CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761072Orig1s000

PRODUCT QUALITY REVIEW(S)

LABELS AND LABELING REVIEW

Date:	December 13, 2017
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Nilou Sarah Arden, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research II
Application:	BLA 761072
Product:	Ixifi (infliximab-qbtx)
Applicant:	Pfizer Ireland Pharmaceuticals
Submission Date(s):	February 13, 2017, November 15, 2017, December 8, 2017, and December 13, 2017

I) RECOMMENDATION

The container labels (submitted November 15, 2017) and carton labeling (submitted December 13, 2017), and Prescribing Information/Medication Guide (submitted December 8, 2017) for Ixifi (infliximab-qbtx) for Injection 100 mg/vial single-dose vial for intravenous infusion are acceptable from a quality perspective.

II) BACKGROUND AND SUMMARY DESCRIPTION

The Applicant, Pfizer Ireland Pharmaceuticals, submitted BLA 761072 Ixifi (infliximab-qbtx) for Injection 100 mg/vial single-dose vial for intravenous infusion on February 13, 2017 as a proposed biosimilar to US-licensed Remicade.

Table 1 presents relevant product information for Ixifi (infliximab-qbtx) that the Applicant submitted on February 13, 2017, and for U.S. licensed Remicade (BLA 103772).

Table 2. Relevant Product Information for Ixifi and U.S. Licensed Remicade

Product Name	**Biosimilar Product**	**Reference Product**
Proprietary Name:	Ixifi	Remicade
Nonproprietary Name:	infliximab-qbtx	infliximab
Dosage Form:	For Injection	
Strength and Container-Closure:	100 mg/vial single-dose vial	
Route of Administration:	for intravenous infusion	
Storage and Handling:	Refrigerate at 2ºC to 8ºC (36ºF to 46ºF). Unopened vials may also be stored at temperatures up to a maximum of 30°C (86°F) for a single period of up to 6 months but not exceeding the original expiration date. The new expiration date must be written on the carton. Upon removal	

	from refrigerated storage, vials cannot be returned to refrigerated storage	
Indication Dose and Frequency:	**Crohn's Disease: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response.** **Pediatric Crohn's Disease: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.** **Ulcerative Colitis: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.** **Rheumatoid Arthritis: In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks.** **Ankylosing Spondylitis: 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.** **Psoriatic Arthritis and Plaque Psoriasis: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.**	**Crohn's Disease: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response.** **Pediatric Crohn's Disease: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.** **Ulcerative Colitis: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.** **Pediatric Ulcerative Colitis: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks** **Rheumatoid Arthritis: In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks.** **Ankylosing Spondylitis: 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.** **Psoriatic Arthritis and Plaque Psoriasis: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.**

III) MATERIALS REVIEWED

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

Table 1: Materials Considered for this Label and Labeling Review

Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Other	B
Relevant Code of Federal Regulations and CDER Labeling Best Practices	C

Acceptable Labels and Labeling	D

n/a = not applicable for this review

IV) DISCUSSION

The proposed labels and labeling were evaluated for compliance with the applicable requirements in the Code of Federal Regulations (CFR), USP standards, and CDER Labeling Best Practices (see Appendix C).

V) CONCLUSION

The prescribing information/medication guide, container labels, and carton labeling for Ixifi (infliximab-qbtx) for Injection 100 mg/vial single-dose vial for intravenous infusion were reviewed and found to comply with relevant regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100 and United States Pharmacopeia (USP). The container labels (submitted November 15, 2017) and carton labeling (submitted December 13, 2017), and Prescribing Information/Medication Guide (submitted December 8, 2017) are acceptable (see Appendix D) from a quality perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information/Medication Guide submitted 17May17
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Container Labels submitted 13Feb17

Carton Labeling submitted 13Feb17

Appendix B: Other

Appendix C: Relevant Code of Federal Regulations and CDER Best Labeling Practices

Table 2: Label[1,2] and Labeling[3] Standards

[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.

Container[4] Label Evaluation

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
Proper Name 21 CFR 610.60 21 CFR 201.50 21 CFR 201.10			x	considered a partial label
Manufacturer name, address, and license number 21 CFR 610.60				considered a partial label
Lot number or other lot identification 21 CFR 610.60 21 CFR 201.18 21 CFR 201.100				considered a partial label
Expiration date 21 CFR 610.60 21 CFR 201.17				considered a partial label
Multiple dose containers (recommended individual dose) 21 CFR 610.60			x	
Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100	x			
Medication Guide 21 CFR 610.60 21 CFR 208.24	x			
No Package for container 21 CFR 610.60			x	
Partial label 21 CFR 610.60 21 CFR 201.10		x		Ensure the licensed manufacturer appears as the listed Applicant on the submitted Form FDA 356h per 21CFR 610.60 (a)(2). Revise from "Mfg. by Pfizer Ireland Pharmaceuticals" to read "Mfd. By: (b) (4) US License No. xxx"

[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.

