIAC method. All tested lots at initial time point (0 month) subvisible particulates size ≥10 µm and ≥25 µm were below the USP <788> recommended limit. In addition, the release data from 6 PF-05280586 DP lots (data in section 3.2.P.8.3) show that subvisible particulates size ≥10 µm and ≥25 µm were respectively in ranges 38 -268 and 0-106.

Based on above points, it is acceptable for not providing a separate assessment of the subvisible particulates in analytical similarity assessment.

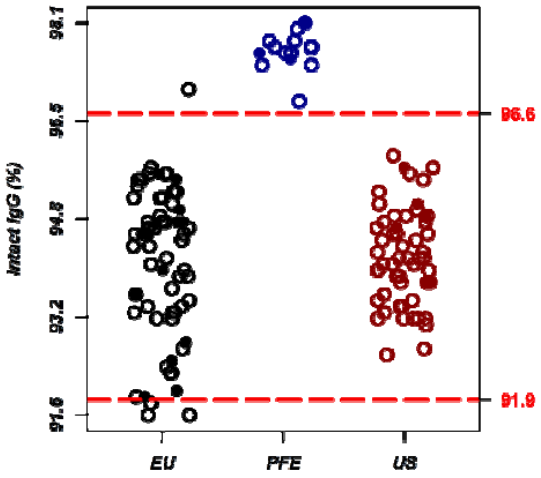
Intact IgG:

The level of intact IgG present in PF-05280586, Rituxan and MabThera was analyzed by capillary gel electrophoresis (CGE) under non-reducing conditions, and the similarity assessment (quality range) included 15 independent PF-05280586 lots, 55 Rituxan and 65 MabThera DP lots. The summary of the data and plot analysis are shown in Table 3.2.R.3.2.5-7 and Figure 3.2.R.3.2.5-11.

Table 3.2.R.3.2.5-7: Summary of Descriptive Statistics for in PF-05280586, Rituxan and MabThera lots intact IgG by CGE (non-reducing)

Intact IgG (%)						
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	65	94.2	1.23	1.3	91.6	97.0
PFE	15	97.7	0.32	0.3	96.8	98.1
US	55	94.2	0.79	0.8	92.6	95.9

Figure 3.2.R.3.2.5-11: Statistical quality ranges of intact IgG levels in PF-05280586, Rituxan and MabThera lots



***Reviewer's comment**: The intact IgG% data show that none of the PF-05280586 lots fall within the Rituxan quality range. Higher intact IgG levels were observed for PF-05280586 lots compared to the approved product lots, thus do not impose increased risk (immunogenicity, safety and potency) in PF-05280586. Therefore, these data do not preclude a demonstration that PF-05280586 is highly similar to Rituxan.*

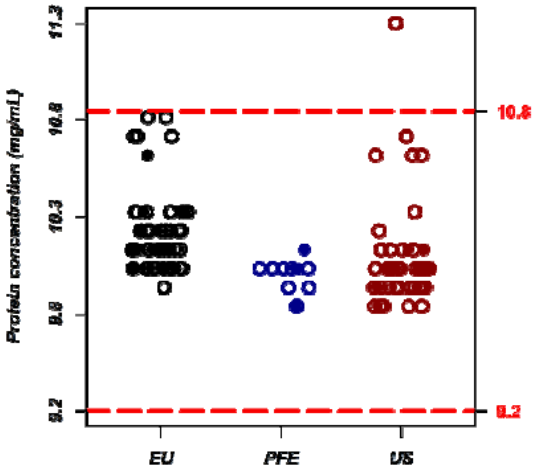
- Protein Concentration [from 3.2.R.3.2.8.]:

In similarity assessment the applicant used both 100 mg/10 mL and 500mg/50 mL presentations for all three products. The similarity assessment included quantitative comparisons of 12 PF-05280586 DP lots with 55 Rituxan and 65 MabThera DP lots. The summary data and plot analysis are shown in Table 3.2.R.3.2.8-1 and Figure 3.2.R.3.2.8-1.

Table 3.2.R.3.2.8-1: Summary of Protein concentration in PF-05280586, Rituxan and MabThera lots

Protein Concentration (mg/mL)						
Region	N	Mean	SD	CV (%)	Min	Max
EU	65	10.2	0.20	2.0	9.9	10.8
Pfizer	12	10.0	0.09	0.9	9.8	10.1
US	55	10.0	0.26	2.6	9.8	11.3

Figure 3.2.R.3.2.8-1: Statistical quality ranges of protein concentration in PF-05280586, Rituxan and MabThera lots



***Reviewer's comment**: The analysis of protein concentration shows that 100% of PF-05280586 lots fall within the quality range of Rituxan (as well 100% of MabThera lots fall within the quality range of Rituxan). These protein concentration results support a demonstration that PF-05280586 is highly similar to Rituxan.*

Tier 3 Quality Attributes:

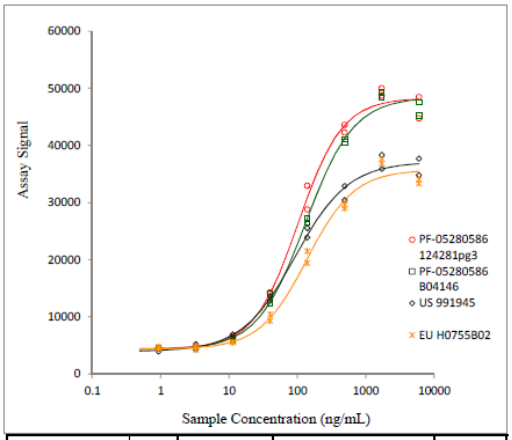
The applicant used side-by-side graphical comparison of raw data for Tier 3 QAs to support the demonstration of similarity. For some QA assessments, only single lots of PF-05280586, Rituxan

and MabThera were included, which was communicated to and addressed by the applicant (the results are discussed in each QA similarity section below).

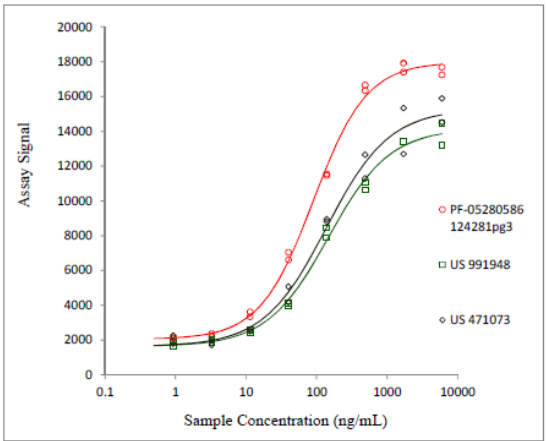
- FcγRIIIa reporter gene assay (RGA)

FcγRIIIa RGA was used as an orthogonal method to assess the binding of the rituximab products to FcγRIIIa. The FcγRIIIa RGA uses Jurkat effector cells stably transfected with FcγRIIIa 158V and a luciferase reporter gene under the control of nuclear factor of activated T-cell (NFAT) response elements. The CD20-expressing Ramos cells were used as the target cells. The similarity assessment included the comparison of a total of 18 lots of PF-05280586 (10 independent DS and DP lots), 13 Rituxan and 14 MabThera DP lots (the same set used in the primary NK cell ADCC assay). Representative dose response curves and the corresponding N-linked glycosylation profile of PF-05280586, Rituxan and MabThera are provided in the submission Figure 3.2.R.3.2.2-19. A difference was observed in the upper asymptote of the dose-response curve between PF-05280586, and Rituxan and MabThera. This variability in the upper asymptote was observed within the Rituxan lots as well as within the MabThera lots. This variability was correlated with the total afucosylation and G0 levels. The applicant states that the % EC50 values would not give meaningful information due to the observed difference in the upper asymptote and non-parallel curves. Representative dose-response curves in FcγRIIIa RGA (tested side-by-side) and corresponding N-linked glycan values of the samples are shown in Figure 3.2.R.2.2-19 (*partial copy*).

Figure 3.2.R.3.2.2-19. Representative dose response curves of PF-05280586, Rituximab and MabThera in FcγRIIIa RGA



		Lot #	Afucosylation (%)	G0 (%)
PF-05280586	DS	124281pg3	4.7	2.6
PF-05280586	DP	B04146	4.5	2.4
US	DP	991945	3.9	1.1
EU	DP	H0755B02	3.8	0.7



		Lot #	Afucosylation (%)	G0 (%)
PF-05280586	DS	124281pg3	4.7	2.6
US	DP	991948	3.5	0.8
US	DP	471073	3.6	1.0

In PF-05280586 characterization section 3.2.S.3.1.11.6, PF-05280586 activity in the FcγRIIIa RGA suggest that this assay is very sensitive to the small difference in the levels of total afucosylated glycan content (4-8% total afucosylation) in PF-05280586 (*see the reviewer's discussion regarding the afucosylation above*).

***Reviewer's comment**: The apparent difference between products in the amplitude of response in the RGA is difficult to interpret, as a simple difference in affinity to the FcγRIIIa receptor would be expected to impact the EC50 values rather than response amplitude. The applicant's assessment of the FcγRIIIa RGA results reasoning from the assay sensitivity to small differences in the total afucosylated N-glycan species appears plausible. Besides, as shown above the results of NK cell ADCC assay and FcγRIIIa SPR binding assay support that PF-05280586, Rituxan and MabThera are similar in their ability to bind FcγRIIIa and induce ADCC effector function. The NK cell assay directly probes cell killing and therefore more closely reflects the MoA. Taken together, the totality of results for attributes related to ADCC activity support similarity, and the inconclusive results for the reporter gene assay do not preclude a demonstration that PF-05280586 is highly similar to US-Rituxan.*

- FcγRI, FcγRIIb and FcγRIIIb binding (SPR)

The affinities of the rituximab products to other Fcγ receptors (FcγRI, FcγRIIb, FcγRIIIb) were determined by SPR. Representative SPR sensorgrams demonstrated comparable binding profiles of PF-05280586, and Rituxan and MabThera to FcγRI, FcγRIIb, FcγRIIIb (in Figure 3.2.R.3.2.2-23 of section 3.2.R.3.2.2.4). The % K_D values for FcγRI binding were summarized in the Table 3.2.R.3.2.2-18 below.