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
				Pfizer's response: The Applicant will submit an amended 356h form to align with the "Pfizer Ireland" details submitted in the IXIFI vial container, carton, and USPI labelling. *The Applicant submitted revised 356h form on November 17, 2017 as proposed. We find the revision acceptable.* Remove the word "(b) (4) from the US license number statement. Ensure that the license number appears underneath the manufacturer statement. *The Applicant revised as requested*
No container label 21 CFR 610.60			x	
Ferrule and cap overseal		x		Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <1> Injections, Packaging, Labeling on Ferrules and Cap Overseals. *The Applicant confirmed*
Visual inspection 21 CFR 610.60		x		Confirm there is sufficient area on the container to allow for visual inspection when the label is affixed to the vial and indicate where the visual area of inspection is located per 21 CFR 610.60(e). *The Applicant confirmed*

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
				
NDC numbers 21 CFR 201.2 21 CFR 207.35	x			Although not required for partial labels per 21 CFR 610.60(c).
Route of administration 21 CFR 201.5 21 CFR 201.100	x			
Preparation instructions 21 CFR 201.5			x	
Package type term 21 CFR 201.5	x			
Drugs Misleading statements 21 CFR 201.6			x	
Strength 21 CFR 201.10 21CFR 201.100	x			
Drugs Prominence of required label statements 21 CFR 201.15	x			
Bar code label requirements 21 CFR 201.25 21CFR 610.67	x			
Net quantity 21 CFR 201.51	x			

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
Usual dosage statement 21 CFR 201.55 21 CFR 201.100		x		Revise the usual statement from [redacted] (b) (4) " to read "Dose: See package insert." *The Applicant revised as requested*
Inactive ingredients 21 CFR 201.100			x	container label lacks space, then this information must appear on the carton, PI, and IFU (if applicable).
Storage requirements	x			
Dispensing container 21 CFR 201.100			x	

Package Label[5] Evaluation

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
Proper name 21 CFR 610.61 21 CFR 201.50 21 CFR 201.10	x			For biosimilars, ensure the nonproprietary name contains the suffix as determined by DMEPA.
Manufacturer name, address, and license number 21CFR 610.61		x		Ensure the licensed manufacturer appears as the listed Applicant on the submitted Form FDA 356h per 21 CFR 610.61(b). Revise from "Manufactured by Pfizer Ireland Pharmaceuticals Ringaskiddy, Co. Cork, Ireland" to read "Manufactured by: [redacted] (b) (4) US License No. xxx" *Pfizer's response: The Applicant will submit an amended 356h form to align with the "Pfizer Ireland" details submitted in the IXIFI vial container, carton, and USPI labelling.* *The Applicant submitted revised 356h form on November 17, 2017 as proposed. We find the revision 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.

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				Remove the word (b) (4)" from the US license number statement. Ensure that the license number appears underneath the manufacturer statement. *The Applicant revised as requested* The Applicant may include the Country of Origin per U.S. Customs Border and Protection regulations 19 CFR 134.11. Revise the statement from "Made in Belgium" to appear as: "Product of Belgium" *Country of Origin (CoO) regulations (19 CFR 134.11 and 19 CFR 134.22) enforced by U.S. Customs and Border Protection (CBP), which require every product imported into the United States to display an accurate CoO. In line with these regulations, as well as CBP's Informed Compliance Publication (https://www.cbp.gov/trade/rulings/informed-compliancepublications/marking-country-origin-us-imports), Pfizer's established policies and procedures (a) set forth "Made in [applicable country]" as the language to be displayed on all of its products; and (b) require the CoO statement to be uniform across all products. Recognizing the applicable CFR and United States Code (19 USC 1304) sections allow for flexibility in the wording of such a CoO, we acknowledge that both "Product of Belgium" and "Made in Belgium" are appropriate terms. In order, however, for Pfizer to follow its current labeling practices and maintain consistency with its exiting marketed product line, we respectfully request leeway to maintain the current CoO language ("Made in Belgium") for the IXIFI USPI container and vial labeling. Does the Agency have any comments on this proposal?* *We find the Applicant's proposal acceptable*
Lot number or other lot identification 21 CFR 610.61	x			
Expiration date 21 CFR 610.61 21 CFR 201.17	x			

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
Preservative 21 CFR 610.61	x			
Number of containers 21 CFR 610.61	x			
Strength/volume 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100	x			
Storage temperature 21 CFR 610.61	x			
Handling: "Shake Well", "Do not Freeze" or equivalent 21 CFR 610.61	x			
Multiple dose containers (recommended individual dose) 21 CFR 610.61			x	single dose vial
Route of administration 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	x			
Known sensitizing substances 21CFR 610.61			x	
Antibiotics added during manufacturing 21 CFR 610.61			x	
Inactive ingredients 21 CFR 610.61 21 CFR 201.100		x		Revise the list of ingredients by placing the inactive ingredients in alphabetical order per USP General Chapters: <1091> (Labeling of Inactive Ingredients) followed by their quantitative information using the metric system of weight in parenthesis (xx mg) except for those inactive ingredients added to adjust pH or

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				tonicity or water for injection. *The Applicant revised as requested*
Adjuvant, if present 21 CFR 610.61			x	
Source of the product 21 CFR 610.61			x	
Identity of each microorganism used in manufacturing 21 CFR 610.61			x	
Minimum potency of product 21 CFR 610.61	x			
Rx only 21CFR 610.61 21 CFR 201.100	x			
Divided manufacturing 21 CFR 610.63			x	
Distributor 21 CFR 610.64	x			
Bar code 21 CFR 610.67 21 CFR 201.25	x			
NDC numbers 21 CFR 201.2 21 CFR 207.35	x			
Preparation instructions 21 CFR 201.5	x			
Package type term 21 CFR 201.5	x			
Drugs Misleading statements 21 CFR 201.6			x	
Drugs Prominence of required label	x			

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
statements 21 CFR 201.15				
Net quantity 21 CFR 201.51	x			
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	x			
Dispensing container 21 CFR 201.100			x	
Medication Guide 21 CFR 610.60 21 CFR 208.24	x			

Prescribing Information and Patient Labeling Evaluation

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
PRESCRIBING INFORMATION				
Highlights of prescribing information				
PRODUCT TITLE 21 CFR 201.57(a)(2)	x			
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	x			
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)		x		Added the dosage form per 21 CFR 201.57(a)(8) *The Applicant revised as requested*
Full Prescribing Information				
DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)		x		We added the final concentration of the reconstituted solution as this is important information for the healthcare provider per 21 CFR 201.57(c)(3). *The Applicant revised as requested* We revised the identifying characteristics per your response to the November 1, 2017 IR (changed to light brown)

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				The Applicant revised as requested
3 DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(c)(4)		x		Added dosage form per 21 CFR 201.57(c)(4) *The Applicant revised as requested*
6.2 IMMUNOGENICITY	x			
11 DESCRIPTION 21 CFR 201.57(c)(12)		x		Added dosage form per 21 CFR 201.57(c)(12) *The Applicant revised as requested* List the inactive ingredients in alphabetical order (see USP Chapter <1091>) *The Applicant revised as requested*
16 HOW SUPPLIED/ STORAGE AND HANDLING 21 CFR 201.57(c)(17)	x			
MANUFACTURER INFORMATION 21 CFR 610.61, 21 CFR 610.64				Ensure the licensed manufacturer appears as the listed Applicant on the submitted Form FDA 356h per 21 CFR 610.61(b). Add "Manufactured by: (b) (4). (b) (4) US License No. xxx" *Pfizer's response: The Applicant will submit an amended 356h form to align with the "Pfizer Ireland" details submitted in the IXIFI vial container, carton, and USPI labelling.* *The Applicant submitted revised 356h form on November 17, 2017 as proposed. We find the revision acceptable.*
MEDICATION GUIDE, INSTRUCTIONS FOR USE, AND PATIENT INFORMATION				
TITLE (NAMES AND DOSAGE FORM)	x			
STORAGE AND			x	

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
HANDLING				
INGREDIENTS		x		List inactive ingredients in alphabetical order per USP <1091> Labeling of Inactive Ingredients. *The Applicant revised as requested*
MANUFACTURER INFORMATION 21 CFR 610.61, 21 CFR 610.64				Ensure the licensed manufacturer appears as the listed Applicant on the submitted Form FDA 356h per 21 CFR 610.61(b). Revise from "Manufactured by Pfizer Ireland Pharmaceuticals Ringaskiddy, Co. Cork, Ireland" to read "Manufactured by: (b) (4) US License No. xxx" Ensure that the license number appears underneath the manufacturer statement. *Pfizer's response: The Applicant will submit an amended 356h form to align with the "Pfizer Ireland" details submitted in the IXIFI vial container, carton, and USPI labelling.* *The Applicant submitted revised 356h form on November 17, 2017 as proposed. We find the revision acceptable.*

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N. Sarah Arden

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U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Date: 20 October 2017

To: Administrative File, **STN 761072/0**

From: Kathleen R. Jones, Ph.D., Primary Reviewer, CDER/OPQ/OPF/DMA/BIV

Through: Patricia Hughes, Ph.D. Actg Branch Chief, CDER/OPQ/OPF/DMA/BIV

Subject: New 351 (k) Biologic License Application (BLA)

Applicant: Pfizer, Inc.

US License: 2060

Product: PF-06438179, a proposed biosimilar to Remicade® (infliximab)

Dosage: Lyophilized 100 mg per15 mL vial for intravenous infusion

Indication: For treatment of Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, rheumatoid arthritis (in combination with methotrexate), ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis

Facilities: (b) (4)

FEI: (b) (4)

Receipt Date: 13 February 2017

Action date: 13 December 2017

Recommendation for Approvability: The recommendation for approval of the drug substance part of BLA 761072/0 from a microbial control and microbiology product quality perspective is pending until additional information on in-process bioburden sampling points and post market commitments (PMCs) are submitted, reviewed and the BLA is appropriately amended.

Post-Marketing Commitments:

1. *Reassess and tighten all in-process endotoxin acceptance criteria based on process capability after 20-30 data points are obtained.*
2. *Conduct bioburden method qualification using in-process samples from two additional batches of PF-06438179.*

Review Addendums:

The following information will be reviewed in an addendum:

1.) Verify that the BLA was updated with information submitted via email dated 08 November 2017 in response to an information request dated 06 November 2017.
2.) (b) (4)
3.) (b) (4)
.
4.) Update Module 3 of the BLA as appropriate.

Review Summary

Pfizer, Inc. has submitted 351 (k) BLA 761072 to obtain approval of PF-06438179. PF-06438179 is a chimeric human-murine immunoglobulin (IgG) 1 kappa monoclonal antibody that is a proposed biosimilar to Remicade® (infliximab). PF-06438179 proports to binds soluble and membrane-bound forms of TNFα. BLA 761072 was submitted in eCTD format on 13 February 2017. This review contains the assessment of the microbial quality attributes of the PF-06438179 bulk drug substance from a microbiological quality perspective. For review of drug product aspects of the application, please see the review by Dr. Aimee Cunningham.

Drug Substance and Drug Product Quality Microbiology Information Reviewed

Document Type	eCTD Sequence	Date	Modifications
Original BLA	0001	13 Feb 2017	Original BLA
Response to Information Request #1	0019	02 Oct 2017	Sections 3.2.S.2.2, 3.2.S.2.4, 3.2.S.25, 3.2.S.2.6, and 3.2.S.4.3
Response to Information Request #2	0023	30 Oct 2017	Sections 3.2S.2.2, 3.2.S.2.5, 3.2.S.2.6
Response to Information Request #3	Email copy, hasn't been submitted via eCTD		

A summary of the responses to FDA Information Requests are provided at the end of this review memo.