Table 3.2.R.3.2.2-18: Summary of FcγRI binding activity of PF-05280586, Rituxan and MabThera lots

Relative K_D (%)						
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	5	94	7.2	7.7	87	105
Pfizer	6	100	4.2	4.2	94	104
US	5	96	3.9	4.1	90	100

The applicant stated that the % K_D values for the FcγRIIb and FcγRIIIb binding were not able to be determined due to low binding affinities (K_D >2500 nM). *The following comment was sent to the applicant in IR (dated 3/04/2019) "21. The binding affinities of PF-05280586, US-licensed Rituxan and EU-approved MabThera to FcγRIIa 131R, FcγRIIb and FcγRIIIb assayed by SPR were reported as KD >2500 nM, because binding saturation was not achieved at your highest experimental concentrations (sections 3.2.R.3.2.2 – Functional Characterization of the Fc Domain and 3.2.R.3.5 Appendix – Raw Data). Provide scientific justification of how these non-quantitative,>2500 nM FcγR binding results support analytical similarity. Include risk assessments of the potential for differences in biological activities between PF-05280586 and US-licensed Rituxan that may result from undetected differences in binding affinity to these FcγRs. Alternatively, provide quantitative analytical data that directly compares precisely measured binding affinities of PF-05280586, US-licensed Rituxan and EU-approved MabThera to these FcγRs."*
In the response (3/11/2019), the applicant stated that the binding affinities of PF-05280586, Rituxan and MabThera to FcγRIIa 131R, FcγRIIb and FcγRIIIb (reported as KD > 2500 nM) are in the range of very weak binding affinity which is known for human IgG1 mAb interactions with these receptors. Due to the observed fast binding and dissociation kinetics, binding saturation was not achieved at the highest experimental concentrations and an accurate measurement of binding affinity was not obtained. The applicant's explanation appears reasonable. The applicant used visual examinations of representative SPR binding sensorgrams of PF-05280586,

Rituxan, and MabThera for similarity assessment. The applicant provided representative SPR sensorgrams that show comparable binding profiles of PF-05280586, Rituxan and MabThera to FcγRIIa 131R, FcγRIIb, and FcγRIIIb.
Visual examinations of representative SPR binding sensorgrams of PF-05280586 and originator products demonstrate similar sensorgram shapes and binding responses. In addition, the observed low binding affinities for FcγRIIa 131R, FcγRIIb and FcγRIIIb do not play a key role in the known MoAs of rituximab. Therefore, I agree that it is a low risk of any potentially undetected differences in these binding in regards to biological activity between PF-05280586 and originator products.

- Sialic acid:

Two forms of sialic acid (Nacetylneuraminic acid (Neu5Ac) and N-glycolylneuraminic acid (Neu5Gc) were identified in rituximab using ultra high resolution ESI-QTOF MS. It has been published that the sialic acid content in antibody products can impact Fc effector functions, such as CDC and ADCC activity. *Results of sialic acid forms and relative abundance in PF-05280586, Rituxan and MabThera lots were shown in Table 3.2.R.3.2.3-1 in section 3.2.R.3.2.3. The applicant used single lots from Rituxan and MabThera for the similarity assessment.*

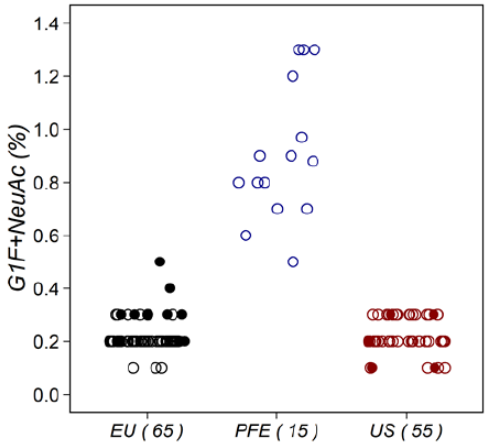
Therefore, the following comment was sent to the applicant in IR (dated 12/21/2018) "13. Five lots of PF-05280586 and a single lot each of US-Rituxan and EU-MabThera were used for the assessment of sialic acid (in Table 3.2.R.3.2.3-1). Although levels of sialic acid are generally low, some data suggest it can impact CDC and ADCC activity. Multiple lots of each product should be evaluated to support a meaningful quantitative comparison. Thus, provide sialic acid content data from additional US-Rituxan and EU-MabThera lots."
In the response (1/08/2019), the applicant provided HILIC results of sialylated N-glycan species in multiple lots, I have summarized the results in reviewer-generated Table R.3.17.

Reviewer's Table R.3.7 Summary of G1F+NeuAc, G2F+NeuAc, and G2F+2NeuAc in PF-05280586 DS lots, Rituxan and MabThera DP lots

Product	N	G1F+NeuAc %		G2F+NeuAc %		G2F+2NeuAc %	
		Mean	SD	Mean	SD	Mean	SD
MabThera	65	0.2	0.06	1.2	0.27	0.5	0.19
PF-05280586	15	0.9	0.26	1.7	0.21	1.0	0.22
Rituxan	55	0.2	0.07	1.3	0.30	0.6	0.22

As shown in Reviewer Table R.3.17, sialylated G2F+NeuAc and G2F+2NeuAc glycan profiles for PF-05280586, Rituxan and MabThera materials are similar, however, differences are observed between PF-05280586 and the approved products for G1F+NeuAc (a graphical comparison is in Figure 1).

Figure 1: G1F+NeuAc in PF-05280586, Rituxan and MabThera lots



The total level of G1F+NeuAc for any lot tested does not exceed 1.4%. Differences in G1F+NeuAc at such low levels are not expected to be clinically relevant. The mean level of G1F+NeuAc in PF-05280586 is 0.7% higher than that observed in Rituxan and MabThera. There is no concern due to these minor differences in G1F+NeuAc because there are no differences observed in CDC and ADCC activities. Therefore, these data do not preclude a demonstration that PF-05280586 is highly similar to Rituxan.

- Tier 3 Physicochemical Quality Attributes

The reviewer generated the following summary of the Tier 3 physiochemical attributes and assessments of similarity.

Reviewer's Table R.3.8: Summary of Tier 3 physicochemical quality attributes

Attribute	Test Method	Measurement	3-way Similarity
Primary Structure and Molecular Mass			
Amino acid sequence	Literature search	Sequence alignment	Confirmed all residues are present in 4-way alignment (Patent sequence, Literature, Swiss-P and experimental sequence)
	LC/MS – subunit analysis	Molar mass (Da)	Molar masses of L chain, H chain scFc (residues 241-450) and Fd' (residues 1-240) domains in each rituximab product are similar
	Edman degradation and LC/MS – peptide mapping	Sequence identity	Confirmed identical sequence between PF-05280586, and Rituxan and MabThera
	N-terminal sequencing	Sequence identity	All tested PF-05280586, and Rituxan and MabThera lots conform to expected sequence(s)
	C-terminal sequencing	Sequence identity	All tested PF-05280586, and Rituxan and MabThera lots conform to expected sequence(s)
Post-translational Modifications			
Deamidation	LC/MS/MS Peptide mapping	% deamidation Asn55, Asn388, and Asn393	Similar levels of deamidation at Asn55 (<6%), Asn388 (<5%), and Asn393 (<2%) were observed in PF-05280586, Rituxan and MabThera lots (see Figure 1 below)
Oxidation	LC/MS/MS Peptide mapping	% oxidation at Met256 and Met432	Similar levels of oxidation at Met256 (<2%) and Met432 were observed in PF-05280586, Rituxan and MabThera lots (see Figures 3 and 4 below)
Glycation	SEC/ESI/MS	Relative abundance of glycation levels	Similar levels of overall glycation (<13%) are observed in de-N-glycosylated PF-05280586, Rituxan and MabThera lots (see Figure 2 below)
Purity			
Fragments	CGE (reducing)	% Fragments	The similarity assessment for % fragments and % HC+LC included quantitative comparison of 27 PF-05280586, 55 Rituxan and 65 MabThera lots. Similar levels of % fragments and % HC+LC content observed in PF-05280586, Rituxan and MabThera lots
HC and LC	CGE (reducing)	% HC + LC	

Size variants	SDS-PAGE (reducing) and Western blotting	Banding pattern	Similar banding patterns are observed for PF-05280586, Rituxan and MabThera samples
Higher order structure			
Disulfide bonds	LC/MS Peptide mapping/VIS spectroscopy using Ellman's reagent	Disulfide bond connectivity/ sulfhydryl analysis	Similar disulfide bond pattern and similar levels of sulfhydryl are observed for PF-05280586, Rituxan and MabThera lots.
Secondary structure	Far-UV Spectroscopy	Protein structural integrity	Overlapping far-UV CD spectra is observed for PF-05280586, Rituxan and MabThera lots
	FTIR spectroscopy	Protein structural integrity	Overlapping FTIR spectra is observed for PF-05280586, Rituxan and MabThera lots
Tertiary structure	Near-UV CD spectroscopy	Protein structural integrity	Overlapping near-UV spectra is observed for PF-05280586, Rituxan and MabThera lots
	Intrinsic Florescence emission spectroscopy	Protein structural integrity	Overlapping intrinsic fluorescence spectra is observed for PF-05280586, Rituxan and MabThera lots
Thermal stability	DSC	Protein folding	Overlapping spectra is observed for PF-05280586, Rituxan and MabThera lots

Reviewer's comment: *The original submission did not include similarity assessment of the amounts of post-translational modifications (deamidation, oxidation, glycation) in PF-05280586, Rituxan and MabThera lots. Therefore, the following comment was sent to the applicant (in IR dated 12/21/2018) "11. The analytical similarity assessment of PF-05280586, US-licensed Rituxan and EU-approved MabThera does not include assessment of the amounts of individual post-translational modifications, i.e., deamidation, oxidation, glycation, in each product. Provide three pairwise comparative assessments of the quantitative levels of these post-translational modifications in each product using an appropriate method of evaluation (e.g., graphical comparison)."*
In the response (1/08/2019), the applicant provided the results deamidation, oxidation, except Met256 oxidation (included in Figure 3), and glycation from single lots from each product that is not meaningful for comparison of distribution. Therefore, the following follow-up comment was sent on 3/04/2019 "22. In response to IR comment 11 (submitted on 1/08/2019), Pfizer provided results of deamidation, oxidation, glycation obtained from single lots of PF-05280586, US-licensed Rituxan and EU-approved MabThera (except for Met256 oxidation). As we noted in our comment 13 of the same IR, multiple lots of each product should be evaluated to support a meaningful quantitative comparison. Thus, provide deamidation, oxidation, glycation data from at least 2 additional PF-05280586, US-licensed Rituxan and EU-approved MabThera lots with three pairwise comparative assessments of the quantitative levels of these post-translational modifications in each product."

In the response (3/11/2019), the applicant provided the results of deamidation (Figure 1), glycation (Figure 2) and oxidation (Figure 3) and results of three lots each of PF-05280586, MabThera and Rituxan. No significant difference was observed in any of these post-translational modifications, thus the results support similarity of the rituximab products.