Product Quality Microbiology Assessment: Drug Substance

MODULE 3.2.S DRUG SUBSTANCE

S.1 General Information

PF-06438179 is a chimeric human-murine IgG1 kappa monoclonal antibody produced in (b) (4) cells. PF-06438179 is proposed to bind to human TNF in a dose-dependent manner, thereby neutralizing its effects.

The description is satisfactory.

S.2 Manufacture

S.2.1 Manufacturer(s)

The following facilities are used for the manufacture, release testing, and stability testing of PF-06438179 drug substance.

Table 3.2.S.2.1-1. Sites and Responsibilities for Manufacture and Testing of PF-0643817. This table is provided in the submission.

Site	Responsibility
*Wyeth BioPharma Division of Wyeth Pharmaceuticals Inc. One Burtt Road Andover, MA 01810 USA	Cell bank manufacture and storage
(b) (4)	Manufacture, in-process control testing, release testing, drug substance storage, cell bank storage
Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin, Dublin 22 Ireland	Cell bank storage, release and stability testing
(b) (4)	Cell-based assay for release and stability testing

*Wyeth is a wholly owned subsidiary of Pfizer Inc.

The description is satisfactory.

S.2.2 Description of Manufacturing Process and Process Controls

(b) (4)

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Patricia Hughes Troost

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U.S. FOOD & DRUG ADMINISTRATION

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Date: 01 December 2017

To: Administrative File, **STN 761072/0**

From: Kathleen R. Jones, Ph.D., Primary Reviewer, CDER/OPQ/OPF/DMA/BIV

Through: Patricia Hughes, Ph.D. Actg Branch Chief, CDER/OPQ/OPF/DMA/BIV

Subject: Amended 351 (k) Biologic License Application (BLA)

Applicant: Pfizer, Inc.

US License: 2060

Product: PF-06438179, a proposed biosimilar to Remicade® (infliximab)

Dosage: Lyophilized 100 mg per15 mL vial for intravenous infusion

Indication: For treatment of Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, rheumatoid arthritis (in combination with methotrexate), ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis

Facilities: (b) (4)

FEI: (b) (4)

Receipt Date: 13 February 2017

Action date: 13 December 2017

Recommendation for Approvability: The drug substance section of BLA 761072/0, as amended, is recommended for approval from a microbial control and microbiology product quality perspective.

Post-Marketing Commitments:

1. *Reassess and tighten all in-process endotoxin acceptance criteria based on process capability after 20-30 data points are obtained.*
2. *Conduct bioburden method qualification using in-process samples from two additional batches of PF-06438179.*

Drug Substance and Drug Product Quality Microbiology Information Reviewed

Document Type	eCTD Sequence	Date	Modifications
Response to Information Request #3	0027	09 Nov 2017	3.2.S.2.4
Response to Information Request #4	0029	17 Nov 2017	3.2.S.2.4

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Patricia Hughes Troost

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Recommendation: BLA Approval

BLA Number: 760172
Review Number 1 (original BLA submission)
Review Date: December 1, 2017

Drug Name/Dosage Form	PF-06438179; proposed tradename Ixifi; proposed USAN name infliximab-qbtx/ lyophilized concentrate for injection
Strength/Potency	100 mg of lyophilized product in a 15 mL vial to be reconstituted in 10 mL of sterile water for injection
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	All indications for US-licensed Remicade
Applicant/Sponsor	Pfizer
US agent, if applicable	n/a

Product Overview

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Yanming An	OPQ/OBP/DBRR II
Drug Product	Sarah Arden[1]	OPQ/OBP/DBRR II
Immunogenicity Assays	Sarah Arden	OPQ/OBP/DBRR II
Labeling	Vicky Borders-Hemphill	OPQ/OBP
Facilities	Marion Michaelis	OPQ/OPF/DIA
Drug Substance Microbiology	Kathleen Jones (Drug	OPQ/OPF/DMA
Drug Product Microbiology	Aimee Cunningham	OPQ/OPF/DMA
Product Quality Team Lead	Christopher Downey	OPQ/OBP/DBRR II
Facilities Team Lead	Peter Qiu	OPQ/OPF/DIA
Microbiology Team Lead	Patricia Hughes	OPQ/OPF/DMA
Application Technical Lead	Christopher Downey	OPQ/OBP/DBRR II
OPQ RBPM	Kelly Ballard	OPQ/OPRO/DRBPMI/RBPMBI

[1]Sarah Arden also reviewed analytical assay validation data submitted in eCTD module 3.2.S.4.3 and 3.2.R.

Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
RPM	Sadaf Nabavian	ODEII/DPARP
Cross-disciplinary Team Lead	Nikolay Nikolov	ODEII/DPARP
Medical Officer	Erika Torjusen	ODEII/DPARP
Pharm/Tox	Matthew Whittaker	ODEII/DPARP
Clinical Pharmacology	Manuela Grimstein	OCP/DCPII
Statistics	William Koh	OB/DBII
CMC Statistics	Yu-Ting Weng	OTS/OB/DBVI

1. Names:
    a. Proprietary Name: PF-06438179
    b. Trade Name: Ixifi
    c. Non-Proprietary/USAN: infliximab-qbtx
    d. CAS name: 170277-31-3
    e. INN Name: pending

f. Compendial Name: not applicable
g. OBP systematic name: MAB CHIMERIC (IGG1) ANTI P01375 (TNFA_HUMAN) [PF-06438179]

Submissions Reviewed:

Submissions Reviewed	Document Date
761072/0000[a,b]	February 13, 2017
761072/0008[a]	May 17, 2017
761072/0009[a]	May 22, 2017
761072/0010[b]	May 26, 2017
761072/0011[a,b]	June 13, 2017
761072/0014[a]	August 18, 2017
761072/0015[a]	August 28, 2017
761072/0017[a]	September 11, 2017
761072/0018[b]	September 20, 2017
761072/0020[a]	October 6, 2017
761072/0021[b]	October 20, 2017
761072/0023[a,b]	October 30, 2017
761072/0024[a]	November 6, 2017

[a] Reviewed by OPQ/OBP/DBRR II
[b] Reviewed by OPQ/OPF/DMA

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
(b) (4)	Type II		(b) (4)	3	2	N/A
	Type III			2	2	N/A
	Type III			2	2	N/A
	Type V			1	Adequate with Information Request	11/21/2017
	Type III			3	2	N/A

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

B. Other documents:

Document	Application Number	Description
IND	114828	Pfizer-sponsored IND under which PF-06438179 was developed and BPD meetings were held
BLA	103772	BLA for US-licensed reference product

3. Consults: None

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Biotechnology Products, OPQ, CDER, recommends approval of BLA 760172 for PF-06438179 manufactured by Pfizer, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of PF-06438179 is well-controlled and leads to a product that is pure and potent. We recommend that this product be approved for human use under conditions specified in the package insert.

B. Summary of Complete Response Issues: None.

C. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance: (b) (4)
  - Drug Product:
    Pfizer Manufacturing Belgium NV
    Rijksweg 12,
    2870 Puurs
    Belgium
- Fill size and dosage form:
  - 100 mg lyophilized solid in a single-use 15 mL vial to be reconstituted with 10 mL sterile water for injection
- Dating period:
  - Drug Product: 42 months: 2 to 8°C; up to a maximum of 30°C for a single period of up to 6 months but not exceeding the original expiration date
  - Drug Substance: (b) (4) months: (b) (4) °C; (b) (4)
  - For packaged products: Not packaged
  - Stability Option:
    - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

- Exempt from lot release:
    - Yes, this is a specified product according to 21 CFR 601.2a.

D. Benefit/Risk Considerations:

PF-06438179 is a proposed biosimilar to US-licensed Remicade. The analytical similarity of PF-06438179 to US-licensed Remicade was evaluated using methods to assess physicochemical and functional properties of the products. Additionally, to establish an analytical bridge for the use of clinical data derived from European Union (EU)-approved Remicade in support of this BLA, the applicant also provided pairwise analytical comparisons between US-licensed and EU-approved Remicade and between PF-06438179 and EU-approved Remicade.

The totality of the analytical data demonstrate that these products are highly similar in terms of protein sequence, protein structure, and biological functions linked to the mechanisms of action, as summarized below:

- Primary sequence
- TNF-α binding and neutralization (potency)
- Secondary structure
- Tertiary structure
- Total afucolysated (including high mannose) and terminally galactosylated glycoforms
- Fc effector functions (ADCC, CDC) and Fc receptor binding
- Membrane-bound TNF-α binding and associated "reverse signaling" activity
- Induction of regulatory macrophages

The primary mechanism of action of PF-06438179 is generally regarded as the binding and neutralization of soluble TNF-α. All assays probing this mechanism supported similarity between PF-06438179 and US-licensed Remicade.

Biological functions mediated by the Fc domain of PF-06438179, such as antibody-dependent cell mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC), are potential secondary mechanisms of action. The interaction of the Fc domain with its various receptors, including those linked to effector functions, is sensitive to the glycan structures present in the Fc domain. The analytical similarity data support that in vitro effector functions, Fc receptor binding, and the percentage afucusylated and terminally galactosylated glycans are all similar between PF-06438179 and US-licensed Remicade. There is a risk that relatively small changes in these key glycoforms can have significant effects on affinity to Fc receptors and on the resulting Fc effector activities. To mitigate this risk, the applicant implemented quantitative specifications for glycan species, which are known to be linked to ADCC and CDC activity. Additionally, there is a post-marketing commitment to implement at specification test for affinity to the FcγRIIIa receptor linked to ADCC function to further mitigate risk of potential long-term risk of drift in this attribute. For all previously approved biosimilars to Remicade, FDA requested either release tests for FcγRIIIa affinity or PMCs to implement such a test. For more details, see Post-Marketing Commitments in Section B below and discussion of the Analytical Similarity Assessment in Section IIB of this memo.

The data submitted in this application also support the conclusion that the manufacture of PF-06438179 is well controlled and yields a consistently high quality product. The conditions used

in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. From a product quality perspective, this product is approvable for human use.

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

PMCs:

1) Repeat the capping/crimping validation using a dye ingress method which has been shown to reliably detect breaches ≤ 20 µm.[1]

2) Perform 3 consecutive media fills simulating the entire PF-06438179 DP manufacturing process using the PF-06438179 container closure system. The media fills will include worst-case hold and processing times, and be performed on (b) (4).[1]

3) Complete PQ shipping validation studies (b) (4) using PF-06438179 DP and submit the validation report.[1]

4) Conduct bioburden method qualification using in-process samples from 2 additional batches of PF-06438179 DS.[1]

5) Reassess and tighten all in-process DS endotoxin acceptance criteria based on process capability after 20-30 data points have been collected.[1]

6) Implement an assay assessing binding to FcγRIIIa into the Drug Substance release specification. Submit the proposed release specification as a Prior Approval Supplement described under 21 CFR 601.12 (b).[2]

II. Summary of Quality Assessments:

A. Analytical Similarity Assessment

The totality of the analytical data provided is sufficient to conclude that PF-06438179 is "highly similar" to US-licensed Remicade. Clinical studies submitted in support of this application used a non-US-licensed comparator product, EU-approved Remicade. To support analytical similarity to US-licensed Remicade and to justify a scientific bridge the use of comparative clinical data derived from EU-approved Remicade, the Applicant performed an analytical study to establish an adequate scientific bridge for the products. The applicant performed a 3-way evaluation of analytical similarity of PF-06438179, US-licensed Remicade, and EU-approved Remicade using multiple lots of each of the three products. The results of these comparisons show that the three products (PF-06438179, US-licensed Remicade, and EU-approved Remicade) met expectations for analytical similarity.