Figure 1: Comparative Assessment of Deamidation Levels in PF-05280586, Rituxan, and MabThera by LC/MS/MS-Peptide Mapping (Lys-C/Trypsin)

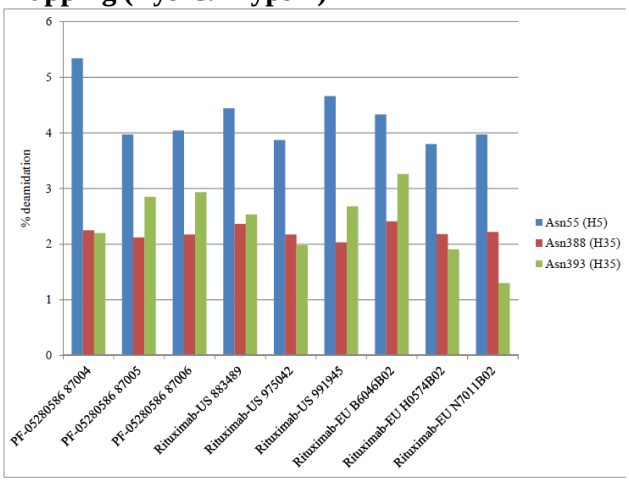


Figure 2: Comparative Assessment of Glycation Levels in PF-05280586, Rituxan, and MabThera by SEC/ESI MS

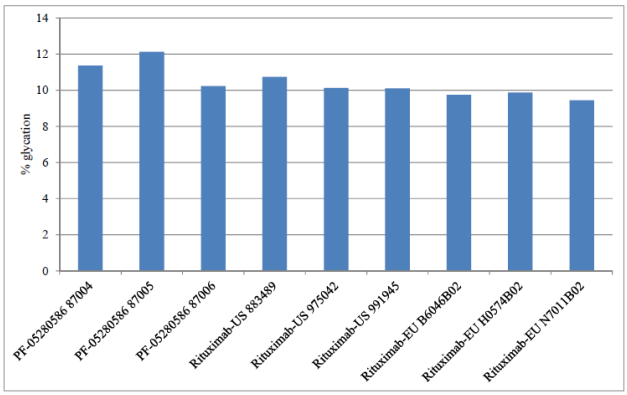


Figure 3: Comparative Assessment of Oxidation Levels in PF-05280586, Rituxan, and MabThera by LC/MS/MS-Peptide Mapping (Lys-C/Trypsin)

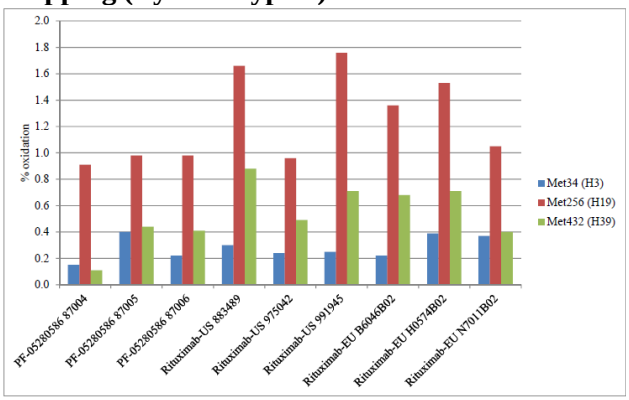
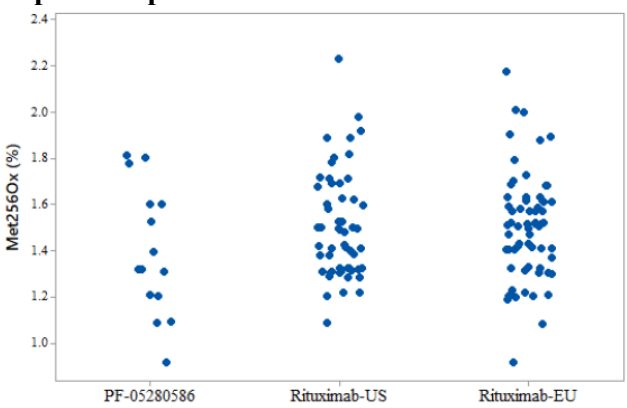


Figure 4: Comparative Assessment of Met256 Oxidation Levels in PF-05280586, Rituxan, and MabThera by Lysyl Endopeptidase Peptide Map



The data for the physiochemical QAs demonstrate that the overall primary structure, protein, post-translational modifications, purity and higher order structures of PF-05280586, Rituxan and MabThera are similar.

Comparative Forced Degradation Study

Comparative forced degradation studies were performed using PF-05280586, Rituxan and MabThera lots subjected to temperature, light, deamidation, and oxidation stresses.

Representative lots from both 100 mg/10 mL and 500 mg/50 mL DPs were used for the elevated temperature study. However, a single presentation of Rituxan (100 mg/10 mL) and MabThera (500 mg/10 mL) were used in the other degradation studies. In each study, relative changes in stability indicating QAs were assessed and compared between PF-05280586, Rituximab and MabThera lots.

Reviewer's comment: *One DP lot of each product is used the forced degradation study, this is acceptable because these studies are semi-quantitative, and the degradation mechanism(s) is likely dominated by the excipients and the nature of the stress rather than the protein concentration.*
The detailed results of the forced degradation studies were provided in 3.2.R.3.3 - Comparative Forced Degradation Study, and I included only summaries for each degradation study.

Elevated temperature studies:
Twelve PF-05280586 DP lots (including 5 independent lots), 6 Rituximab and 6 MabThera DP lots were exposed to 40 °C for 3 months.

Reviewer's comment: *The changes observed are:*

- *PF-05280586 100 mg/mL and 500 mg/10 mL: Between the 0 and 3 month time points, notable increases in acidic species (~20% to ~62% by CEX-HPLC), LMMS (~0.1% to ~9% by SEC) and fragments (~0.3% to ~4% by CGE reducing) were observed; decreases in main species (~ 52% to ~24% by CEX-HPLC), basic species (~ 30% to ~13% by CEX-HPLC) and potency (~110 % to ~ 44% by CDC assay). Modest changes were observed for monomer (SEC), and intact IgG. No other trends were observed.*
- *Rituxan 100 mg/10 mL and 500 mg/mL: At 3 months' time point, notable increases in acidic species (~20% to ~68% by CEX-HPLC), LMMS (~0.1% to ~8.5% by SEC) fragments (~0.4% to~6% by CGE reducing) and subvisible particulates ≥ 10 µm size (~ 5 to ~ 6900 by HIAC) were observed; decreases in main species (~ 71% to 28% by CEX-HPLC), basic species (~ 10% to ~3% by CEX-HPLC) and potency (~100 % to ~ 60% by CDC assay). Modest changes were observed for monomer (SEC), and intact IgG. No other trends were observed.*
- *MabThera 100 mg/mL and 500 mg/10 mL: Between the 0 and 3 month time points, notable increases in acidic species (~20% to ~67% by CEX-HPLC), LMMS (~0.1% to ~9% by SEC), fragments (~0.4% to ~5% by CGE reducing) and subvisible particulates ≥ 10 µm size (only for 500 mg/10 mL presentation, ~ 3 to ~ 6300 by HIAC) were observed; decreases in main species (~ 69% to ~28% by CE-HPLC), basic species (~ 10% to ~3% by CEX-HPLC) and potency (~100 % to ~ 50% by CDC assay). Modest changes were observed for monomer (SEC), and intact IgG. No other trends were observed.*

In summary, the elevated temperature degradation study shows similar patterns of degradation for all lots and all presentations of PF-05280586, Rituxan and MabThera, except increasing subvisible particulates (by HIAC) for only the approved product lots. No new degraded species were observed in PF-05280586 as compared to Rituxan and MabThera lots. The statistical analysis shows statistical difference in degradation rates between the PF-05280586 DP lots to both Rituxan and MabThera DP lots for all above attributes, except for rates for monomer and LMMS. There is no concern due to the observed statistical differences in degradation rates

because the degradation trends are consistent and directionally similar among three products, and the degradation rates are lower for PF-05280586 than for the licensed products.

Light Exposure Study:
Two PF-05280586 DP lots of 100 mg/10 mL and 500 mg/10 mL presentation and 1 Rituxan DP lot (500 mg/10 mL presentation) and 1 MabThera DP lot (100 mg/10 mL presentation) were used this study. All the lots were placed in a light chamber and exposed to approximately 5.1 klux of light for 14 days at a controlled temperature of 25 °C.

Reviewer's comment: *The changes observed after light exposure at 25 °C for 14 days are: Light exposure resulted in increase of acidic species (by CEX-HPLC), fragments (by CGE non-reduce), oxidize species (W106, M256, M432 by LC/MS peptide mapping), HMMS and LMMS (by SE-HPLC); and decrease of main species (by CEX-HPLC), intact IgG (by CGE non-reducing), potency (by CDC bioassay) that were observed in all lots of PF-05280586, Rituxan and MabThera. No new degraded species were observed in PF-05280586 as compared to Rituxan and MabThera.*

Deamidation by phosphate buffer incubation:
The same sets of samples as in the Light Exposure Study were used this study. All the lots were dialyzed into 100 mM sodium phosphate, pH 8.0 and incubated for 14 days at a controlled temperature of 37 °C.

Reviewer's comment: *The LC/MS-peptide mapping (trypsin) showed that deamidations for H5, H13, and H35 peptides are observed in all tested lots when the samples are incubated with phosphate buffer for 14 days. The changes observed after phosphate buffer incubation at 37 °C for 14 days are: Increase of acidic species (by CEX-HPLC), HMMS and LMMS (by SE-HPLC), fragments (by CGE non-reducing); decrease of main species and basic species (by CEX-HPLC), intact IgG (by CGE non-reducing), potency (by CDC bioassay) were observed for all lots of PF-05280586, Rituxan and MabThera.*

Oxidation by peracetic acid:
The same sets of samples as in the Light Exposure Study were used in this study. All samples were incubated with increasing concentrations of peracetic acid to determine the most susceptible sites for oxidation. The samples were compared side-by-side using LC/MS – peptide mapping (trypsin), limited lysyl endopeptidase proteolytic peptide mapping, cell-based CDC assay, and binding to FcRn by SPR method.