[1] PMC requested by CMC-Microbiology
[2] PMC requested by CMC-Product Quality

The expiration dates of the US-licensed Remicade and EU-approved Remicade lots was sufficiently broad and ranged over a span of approximately 5 years. For product quality attributes that were evaluated using equivalency testing, 53 lots each of US-licensed and 60 lots EU-approved Remicade were analyzed, and 11 independent lots of PF-06438179 were analyzed, including 6 lots of Drug Product, each derived from a unique lot of Drug Substance, and 5 additional unique lots of Drug Substance. A minimum 7 independent lots Drug Product and Drug Substance lots were assessed for each attribute evaluated using quality range testing. The applicant also provided a comparison of stability under thermal forced degradation conditions of 50°C for the lyophilized products and 40°C for the reconstituted products, forced-deamidating conditions (20 mM sodium phosphate pH 8.0), and light exposure conditions.

The analytical similarity assessment of PF-06438179, US-licensed Remicade and EU-Approved Remicade used a comprehensive set of assays, as listed in Table 1 below:

Table 1. Analytical methods used in the analytical similarity assessment

Quality Attribute	Analytical Methods
Primary Structure	- Amino acid sequencing by LC-MS/MS/MS peptide mapping, and peptide mapping/Edman degradation - Molecular weight determination by nanoESI-MS - Peptide mapping, post-translational modifications by LC-MS peptide mapping and LS-MS subunit analysis and by LC/UV - Disulfide bond location determination by peptide mapping with LC-MS under non-reducing conditions - Free sulfhydryls by Ellman's reagent + UV/VIS spectroscop and by fluorescent labeling of free suflydryls + SE-HPLC - Methionine oxidation by LC-MS and LS-MS with peptide mapping - Deamidation by peptide mapping and LC/MS - C-terminal variants analysis by MS and by carboxypeptidase A treatment followed by iCE - Primary structure, post-translational modifications, multichain structure by SEC/ESI MS
Carbohydrate structure	- N-glycan profile and abundance individual glycans by hydrophobic interaction liquid chromatography (HILIC) - N-linked Glycan Mapping by HILIC/MS - Sequential glycosidase digestion of N-linked glycans - Sialic acid analysis
High molecular mass species /aggregates	- %monomer and %high molecular mass species (HMMS) analysis by SE-HPLC - HMMS and self-association by analytical ultracentrifugation-sedimentation equilibrium (AUC-SE)
Charge heterogeneity	- Charge heterogeneity analysis by imaged capillary electrophoresis (iCE) - iCE of carboyxypeptidase-treated (C-terminal lysine removed) product - Charge isoforms by cation Exchange-HPLC (CEX-HPLC)/Mass Spectrometry
Intact protein purity	- %IgG analysis by capillary gel electrophoresis (CGE) (non-reducing) - %Heavy Chain+%Light Chain and size variants by CGE (reducing) - %Heavy Chain+%Light Chain by SDS-PAGE (reducing)
Higher order structure	- Protein secondary and tertiary structure analysis by Circular Dichroism (Far-UV and Near-UV) - Secondary structure by Fourier transform infrared spectroscopy (FTIR) - Tertiary structure characterization by intrinsic fluorescence - Tertiary structure analysis by X-ray crystallography
Protein Content	- Protein content determination by UV/VIS at 280 nm
Sub-visible particles	- Sub-visible particles analysis by low volume HIAC method

Fab-related Biological Activity and Fab-related Target Binding Affinity	- Inhibition of apoptosis induced by TNF-α (TNF-α neutralization assay) (potency assay for lot release) - Soluble TNF-α binding assay by SPR - Inhibition of ELAM-1 expression assay - Binding to membrane-bound TNF-α by flow cytometry
Fc-related Biological Activity and Receptor Interactions	- Antibody-dependent Cell-mediated Cytotoxicity (ADCC) assay using primary NK cells - Complement-dependent Cytotoxicity (CDC) bioassay - FcγRIIIa binding and mTNF binding by reporter gene assay - FcγRIIIa (158V variant) binding by SPR - FcγRIIIa (158F variant) binding by SPR - C1q binding by ELISA - FcγRI binding assay by SPR - FcγRIIa 131H and 131R binding assay by SPR - FcγRIIIb binding by SPR - FcRn binding by SPR - Natural killer cell binding assay
Additional Biological Activity Assays	- "Reverse signaling" assay - Inhibition of T Cell Proliferation in Mixed Lymphocyte Reaction (MLR) Assay

The following attributes for PF-06438179 are similar to the US-licensed Remicade, with the exceptions described later in this section:

- Amino acid sequence/primary Structure
- TNF-α binding and neutralization
- Fc-mediated *in vitro* biological activities (bioactivities)
- Fc receptor binding affinity
- Additional *in vitro* bioactivities (membrane TNF-α binding, reverse signaling, inhibition of T cell proliferation via regulatory macrophage induction)
- Purity
- Protein concentration after reconstitution
- Protein content
- Physicochemical Attributes
- High Molecular Weight Variants/Aggregates
- Higher order structure

TNF-α binding and neutralization is generally regarded as the main mechanism of action for infliximab products. The analytical similarity assessment included two assays probing this mechanism that were analyzed by statistical equivalence testing (Tier 1): 1) inhibition of cellular apoptosis induced by TNF-α and 2) relative binding affinity to TNF-α assayed by surface plasmon resonance (SPR). For the inhibition of apoptosis assay, the applicant provided data for 11 lots of PF-06438179, 53 lots of US-licensed Remicade, and 60 lots of EU-approved Remicade. For the TNF-α binding assay, the applicant provided data for 11 lots of PF-06438179, 11 batches of US-licensed Remicade, and 11 batches of EU-approved Remicade. OBP reviewed the justification of lots selection and concluded that the lots selected for each product were representative. The CMC Statistics reviewer assessed statistical equivalence testing and determined that the data met the equivalence margins for all 3 pairwise comparisons.