Reviewer's comment: *Note that the applicant tested only directly affected QAs were examined (i.e. specific methionine species that become oxidized), while size and charge variants were not tested in the oxidation study. This is acceptable.*
The changes observed after incubation with peracetic acid are: LC/MS peptide mapping results show major oxidation at HC Met34, Met256 and Met432, located in peptides H3, H19 and H39, respectively, and low levels oxidation at HC Met20 located in peptide H2 in PF-05280586, Rituxan and MabThera lots. No significant change in oxidation at HC Met81 and LC Met21, located in peptides H9 and L2, respectively for all products. Oxidation at HC Met256 is known to affect FcRn binding affinity for monoclonal antibody products. The levels of oxidation at

Met256 and potency (by CDC assay) in all PF-05280586, Rituxan and MabThera lots were peracetic acid concentration dependent and are similar among all three products (in Table 3.2.R.3.3-26 in the submission).

Overall, no significant differences between PF-05280586, Rituxan and MabThera were observed in the studied conditions in the force degradation studies, and the results do not preclude a demonstration that PF-05280586 is highly similar to Rituxan.

Analytical Similarity Assessment Summary:

To support a demonstration that PF-05280586 is highly similar to the US-licensed Rituxan reference product, and to establish a 3-way scientific bridge, the applicant performed an analytical similarity assessment using adequate number of independent PF-05280586 DS (10 lots) and DP (5 lots), US-licensed Rituxan DP (55 lots), and EU-approved MabThera DP (65 lots). The similarity assessment involved a range of orthogonal functional and physicochemical assays, as well as forced degradation studies. Rituximab molecular attributes are collectively assigned to the correct tiers with respect to potential clinical impact, and attribute similarity was evaluated using appropriate statistical methods. CDC, ADCC, apoptosis and CD20 binding activities were assessed using equivalency testing (Tier 1 similarity assessment) based on primary mechanisms of action of rituximab. The similarity data provided in the submission was generated using methods that are appropriately validated or qualified for their intended purpose. Overall, analytical data, including the statistical analyses, provided in the original submission and in response to information requests support a demonstration that PF-05280586 is highly similar to US-licensed Rituxan, while observed differences in basic and main species (by CEX), G0, G2 and Man5 glycans (by HILIC), monomer and HMMS (by SEC-HPLC) and intact IgG (by non-reducing CGE) do not preclude this demonstration.
In addition, the data support the adequacy of the analytical component of scientific 3-way bridge to justify the use of clinical data generated using EU-approved MabThera. PF-05280586 meets the statutory "same strength" requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.

Rukman De Silva

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Bazarragchaa Damdinsuren

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Date: 4/11/2019 10:29:22PM
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Christopher Downey

Digitally signed by Christopher Downey
Date: 4/16/2019 04:46:31PM
GUID: 508da6d9000264ed71c49d80cfe4e31a

OPQ/OBP 351(k) BLA IMMUNOGENICITY ASSAY REVIEW

Application Type	BLA
Application Number	761103
Submit Date	07/25/2018
Received Date	07/25/2018
BsUFA Goal Date	07/25/2019
Division/Office	DHP / OHOP
Review Completion Date	4/11/2019
Product Code Name	PF-05280586 (rituximab-xxxx)
Proposed Proper Name[1]	rituximab-xxxx
Proposed Proprietary Name[1]	Ruxience
Pharmacologic Class	CD20-directed cytolytic monoclonal antibody
Applicant	Pfizer, Inc.
Applicant Proposed Indication(s)	Biosimilar to US-licensed Rituxan, seeking approval for the same clinical indications approved for US-licensed Rituxan: rheumatoid arthritis, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and granulomatosis with polyangiitis and microscopic polyangiitis

Immunogenicity Reviewers

Primary Reviewer(s)	Rukman De Silva, Ph.D.
Secondary Reviewer(s)	Haoheng Yan, MD, Ph.D.
Tertiary Reviewer(s)	Christopher Downey, Ph.D.

[1] The proposed proper and proprietary names are conditionally accepted until such time that the application is approved.

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1.0 Immunogenicity Assay Executive Summary and Recommendation

PF-05280586 (rituximab-xxxx; Ruxience) is a recombinant, chimeric, IgG1k monoclonal antibody (mAb) specific to human CD20 antigen. PF-05280586 is a proposed biosimilar to US-licensed Rituxan (US-Rituxan) and seeking approval for same clinical indications of US-Rituxan. PF-05280586 drug product is provided as a liquid concentrate for solution for infusion at 10 mg/mL (100 mg per 10 mL and 500 mg per 50 mL presentations) in single use vials, IV route of administration, and dosing regimen as the US-Rituxan.

To demonstrate there is no clinically meaningful differences in immunogenicity between PF-05280586 and US-Rituxan, Pfizer performed three clinical studies to assess immunogenicity rates 1) Study B3281001: a controlled, multicenter, multinational, randomized, double-blind, a three- way single dose PK/PD study in subjects with active rheumatoid arthritis (RA) comparing PF-05280586 to US-Rituxan and EU-MabThera ; 2) Study B3281004: a subsequent extension study of B3281001 and 3) Study B3281006: a comparative, randomized, double-blind study in patients with CD20-positive, low tumor burden-follicular lymphoma using PF-05280586 and EU-MabThera.

This review contains details of ADA and Nab assay description and validation data with serum from representative patient population. The applicant provided anti-drug antibody (ADA) and neutralizing anti-drug antibody (NAb) assays validation reports in the submission. The assay validation includes screening, confirmatory and titer ADA assessment as well as Nab assessment. Submission includes validation data of two validated ADA and Nab assays each: one specific for PF-05280586 and one specific for the EU-MabThera. Serum samples from patients treated with PF-05280586 were tested using the PF-05280586 specific ADA and NAb assay, and serum samples from patients treated with US-Rituxan or EU-MabThera were tested using the EU-MabThera specific ADA and NAb assays. As ADA rates cannot be directly compared between results from two different assays, this was communicated to the applicant in an IR dated 1/9/2019. In response, the applicant re-tested samples from Study B3281006 using a single ADA assay specific for PF-05280586. Pfizer provided data showed that the ADA assay specific for PF-05280586 responds similarly to PF-05280586, US-Rituxan or EU-MabThera by competitive inhibition, which supports the suitability of using the ADA assay specific to PF-05280586 to test sample from patients treated with all three drugs. Re-testing for NAb was not requested by the Agency due to the insufficient NAb assay sensitivity. The ADA and NAb assay validation data was assessed for the PF-05280586 specific assay.

The ADA assay is an electrochemiluminescence (ECL) based bridging assay. The screening assay sensitivity is 2.0 ng/mL as assessed using a rat monoclonal antibody positive control. The assay can detect 400 ng/mL positive control in the presence of 50 µg/mL PF-05280586, while drug Ctrough is around 80µg/mL in Study B3281001(comparative PK study in RA patients) and 70 to 170µg/mL in Study B3281006(clinical comparative study in lymphoma patients) during dosing. The assay sensitivity is significantly reduced when the rituximab products are present in the sample. Therefore, the ADA rates are under-reported during dosing period for all treatment groups, and the rates increase during and after the wash-out period.

The assay Nab assay is a cell-based assay measuring complement dependent cytotoxicity (CDC). The NAb assay sensitivity was validated to 69 µg/mL), which is insufficient to detect NAb present at levels that may inhibit biological activities of the product in vivo. No NAb was detected in the clinical samples.

The shortcoming identified in ADA assays (insufficient drug tolerance during dosing period) and the deficiency of the Nab assays (insufficient assay sensitivity) was discussed with the review team during mid- and late-cycle meetings. The review team will consider the totality of the evidence, including consideration of the relatively low risk of immunogenicity for Rituximab, to reach a regulatory decision.

2.0 Review

Document Reviewed	Submission Date
BLA 761103 SN 0001	07/25/2018
BLA 761103 SN 0025	01/22/2019
BLA 761103 SN 0028	02/02/2019
BLA 761103 SN 0036	03/28/2019

2.1 Immunogenicity Risk Assessment

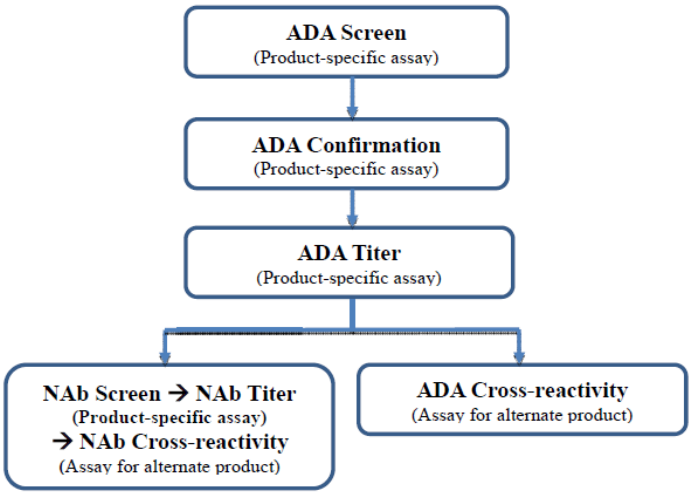
According to the US prescribing information of US-Rituxan, the correlation of clinical relevance of anti-rituximab antibody formation in US-Rituxan treated patients is well reported. In 4 of 356 (1.1%) and 273 of 2578 (11%) patients treated with US-Rituxan observed formation of ADA in ST and RS patent populations, respectively. None of the ADA positive patients were associated with infusion-related reactions or other adverse events (AEs). Low incidences of ADA formation were observed in US-Rituxan patient populations, and ADA positive patients were not associated with AEs.

2.2 Validation of Anti-Drug Antibody Assay

The immunogenicity measurement of PF-05280586 was conducted using ADA assay and Nab assay for testing samples from clinical studies B3281001, B3281004 and B3281006. The ADA assay is based on electrochemiluminescence (ECL) method and Nab assay is a cell-based method measuring CDC activity.

The applicant used a tiered approach for screening, confirmation and titer determination for the ADA assay. Initially, all human ADA samples were screened using validated ADA assay probing with the product that patient received, then the ADA positive samples were identified, and titer was determined for the ADA positive samples. Samples confirmed to be positive for ADA were then assayed for cross-reactivity using the alternative assay probing with the comparator product not given to that patient. Finally, ADA-positive samples with titer values were evaluated for Nabs using a validated Nab assay. The Nab assay is based on the assessment of inhibition of CDC activity of rituximab products on CD20 positive WIL2-S cells. The immunogenicity testing approach to ADA/NAb testing is presented in Figure 1.

Figure 1: The approach used in ADA and Nab sample testing



Abbreviations: ADA = Anti-drug antibody; NAb = neutralizing antibody

In the original submission, the applicant developed two ADA assay methods (one for anti-EU-MabThera antibodies and one for anti-PF-05280586 antibodies) to support immunogenicity assessment of the three clinical studies (B3281001, B3281004, and B3281006). In each study ADA positive serum samples were analyzed for the presence or absence of neutralizing anti-EU-MabThera antibodies or neutralizing anti-PF-05280586 antibodies using the validated drug-specific NAb assays.

Reviewer's comment: *The applicant performed immunogenicity assessments in clinical serum samples using two product-specific ADA assays: one specific for PF-05280586 and one specific for EU-MabThera. Patient samples in study B3281001 and B3281006 were tested using one of the product-specific assays based on the dosed product. The serum samples confirmed positive for ADA to the dosed product were assessed for cross-reactivity using the alternative assay. We discuss this with the OBP immunogenicity working group and the working group did not recommend use of two different assays to compare the ADA incidences (anti-PF-05280586, anti-US-Rituxan and anti-EU-MabThera). In addition, clinical study B3281001 and B3281006 data show low cross reactivity between the two assays (cross reactivity rates range from 50%-100%). Therefore, during the mid-cycle communication, we requested the applicant to test serum samples of clinical study B3281001 and B3281006 (from immunogenicity perspective, B3281004 is of less importance due to its cross over design) using both ADA assay's specific for PF-05280586 and EU-MabThera or at minimum the ADA assay specific for PF-05280586. In response dated January 22, 2019 (submission # 0025) the applicant stated that serum samples from clinical Study B3281006 will be tested using ADA assay specific for PF-05280586. In addition, the applicant provided immunogenicity data of clinical study B3281004 serum samples (incidence of ADA, NAbs and titers) analyzed using the ADA assay specific for PF-05280586. Furthermore, the applicant stated that serum samples from clinical study B3281001 are no longer available for reanalysis. In response (dated 03/28/2019), the applicant provided ADA data for both treatment groups (EU-MabThera and PF-05280586) from study B3281006 using anti-PF-05280586 antibody assay.*

2.2.1 Method Principle

The screening assay to detect anti- PF-05280586 antibodies (ADA) in human serum uses ECL technology and a bridging format. The method uses biotinylated PF-05280586 to capture ADA and ruthenylated PF-05280586 to detect antibodies which bind to the PF-05280586. Briefly, human serum samples, positive controls (PS) and negative controls (NC) are diluted with assay buffer containing rabbit anti-IgM antibody (to eliminate any cross-reactive IgM antibody interference in RA samples), and incubated with biotinylated- PF-05280586 and ruthenylated PF-05280586. During this time, anti-PF-05280586 antibodies will bind to both the biotinylated-PF-05280586 and ruthenylated- PF-05280586 molecules to form an antibody complex. The antibody complex is then added to a streptavidin-coated MesoScale Discovery (MSD) plate. The chemiluminescent signal readout is obtained from an ECL reaction (sTag/ tripropylamine) and measured by in relative light units using MSD plate reader. The samples tested positive in the screening assay will be further confirmed by a confirmatory assay. The confirmatory assay is a competitive inhibition assay where serum samples are spiked with PF-05280586 and compared with unspiked samples.

ADA and Nab assay validation report for anti-PF-05280586 antibodies are provided in validation report (b) (4)-15-1133 and (b) (4)-15-1134, respectively. The validated methods were used to support the efficacy, safety, PK and immunogenicity studies B3281001 and B3281006. The methods were validated at (b) (4).

2.2.2 Validation Exercises

The validations using healthy volunteer's serum were exploratory and not assessed in this review. The results of ADA assay validation (Report # (b) (4) 15-113) and reviewer's assessment are provided in Table 2.1.

Table 2.1: Validation Results and Reviewer Assessment for ADA assays used in comparative PK study (B3281001) and comparative clinical study (B3281006)

Validation Parameter	Validation Results	Reviewer Comment
Contract Research Org	(b) (4)	
Assay principle	ECL based bridging with bioti-PF-05280586 and ruth- PF-05280586. Human serum samples, positive controls and negative controls were diluted with assay buffer containing rabbit anti-IgM antibody to eliminate any cross-reactive IgM antibody interference in samples.	*Standard ECL based approach used.* *Commercially available rabbit anti-IgM antibody is used* (b) (4) *, to reduce interference from rheumatoid factor (IgM antibody against Fc of IgG)*
Positive control (PC)	Rat anti-Rituximab monoclonal antibody, it is the primary PC (at 400ng/mL)	(b) (4). *Immunogen is F(ab)$_2$ fragment of Rituximab.*

Other PCs	Affinity purified commercial Rabbit Anti-Rituximab Polyclonal Antibody Mouse Anti-PF-05280586 Monoclonal Antibody	*Used in validation for a few selected parameters (precision and stability).*
LPC	50 ng/mL	*The applicant used a titration approach from 400ng/mL for assay suitability control in the clinical sample testing. PC at 400 ng/mL and 50 ng/mL were used for the confirmatory assay testing.* *Other PC concentrations were used in drug tolerance and in matrix recovery test.*
PC	Primary PC at 400 ng/mL	
Matrix and NC	Pooled normal human serum	
MRD	1: 75	*Same MRD is used for both ST and RA serum samples*
NC system suitability range	Mean NC (N=8) response for each run must be < 212.8 RU (2x mean signal from all validation runs); the %CV must be ≤ 25%	*The NC suitability control is acceptable.*
PC system suitability range	PC=400ng/mL, 7 more serial dilution at 1:3, PC end point Log10 titer range is 3.89-4.95 with CPF 1.21, %CV associated with the sample duplicates must be ≤ 25%	*Subject samples were assessed by raw RU values, not an end point titer. So, using the end point titer to control assay PC signal seems to be irrelevant as a monitor of raw RU variability at the lower end. OSIS inspector Amanda Lewin checked the RU levels of PC dilutions during the clinical sample runs. The %CV of PC at 133ng/mL and 40ng/mL are 15%-22%. All PC at 40ng/mL were tested positive. Assay precision and system suitability at clinical sample runs are acceptable.*
Antigenic Equivalence testing (Competitive DOE)	PC conc. (1.95, 3.91, 7.81, 15.6, 31.3, 62.5, 125, and ng/ml) competed with spiked with EU-MabThera, US-Rituxan and PF-05280586. Competitive inhibition is assessed. % Inhib =100*[(1-(spike RLU/unspiked RLU)]	*All three drug competitive inhibition curves overlapped at all tested concentrations.*
Screening cut- point (SCP) Floating CP	Plate mean NC response x 1.21 (based on 75 individual lots of RA patient serum) Plate mean NC response x 1.07 (based on 50 individual lots of ST patient serum)	*Serum samples are not exposed to PF-05280586.* *Adequate data were provided to support the statistical approach used for the screening cut point determination. The false positive rate is ~ 5% for pre-dosed samples and it is in line with the theoretical value. Sample means are correlate with the NC means; NC is suitable for the normalization factor calculation.*
Confirmatory cut-point (CCP) Floating	19% (use 0.1% FP rate based on 28 individual lots of RA patient serum)	*0.1%FP rate for CCP is acceptable as the ADA rate detected aligns with current*

	18.5 % (use 0.1% FP rate based on 28 individual lots of ST patient serum)	*publication and allows meaningful assessment of immunogenicity impact.*
Assay Drug tolerance	The LPC (50 ng/mL) can tolerate up to 25 µg/mL of PF-05280586 The HPC (400 ng/mL) can tolerate up to 50 µg/mL of PF-05280586	*See the reviewer's comment below*
Sensitivity (mass-based)	2.0 ng/mL by Rat anti-Rituximab mAb. 2.1 ng/mL by Mouse anti-PF-05280586 mAb 26.8 ng/mL by Rabbit anti-Rituximab polyclonal Ab	*The sensitivity for ADA assays is acceptable*
Repeatability/Intra-assay variability	For rat anti-Rituximab mAb: NC %CV is 1.1-5.5% (6 runs) PC %CV is 1.2-15.4% (6 runs) End point log_{10} titer for PC % CV is 5.1 for CPF 1.21	*Assessed for all PCs. The results are within the acceptance criteria of immunogenicity guidance recommended limit of %CV ≤ 20% . See additional comments in PC system suitability row.*
Intermediate Precision (IP)/inter-assay variability	For rat anti-Rituximab mAb NC %CV is 10.1 PC %CV is 12.0% End-point log_{10} titer for PC % CV is 4.0 for CPF 1.21	*Tested for 2 plates each day for 3 days by 2 analysts. Inter-assay precision was determined for 53 runs. The results are within the acceptance criteria of immunogenicity guidance recommended limit of %CV ≤ 20%.*
Selectivity	ST serum spiked at LPC (50 ng/mL): 70% lots tested have recovery between 75% and 125%. ST serum spiked at HPC (800 ng/mL): 80% lots tested have recovery between 75% and 125% RA serum spiked at LPC (50 ng/mL): 80% lots tested have recovery between 75% and 125% RA serum spiked at HPC (800 ng/mL): 100% lots tested have recovery between 75% and 125%	*10 samples of disease human serum (ST or RA)* *Adequate selectivity demonstrated for both disease serum samples*
Stability	Room temperature stability 24 hrs and 5 freeze/thaw cycles at -70 °C stability was assessed using PC 400 ng/mL sample.	*No significant changes in titer were observed for samples stored at room temperature for 24 hours; no significant changes in titer were observed for samples with 5 freezer/thaw cycles at -70°C*

Additional Reviewer Comments: *The ADA assay drug tolerance levels are somewhat lower than the serum drug levels observed in RA (mean drug concentration ~80µg/mL) and ST (mean serum drug concentration 70-170 µg/mL during dosing period) patient samples. The results suggest that the ADA assay may underestimating the ADA rate in patient samples during dosing period.*

2.3 Validation of Neutralizing Antibody Assay

The applicant developed a two-cell based Nab assays: one specific for PF-05280586 and one specific for the EU-MabThera. Both assays were developed and validated at (b) (4). Each assay established SCPF cut points for the RA patient population using 50 individual lots of RA patient serum and for ST population using 50 individual lots of ST patient serum. At least 30 individual lots of RA patient serum and 30 individual lots of ST patient serum were analyzed for confirmatory cut point assessments (immunodepletion). The Nab assay validation report of PF-05280586 Nab assay (B3287002 (b) (4) 15-1134)) and EU-MabThera specific Nab assay B3287004 ((b) (4) 15-11113) were provided in the submission. The NAb assay clinical data along with ADA clinical data were provided in integrated reports (b) (4) 15-1133 (clinical study B328001) and (b) (4) 15-1441 (clinical study B328006), respectively.