Additional potential mechanisms of action have been proposed for infliximab products in the scientific literature. These include antibody dependent cell-mediated cytotoxicity against cells expressing membrane-bound TNF-α (mTNF-α), complement dependent cytotoxicity against mTNF-α positive cells, "reverse signaling" (signal transduction into cells by activation of mTNF-α), and

inhibition of T cell proliferation via induction of regulatory macrophages. It is likely that the relative role for each of these mechanisms differs between indications. Pfizer provided data from in vitro functional assays to assess each similarity between PF-06438179 and US-licensed Remicade and EU-approved Remicade with regard to each of these potential mechanisms. In each case, the results were similar and met applicable Tier 2 or Tier 3 assessment criteria for pairwise comparisons of PF-06438179, US-licensed Remicade, and EU-approved Remicade. There are minor differences in the N-glycan profile, which is expected due to differences in the cell lines used to produce the products. However, the most abundant glycan species are similar, and glycans linked to Fc-effector functions such as afucosylated glycans are similar. Differences in minor (i.e. <3% abundant) glycoforms had no impact on Fc-receptor binding or Fc-mediated activities.

Each protein biochemistry and biological activity attribute described in Table 1 above met the pre-determined criteria for similarity in the pairwise comparisons of PF-06438179, US-licensed Remicade, and EU-Approved Remicade, with the following exceptions:

- Percent basic product-related variants
- C1q binding by ELISA
- Predominant form of sialic acid

In each of these cases, the impact of the slight differences in the attributes and resulting residual uncertainty is mitigated by additional information and analysis provided by the applicant:

- The sponsor demonstrated that the difference in percentage of basic variants (PF-06438179 ranged from 30.2 – 61.4% and US-licensed Remicade from 13.2 – 22.8%) is caused by differences in the presence of C-terminal lysine. It has been demonstrated in the scientific literature that C-terminal lysine is rapidly enzymatically removed in serum. Consequently, these basic variants have little risk of impact in vivo.

- One drug product lot of PF-06438179 fell out of the quality range of US-licensed Remicade for C1q binding ELISA. C1q receptor binding is an obligatory step in the complement dependent cytotoxicity (CDC) Fc-effector function, a potential mechanism of action. PF-06438179 was similar to US-licensed and EU-approved Remicade in the CDC functional assay. C1q affinity is strongly affected by glycoforms in the Fc-region, including terminally galactosylated species. PF-06438179 was similar to US-licensed and EU-approved Remicade for those attributes, meeting the quality ranges for the terminal galactosylation assay and other glycan-related attributes. Additionally, the structure and glycosylation of the Fc domain and resulting CDC activity are unlikely to be affected by drug product manufacture, and the constituent drug substance batch for the out-of-range PF-06438179 drug product lot was near the mean for US-Remicade. This result suggests that assay variability may have contributed to the out of range result. Considering the totality of the data, one lot of PF-06438179 falling just outside of the quality range for C1q binding does not suggest a significant risk that these products differ significantly in CDC activity. Fc glycosylation is also controlled by a PF-06438179 drug substance release test. This release test will ensure that glycans related to CDC and other Fc-mediated activities will be controlled to a range shown to be similar to US-licensed Remicade.

- For all 3 products, the sialylated glycans are <3% of the total N-glycan species. Of the trace levels of sialylated glycans detected, N-acetylneuraminic acid (Neu5Ac) is the predominant sialic acid form in PF-06438179 whereas N-glycolylneuraminic acid (Neu5Gc) is the

predominant form in US-licensed Remicade and EU-approved Remicade. This difference had no apparent effect on any receptor binding or functional assays in vivo. The sponsor provided literature references supporting that these differences are unlikely to be clinically impactful. Sialylation can, in principle, affect pharmacokinetics. The clinical pharmacology review found that all PK comparisons for this application met pre-defined margins and support similarity, further supporting the conclusion that there is no impact from these differences in minor glycoforms.

In summary, the totality of analytical similarity data supports the following conclusions:

- PF-06438179 is highly similar to US-licensed Remicade, notwithstanding minor differences in clinically inactive components.
- A sufficiently robust analytical bridge was established to support the use of EU-approved Remicade as a comparator in clinical studies.
- PF-06438179 and US-licensed Remicade share an identical primary sequence.
- *In vitro* measures of the primary mechanism of action, TNF-α neutralization and TNF-α binding, demonstrate statistical equivalence of PF-06438179 to US-licensed Remicade.
- An appropriate panel of functional assays measuring potential secondary mechanisms of action of anti-TNFα monoclonal antibody products yielded results meeting quality range criteria.
- The strength of U.S.-licensed Remicade is labeled as 100 mg lyophilized infliximab in a vial for intravenous infusion. US-licensed Remicade is filled into single use vials and labeled to be reconstituted with a volume of 10 mL sterile water for injection. Pfizer must seek approval of PF-06438179 for the same strength as U.S.-licensed Remicade. Comparative in vitro potency, protein concentration (mg/mL) upon reconstitution, and extractable volume data reviewed as part of the analytical similarity assessment were used to inform the assessment of whether the proposed presentation of PF-06438179 has the same strength as the presentation of U.S.-licensed Remicade. Based on these comparative data, the PF-06438179 100 mg per single dose vial presentation has the same total content of drug substance in units of mass in a container and upon reconstitution with sterile water for injection has the same concentration of drug substance in units of mass per unit volume as the presentation of U.S.-licensed Remicade. This presentation meets the statutory "same strength" requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.
- Although there are some minor differences in the biochemical attributes noted above, these differences are were within the typical ranges for bioreactor-produced therapeutic monoclonal antibodies and do not preclude a determination of highly similar for PF-06438179 relative to US-licensed Remicade. In all cases, the differences were shown not to impact functional activities related to either the primary or potential secondary mechanisms of action of PF-06438179 and US-licensed Remicade.