Reviewer's comment: *The complement-dependent cytotoxicity (CDC) has been proposed as one of the mechanisms for EU-MabThera, US-Rituxan, and PF-05280586 induced cell death. The assay format is appropriate for the NAb assay.*

2.3.1 Method Principle

Nab assay was developed using WIL2-S cells, which is a CD20-positive human B lymphoma cell line. The assay is based on competitive ligand binding assay format where neutralizing antibodies to PF-05280586 bind to the drug and interfere with CDC activity of WIL2-S cells. Briefly, serum samples confirmed as ADA positive, NCs, and PCs are pre-incubated with PF-05280586 in the presence of WIL2-S cells, and rabbit polyclonal complement is added to the cells. The viable WILS2 cells were measured using CellTiter-Glo® luminescent cell viability assay reagent to determining the number of viable cells based on quantitation of the ATP present, an indicator of metabolically active cells. The presence of a neutralizing antibody inhibits the function of PF-05280586 and results in a higher chemiluminescent signal.

2.3.2 Validation Exercises

The validations using healthy volunteer's serum were exploratory and not assessed in this review. The results of Nab assay validation (Report # (b) (4) 15-1134) and reviewer's assessment are provided in Table 2.2.

Table 2.2: Validation Results and Reviewer Assessment for Nab assays used in comparative PK study (B3281001) and comparative clinical study B3281006)

Validation Parameter	Validation Results	Reviewer Comment
Contract Research Org	(b) (4)	
Assay principle	NAbs inhibit the function of the drug, CDC is measured using chemiluminescent signal.	*The assay format reflects the main MOA of rituximab, therefore acceptable.*

Positive control (PC)	Rat anti-Rituximab monoclonal antibody. 200 µg/mL in 80% human serum	*Commercially available rat anti-Rituximab mAb is used (b) (4)). Immunogen is F(ab)$_2$ fragment of Rituximab.*
Other PCs	Rabbit Anti-Rituximab Polyclonal Antibody Mouse Anti-PF-05280586 Monoclonal Antibody	*same as ADA assay*
Matrix and NC	Pooled normal human serum	
MRD	1:100 (for both ST and RA samples)	
NAb assay cut- point (NACP) Normalized CP: mean S/N-3.09*SD	Plate CPF for screening 1.19 (based on 50 individual lots of RA patient serum) Plate CPF for screening 1.69 (based on 50 individual lots of ST patient serum)	*Serum samples are not exposed to PF-05280586. 5% false positive rate is used in the screening cut point determination. Data provided to support the statistical approach used for the Nab assay screening cut point determination.*
Confirmatory cut point	25.8% (use 0.1% FP rate based on 30 individual lots of RA patient serum) 25.8% (use 0.1% FP rate based on 30 individual lots of ST patient serum)	*The applicant developed a confirmatory assay for the NAb assay. It is based on immunodepleting using protein A/G.*
Sensitivity (mass-based)	69 µg/mL	*Assay sensitivity is low. Please see the reviewer's comment below.*

Additional Reviewer Comments:

The assay sensitivity of the anti-PF-05280586 NAb assay is 69 µg/mL. This assay sensitivity level is more than 10-fold less sensitive than the recommended level in the FDA Draft Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products. Therefore, the assay may be insufficiently sensitive to detect NAb that may inhibit biological activities of the product in vivo. In an IR (dated 01/09/2019) we requested the applicant to provide any available additional assay characterization or validation data to support the suitability of the NAb assays.

In response (02/01/2019), the applicant stated that Nab assay format was selected based on the originator product functional cell-based NAb assay using CDC mechanism of action. Nab assay method development studies include, optimization of NAb assay parameters such as evaluation of multiple cell lines, methods for quantitating viability, drug concentration response, MRD and PC selection (development data provided in the response). In addition, the applicant stated that clinical study B3281001 in RA subjects and B3281006 in lymphoma subjects, serum samples were tested for ADA response within the time frame for which a primary response would be expected to produce maximal titers. The presence of ADAs with neutralizing activity would have inhibited biological activities in vivo, and subjects would thus, not have demonstrated depletion of their CD19 positive B-cells (depletion of CD19 positive B-cells is a robust pharmacodynamic marker for the mechanism of action of rituximab). However, the CD19 positive B-cell counts in both studies (B3281001 and B3281006) showed greater than 95% depletion providing support that there was no inhibition of in vivo biological activity in both studies. The applicant concluded that based on comparable depletion of CD19 positive B-cell counts between B3281001 and B3281006, there is no impact of neutralizing ADAs on pharmacodynamic marker and its comparable between PF-05280586 and US-Rituxan.

In clinical study B3281006, 37 ADA positive subjects (18.9%) from subjects dosed with EU-MabThera and US-Rituxan, were screened in Nab assay specific for EU-MabThera. All were determined to be negative for Nab response. 38 ADA positive subjects (19.3%) from subjects dosed with PF- 05280586, were screened in Nab assay specific for PF-05280586. All of them were negative for Nab response.

Reviewer's Comment:
The development data demonstrated that there might be little room for sensitivity improvement for the current NAb assay. A redesign is needed to improve sensitivity. On the other hand, the applicant tried to use pharmacodynamic data to justify the NAb results. The inadequacy of NAb assay sensitivity was communicated with the entire review team, and the team will use a totality of data approach to reach a regulatory decision.

2.4 Information Requests Sent During Review

Midcycle Immunogenicity Information Request (1/09/2019):
1) You performed immunogenicity assessments in clinical serum samples using two product specific anti-drug antibody (ADA) assays: one specific for PF-05280586 and one specific for EU-approved MabThera. Patient samples in study B3281001 and B3281006 were tested using one of the product-specific assays based on the dosed product. It can be misleading to directly compare the ADA incidences (anti-PF-05280586, anti-Rituxan and anti-MabThera) derived from two different assays. FDA acknowledges that the serum samples confirmed positive for ADA to the dosed product were assessed for cross-reactivity using the alternative assay. However, your clinical study B3281001 and B3281006 data show low cross reactivity between the two assays (cross reactivity rates range from 50%-100%). In order to allow for a direct comparison of the ADA incidence and the magnitude of the immune response, test all immunogenicity samples from clinical study B3281001 and B3281006 using one of the following strategies. Provide a timeline for submitting the test results.
a. Test serum samples (incidence and titer) using both ADA assays.
b. Test serum samples (incidence and titer) using the ADA assay specific for PF-05280586. If this approach is selected, you should submit data demonstrating the assay responds similarly to PF-05280586, US-licensed Rituxan and EU-approved MabThera by competitive inhibition."

2) The assay sensitivity of the two neutralizing antibody (NAb) assays are 69 µg/mL and 63 µg/mL for the anti-PF-05280586 and anti-MabThera based assays, respectively (see validation reports B3287002 ((b) (4) 15-1134) and B3287004 ((b) (4) 15-11113)). This assay sensitivity level is more than 10 fold less sensitive than the recommended level in the FDA Draft Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products. Therefore, the assay may be insufficiently sensitive to detect NAb that may inhibit biological activities of the product in vivo. Provide any available additional assay characterization or validation data to support the suitability of the NAb assays. In addition, you may submit additional data and/or scientific justification to support the neutralizing immune response to PF-05280586 is similar to US-Rituxan."

Rukman De Silva

Digitally signed by Rukman De Silva
Date: 4/11/2019 08:38:23PM
GUID: 508da6db0002668622f9d73ac81c7d27

Haoheng Yan

Digitally signed by Haoheng Yan
Date: 4/12/2019 09:41:06AM
GUID: 54e4d29c0006b60003d1272740430bcc

Christopher Downey

Digitally signed by Christopher Downey
Date: 4/16/2019 04:46:41PM
GUID: 508da6d9000264ed71c49d80cfe4e31a

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

LABELS AND LABELING ASSESSMENT

Date of assessment:	May 31, 2019
Assessor:	Scott Dallas, RPh, Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Ksenija Grgac, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761103
Applicant:	Pfizer Ireland Pharmaceuticals
Submission Dates:	July 25, 2018; March 5, April 11, May 10, May 16, May 29 and May 30, 2019
Product:	RUXIENCE (rituximab-pvvr)
Dosage form:	injection
Strength and Container-Closure:	100 mg/10 mL (10 mg/mL) and 500 mg/50 mL (10 mg/mL) solution in a single-dose vial
Purpose of review:	The Applicant submitted a biologics license application seeking approval as a biosimilar product to the United States licensed product Rituxan (rituximab) injection for the same indications as the reference product. The Applicant indicates the proposed product has the same dosage form, route of administration, and dosing regimen as the reference product.
Recommendations:	The prescribing information, medication guide, container labels, and carton labeling are acceptable from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

DISCUSSION

We evaluated the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations (see Appendix B). In addition, we evaluated the proposed labels and labeling with regard to nomenclature and labeling recommendations found in FDA Guidances and the United States Pharmacopeia (USP).

CONCLUSION

The prescribing information and medication guide submitted on May 30, 2019 and the container labels and carton labeling submitted on May 10, 2019 were reviewed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Medication Guide (submitted on July 25, 2018)
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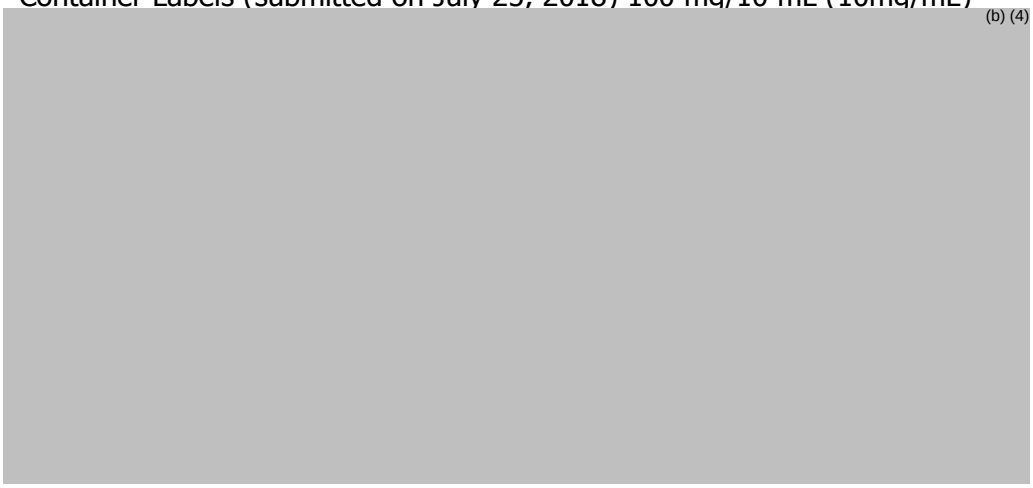
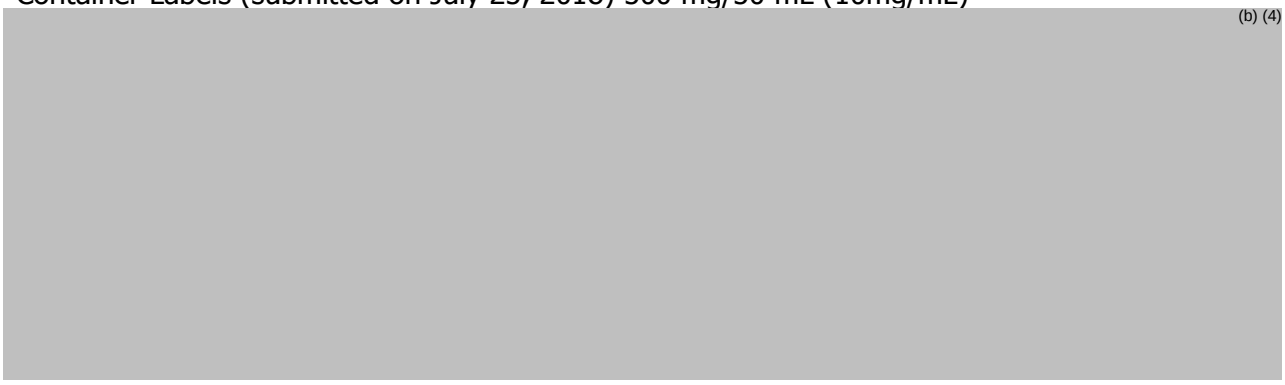
- Container Labels (submitted on July 25, 2018) 100 mg/10 mL (10mg/mL)

(b) (4)



- Container Labels (submitted on July 25, 2018) 500 mg/50 mL (10mg/mL)

(b) (4)



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

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation (vial)

Proper Name *(for container of a product capable of bearing a full label)*	**Acceptable**
21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Recommended labeling practices (placement of dosage form below the proper name):	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: If space permits, consider including the dosage formulation "Injection" to appear directly below the proper name "rituximab-pvvr" on the principal display panel**.** April 11, 2019: Pfizer relocated the dosage formulation to appear directly below the proper name. FDA response: Pfizer's revision is acceptable.	
Manufacturer name, address, and license number (*for container of a product capable of bearing a full label)*	**Acceptable**
21 CFR 610.60 (a)(2), 21 CFR 201, 21 CFR 201.1(a), 21 CFR 201.1(h)(5), 21 CFR 201.1(h)(6), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: If space permits, consider including the postal code "P43 X336". Please refer to 21 CFR 610.60(a)(2). April 11, 2019: Pfizer added the postal code to the label. FDA response: Pfizer's revision is acceptable.	

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Recommended labeling practices (using the following qualifying statement "Manufactured by:"):	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Please revise the abbreviation of United States to appear as U.S. with periods in the presentation of the U.S. license number statement.

April 11, 2019: Pfizer revised the abbreviation of United States to appear as U.S.

FDA response: Pfizer's revision is acceptable.

Lot number or other lot identification *(container capable of bearing a full label shall bear)*	**Acceptable**
21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Expiration date *(container capable of bearing a full label shall bear)*	**Acceptable**
21 CFR 610.60, 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Recommended labeling practices (the expiration date appears on all aspects of the package):	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Product Strength	**Acceptable**
21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Recommended labeling practices (expression of strength for injectable drugs): Reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176 USP General Chapters: <7> Labeling	✓ Yes ☐ No ☐ N/A

Multiple dose containers *(recommended individual dose)*	**Acceptable**
21 CFR 610.60, 21 CFR 201.55	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Statement: "Rx only"	**Acceptable**
21 CFR 610.60, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Recommended labeling practices: To Applicant: Consider debolding the "Rx Only" statement on the 100 mg/10 mL vial. April 11, 2019: Pfizer responded that the Rx only statement has been left in bold text, as this statement is significant for product dispensing, usage, and safety. FDA response: FDA does not agree with Pfizer's response, but the request was to align the label with recommended labeling practices. The RX only statement on the revised label does not appear to be misleading or interfere with the prominence of important information. Thus, the presentation of the statement is acceptable.	✓ Yes ☐ No ☐ N/A
Medication Guide	**Acceptable**
21 CFR 610.60, 21 CFR 208.24	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: The Medication Guide statement shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided. Your proposed statement does not appear to state how the Medication Guide is provided. Consider if the statement "Provide enclosed Medication Guide to each patient" is appropriate and satisfies the regulation 21 CFR 208.24(d). Please revise accordingly. April 11, 2019: Pfizer responded that the carton labeling includes the text "Always dispense with Medication Guide" which is Pfizer's standard statement when product has a medication guide. Therefore, no changes were made to the carton labeling. FDA response: OBP reviewed the labeling for a few of Pfizer's products which included Zoloft, Neurontin, Celebrex, Xanax, Xeljanz. All these products contain the statement "Always dispense with Medication Guide". The product Chantix presents the statement "Always dispense with the enclosed Medication Guide", which would comply with the reg. However, Pfizer's standard statement does not satisfy 21 CFR 208.24(d). May 6, 2019: To Applicant: We continue to reiterate that the Medication Guide Statement does not indicate how the authorized dispenser shall provide the Medication Guide to the patient. Please revise the Medication Guide Statement to include how the Medication Guide is provided (e.g., accompanied, enclosed, or provided separately) in accordance with 21 CFR	

208.24(d). Consider if the statement "Provide enclosed Medication Guide to each patient" is appropriate.

May 10, 2019: The applicant revised the statement to read "Always Dispense Enclosed Medication Guide to each Patient"

FDA response: The applicant's response is acceptable.

No Package for container	**Acceptable**
21 CFR 610.60	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

No container label	**Acceptable**
21 CFR 610.60	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices: *United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals)*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Per 3.2.P.7.3. Seal The crimp seal is a 20 mm flip-off design constructed of aluminum with a polypropylene tamper-evident flip-off cap that has no embossing.

Visual inspection *(for vials only)*	**Acceptable**
21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
C=2 x 3.14 x 25 cm C=157 cm the 100 mg label is 68 cm long so there is room for visual inspection.
C= 2 x 3.14 x 42 cm C= 263.76 cm the 500 mg label is 120 cm long so there is room for visual inspection.

NDC numbers	**Acceptable**
21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Route of administration	**Acceptable**
21 CFR 201.5, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:	
Recommended labeling practices: The route of administration statement appears after the strength statement on the principal display panel. **Comment/Recommendation:**	✓ Yes ☐ No ☐ N/A
Preparation instructions	**Acceptable**
21 CFR 201.5 **Comment/Recommendation:**	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430) **Comment/Recommendation:**	☐ Yes ☐ No ☒ N/A
Package type term	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. USP chapter <659> Packaging and Storage Requirements **Comment/Recommendation:**	✓ Yes ☐ No ☐ N/A
Misleading statements	**Acceptable**
21 CFR 201.6 **Comment/Recommendation:**	☐ Yes ☐ No ☒ N/A
Prominence of required label statements	**Acceptable**
21 CFR 201.15	✓ Yes ☐ No ☐ N/A
Spanish-language (Drugs)	**Acceptable**
21 CFR 201.16	☐ Yes ☐ No ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6	**Acceptable**
21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame	**Acceptable**
21 CFR 201.21	☐ Yes ☐ No ☒ N/A
Sulfites; required warning statements	**Acceptable**
21 CFR 201.22	☐ Yes ☐ No ☒ N/A
Bar code label requirements	**Acceptable**
21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Recommended labeling practices: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)* **Comment/Recommendation:**	✓ Yes ☐ No ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)	**Acceptable**
21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
Net quantity	**Acceptable**
21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Recommended labeling practices: *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463)* *Guidance: Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Please ensure the statements "One Single-Dose Vial" and "Discard Unused Portion" appear in a stacked format (see below) without a hyphen appearing between the words "Vial" and "Discard".

One Single-Dose Vial
Discard Unused Portion

April 11, 2019: Pfizer revised the presentation of the statements on the label.

FDA response: Pfizer's revisions are acceptable.

Usual dosage statement	**Acceptable**
21 CFR 201.55, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A

Inactive ingredients	**Acceptable**
21 CFR 201.100	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:
Partial label

Recommended labeling practices: USP General Chapters <1091> Labeling of Inactive Ingredients	☐ Yes ☐ No ☒ N/A

Storage requirements	**Acceptable**
Recommended labeling practices: *USP General Chapters <7> Labeling* *USP General Chapters <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The storage statement of the reference product reads "Protect vials from direct sunlight". Dr. 's Damdinsuren and Grgac confirmed the DP should be protect from direct sunlight.

To Applicant: Please revise the storage statement from "Protect vials from light" to "Protect vials from direct sunlight."

April 11, 2019: Pfizer revised the light reference in the storage statement to read "direct sunlight".

FDA response: Pfizer's revision is acceptable.

Dispensing container	**Acceptable**
21 CFR 201.100	☐ Yes ☐ No ☒ N/A

Package[5] Label Evaluation (Carton)

Proper name	Acceptable
21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To Applicant: If space permits, consider including the dosage formulation "Injection" to appear below the proper name on the principal display panel.

Ruxience
(rituximab-pvvr)
Injection
Expression of strength

April 11, 2019: Pfizer relocated the dosage formulation to appear directly below the proper name.

FDA response: Pfizer's revision is acceptable.

Manufacturer name, address, and license number	Acceptable
21 CFR 610.61, 21 CFR 201.1(a), 21 CFR 201.1(h)(5), 21 CFR 201.1(h)(6), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Recommended labeling practices: OPQ-OBP-RP-014	✓ Yes ☐ No ☒ N/A

Comment/Recommendation:

To Applicant: Please include the postal code "P43 X336" for the manufacturer's address in Ireland. If space permits, please include the street address of the manufacturer. Please refer to 21CFR 610.61(b).
To Applicant: Please revise the abbreviation of United States to appear as U.S. with periods in the presentation of the U.S. license number statement.

April 11, 2019: Pfizer added the postal code and revised the abbreviation of United States to appear as U.S.

FDA response: Pfizer's revisions are acceptable.

[5] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Lot number or other lot identification	**Acceptable**
21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Expiration date	**Acceptable**
21 CFR 610.61, 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Preservative	**Acceptable**
21 CFR 610.61	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Consider relocating the "NO PRESERVATIVES" statement to appear on the side panel directly below the "No U.S. standard of potency" statement. Also consider only capitalizing the first letter in each word to appear as "No Preservative"

April 11, 2019: Pfizer relocated the "No Preservative" statement to the side panel below the Usual Dosage statement and only capitalized the first letter of each word.

FDA response: Pfizer's revisions are acceptable.

Number of containers	**Acceptable**
21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Strength/volume	**Acceptable**
21 CFR 610.61, 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: *Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176* *USP General Chapters: <7> Labeling* **Comment/Recommendation:**	✓ Yes ☐ No ☐ N/A
Storage temperature/requirements	**Acceptable**
21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: USP General Chapters: <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To Applicant: Please revise the storage information to read "Store vials refrigerated at 2°C to 8°C (36°F to 46°F) in the carton to protect from direct sunlight. Do not freeze or shake."

April 11, 2019: Pfizer revised the storage statement as requested.

FDA response: Pfizer's revisions are acceptable.

Handling: "Do Not Shake", "Do not Freeze" or equivalent	**Acceptable**
21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Multiple dose containers (recommended individual dose)	**Acceptable**
21 CFR 610.61	☐ Yes ☐ No ☒ N/A
Route of administration	**Acceptable**
21 CFR 610.61, 21 CFR 201.5, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement recommended locations):	✓ Yes ☐ No ☐ N/A
Known sensitizing substances	**Acceptable**
21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Inactive ingredients	**Acceptable**
21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Recommended labeling practices: *USP General Chapters <1091> Labeling of Inactive Ingredients* *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To Applicant: Please revise your "Each vial contains …." Statement to read "Each mL of solution contains 10 mg rituximab-xxxx, 0.056 mg of edetate disodium dihydrate, 1.2 mg of L histidine, 2.57 mg of L histidine hydrochloride monohydrate, 0.2 mg of polysorbate 80, 85 mg of sucrose, and Water for Injection, USP."

April 11, 2019: Pfizer revised the inactive ingredient statement as requested.

FDA response: Pfizer's revisions are acceptable**.**

Source of the product	**Acceptable**
21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	

Minimum potency of product	**Acceptable**
21 CFR 610.61	✓ Yes ☐ No ☐ N/A

Rx only	**Acceptable**
21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices:	✓ Yes ☐ No ☐ N/A

Divided manufacturing	**Acceptable**
21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Distributor	**Acceptable**
21 CFR 610.64 (Name and address of distributor)	✓ Yes ☐ No ☐ N/A

Bar code	**Acceptable**
21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011*	☐ Yes ☐ No ☒ N/A

Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)	
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)	**Acceptable**
21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
NDC numbers	**Acceptable**
21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A
Preparation instructions	**Acceptable**
21 CFR 201.5	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430) USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A
Package type term	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. USP chapter <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A
Misleading statements	**Acceptable**
21 CFR 201.6	☐ Yes ☐ No ☒ N/A
Prominence of required label statements	**Acceptable**
21 CFR 201.15	✓ Yes ☐ No ☐ N/A
Spanish-language (Drugs)	**Acceptable**
21 CFR 201.16	☐ Yes ☐ No ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6	**Acceptable**

21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Phenylalanine as a component of aspartame	**Acceptable**
21 CFR 201.21	☐ Yes ☐ No ☒ N/A
Sulfites; required warning statements	**Acceptable**
21 CFR 201.22	☐ Yes ☐ No ☒ N/A
Net quantity	**Acceptable**
21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463)*	✓ Yes ☐ No ☐ N/A
Usual dosage statement	**Acceptable**
21 CFR 201.55, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Dispensing container	**Acceptable**
21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Medication Guide	**Acceptable**
21 CFR 610.60, 21 CFR 208.24	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The Medication Guide statement shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided. Your proposed statement does not appear to state how the Medication Guide is provided. Consider if the statement "Provide enclosed Medication Guide to each patient" is appropriate and satisfies the regulation 21 CFR 208.24(d). Also consider relocating the statement from the top of the principal display panel to the bottom of the panel.

April 11, 2019: Pfizer responded that the carton labeling includes the text "Always dispense with Medication Guide" which is Pfizer's standard statement when product has a medication guide. Therefore, no changes were made to the carton labeling.

FDA response: OBP reviewed the labeling for a few of Pfizer's products which included Zoloft, Neurontin, Celebrex, Xanax, Xeljanz. All these products contain the statement "Always dispense with Medication Guide". The product Chantix presents the statement "Always dispense with the enclosed Medication Guide", which would comply with the reg. However, Pfizer's standard statement does not statisfy 21 CFR 208.24(d).

May 6, 2019: To Applicant: We continue to reiterate that the Medication Guide Statement does not indicate how the authorized dispenser shall provide the Medication Guide to the patient. Please revise the Medication Guide Statement to include how the Medication Guide is provided (e.g., accompanied, enclosed, or provided separately) in accordance with 21 CFR 208.24(d). Consider if the statement "Provide enclosed Medication Guide to each patient" is appropriate.

May 10, 2019: The applicant revised the statement to read "Always Dispense Enclosed Medication Guide to each Patient"

FDA response: The applicant's response is acceptable.

Other	**Acceptable**
	☐ Yes ☐ No ☐ N/A

Comment/Recommendation:

May 17, 2019: To Applicant: The Country of Origin statement on the carton labeling identifies the country Germany (MADE IN GERMANY). Please verify your Country of Origin statement complies with Code of Federal Regulations, Title 19, Part 134 - Country of Origin Marking. If needed, please submit revised labeling.

May 29, 2019: Pfizer's response: Pfizer confirms the Country of Origin statement listed on the carton labeling for rituximab-pvvr is Germany and that this statement complies with Code of Federal Regulations, Title 19, Part 134 - Country of Origin Marking. Therefore, no revision to labeling for this comment is needed.

FDA Response: The applicant's response is acceptable.

Prescribing Information and Patient Labeling Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices: *Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018)*	✓ Yes ☐ No ☐ N/A
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices: USP nomenclature for diluents and intravenous solutions	✓ Yes ☐ No ☐ N/A
DOSAGE FORMS AND STRENGTHS	**Acceptable**
21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: *Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)* *USP chapter <659> Packaging and Storage Requirements* *Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A
Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
21 CFR 201.57(c)(3)(iv)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Dr. Damdinsuren confirmed the acceptability of the diluents 0.9% sodium chloride injection and 5% dextrose injection and the final concentration of 1 mg/mL to 4 mg/mL.

Dr. Damdinsuren confirmed the diluted rituximab solution is stable under refrigeration for 24 hours, and microbiology indicated this storage condition is also acceptable.

Micro does not have data to support the (b) (4) storage. Thus, (b) (4) will be deleted. The wording will be changed to read: "Complete administration within 8 hours from removal from refrigeration."

No additional handling statements will be associated with the diluted solution at this time.

Dr. Damdinsuren confirmed that there was insufficient data to support the statement that there were "(b) (4)". The reference to the (b) (4) will be deleted from the label.

May 10, 2019: Pfizer revised the storage information for the diluted solution to read: Diluted RUXIENCE solutions for infusion may be stored at 2°C to 8°C (36°F to 46°F) for 24 hours. Complete administration within 8 hours from removal from refrigeration. No incompatibilities between RUXIENCE and polyvinylchloride bags have been observed.

FDA response: Pfizer's revisions of the storage statements for the diluted solutions are acceptable.

Recommended labeling practices: *USP nomenclature for diluents and intravenous solutions*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To Applicant: Please revise 5% Dextrose (b) (4) to read 5% Dextrose Injection.

April 11, 2019: Pfizer revised the diluent to read 5% Dextrose Injection, USP.

FDA Response: Pfizer's revision is acceptable.

3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Dr. Damdinsuren confirmed the identifying characteristics "clear to slightly opalescent, colorless to pale brownish yellow" are acceptable.

Recommended labeling practices: *Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)* *USP General Chapters <659>, USP General Chapters <7>*	✓ Yes ☐ No ☐ N/A

11 DESCRIPTION	**Acceptable**
21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Please confirm the molecular weight value.
To Applicant: The proprietary name was deleted from the first 2 paragraphs because this information discusses the drug substance.

April 11, 2019: Pfizer confirmed the molecular weight and deleted the proprietary name from the first two paragraphs.

FDA Response: Pfizer's revisions are acceptable.

Dr. Damdinsuren confirmed the product is sterile, preservative-free, that the quantitative and qualitative info is correct, and there is no U.S. standard of potency.

Recommended labeling practices: *USP General Chapters <1091>, USP General Chapters <7>*	✓ Yes ☐ No ☐ N/A

16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To Applicant: Revised to include the identifying characteristics per 21 CFR 201.57(c)(17).

April 11, 2019: Pfizer revised the first paragraph to include the identifying characteristics.

FDA Response: Pfizer's revisions are acceptable.

Dr. Damdinsuren confirmed the acceptability of the storage and handling conditions for the drug product, which are refrigerate, protect from direct sunlight, do not shake and do not freeze. The overfill is acceptable for the 10 mL and 50 mL vial. Also, no sensitizing material (such as latex) was associated with the product.

Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	☐ Yes ☐ No ☒ N/A

MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.100(e), 21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: *21 CFR 610.61 (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To Applicant: Please include the postal code "P43 X336" for the manufacturer's address in Ireland. If space permits, please include the street address of the manufacturer. Please refer to 21CFR 610.61(b).

April 11, 2019: Pfizer added the postal code to the manufacturer's address.

FDA response: Pfizer's revision is acceptable.

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A
Recommended Labeling Practice: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	☐ Yes ☐ No ☒ N/A
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Please include the suffix to the active ingredient.

April 11, 2019: Pfizer's added a placeholder for the suffix

May 10, 2019: Pfizer included the suffix "pvvr" to the active ingredient.

FDA response: Pfizer's revision is acceptable**.**

MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11, 21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To Applicant: Please include the postal code "P43 X336" for the manufacturer's address in Ireland. If space permits, please include the street address of the manufacturer. Please refer to 21CFR 610.61(b).

April 11, 2019: Pfizer added the postal code to the manufacturer's address.

FDA response: Pfizer's revision is acceptable.

21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
OBP Labeling: To Applicant: Revised the abbreviation of United States to appear as "U.S."

April 11, 2019: Pfizer implemented the requested revision.

FDA Response: Pfizer's revision is acceptable.

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information and Medication Guide (submitted on May 30, 2019)
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(b) (4)

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

Scott Dallas

Digitally signed by Scott Dallas
Date: 5/31/2019 12:33:51PM
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Ksenija Grgac

Digitally signed by Ksenija Grgac
Date: 5/31/2019 12:38:48PM
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