B. CQA Identification, Risk and Lifecycle Knowledge Management

Table 2 below is a summary of critical quality attributes and the associated control strategies for attributes that are relevant to both Drug Substance and Drug Product. For additional information, see the primary reviews, including the Drug Substance Quality Review and Drug Product Quality Review by

OBP/DBRR-II and the Drug Substance Microbiology Review and the Drug Product Microbiology Review by OPF/DMA.

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

CQA (type)	Risk	Origin	Control Strategy	Other
TNF-α binding and neutralization (potency)	Efficacy	Changes to protein composition during manufacture or storage	(b) (4)	
High-molecular mass species; (product-related impurity)	Efficacy, pharmacokinetics, and immunogenicity	Affected by manufacturing and storage conditions. Can form due to agitation, temperature, or light exposure.		
Fragmentation (product-related impurities)	Efficacy, pharmacokinetics, and immunogenicity	Affected by manufacturing and storage conditions. Fragmentation may be caused by agitation, temperature, or light		
Acidic and basic variants (product-related variants and impurities)	Efficacy, pharmacokinetics, and immunogenicity	(b) (4) deamidation during storage		
Glycosylation	Efficacy and pharmacokinetics	(b) (4) process		
Protein content	Efficacy, pharmacokinetics, safety	Manufacturing process		
FcRn binding	Efficacy Pharmacokinetics	(b) (4) process		
ADCC	Efficacy	(b) (4) process		PMC to add a FcγRIIIa binding assay to DS release specification
CDC	Efficacy	(b) (4) process		

CQA (type)	Risk	Origin	Control Strategy	Other
Reverse signaling via mTNF-α	Efficacy	(b) (4) process	(b) (4)	
Identity (identity)	Safety, efficacy	Intrinsic to molecule		
Endotoxin	Safety	Contamination during the manufacturing process		PMC to reassess and tighten all in-process endotoxin acceptance criteria based on process capability after 20-30 data points are obtained
Bioburden	Safety	Contamination during the manufacturing process		PMC to conduct bioburden method qualification using in-process samples from two additional batches
Sterility	Safety, Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced during manufacture or through a container closure integrity failure		PMC to repeat the capping validation using a dye ingress method shown to detect breaches of ≤ 20 µm PMC to perform 3 consecutive media fills simulating the DP manufacturing process using the specific PF-06438179 container closure system

C. Drug Substance Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 3 below summarizes the critical quality attributes and their control strategy that are relevant specifically to the Drug Substance. For additional information, see the primary reviews, including the Drug Substance Quality Review and Drug Product Quality Review by OBP/DBRR-II and the Drug Substance Microbiology Review and the Drug Product Microbiology Review by OPF/DMA. See Table 2 for CQAs related to both the Drug Substance and Drug Product.

Table 3: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
Appearance (color and clarity)	Safety	Manufacturing process	(b) (4)	
Host Cell Proteins (process-related impurity)	Safety and immunogenicity	Derived from host cell line		

CQA (type)	Risk	Origin	Control Strategy	Other
			(b) (4)	
Host Cell DNA (process-related impurity)	Safety	Derived from host cell line		
(b) (4) (process-related impurity)	Safety and immunogenicity	Process-related impurity (b) (4)		
(b) (4) (process-related impurity)	Safety	(b) (4)		
(b) (4) (process-related impurity)	Safety			
(b) (4) (process-related impurity)	Safety			
(b) (4) (process-related impurity)	Safety			
(b) (4) (process-related impurity)	Safety			
Virus Contamination (contaminant)	Safety	Contamination during manufacture		
Retrovirus like particles	Safety	(b) (4)		
(b) (4) content (excipient)	Safety, stability	Manufacturing process		
Endotoxin	Safety	Contamination during the manufacturing process		PMC to reassess and tighten all in-process endotoxin acceptance criteria based on process capability after 20-30 data points are obtained
Bioburden	Safety	Contamination during the manufacturing process		PMC to conduct bioburden method qualification using in-process samples from two additional DS batches

- Description: PF-06438179 is a recombinant chimeric IgG1κ monoclonal antibody that binds human TNF-α. The amino acid sequence of the variable domain is of murine origin and that of the constant region is of human origin. PF-06438179 consists of 4

polypeptide chains (2 identical heavy chains and 2 identical light chains) comprised of a total 1328 amino acids, and PF-06438179 has a molecular weight of approximately 149 kDa. Amino acid sequencing and tryptic peptide mapping with mass spectrometry analysis confirms the correct amino acid sequence. PF-06438179 Drug Substance is formulated for Drug Product filling and is stored as a (b) (4).

- Mechanism of Action (MoA): PF-06438179 binds specifically to TNF-α and blocks its interaction with TNF receptors. TNF-α is a naturally occurring cytokine with stimulatory activities for most cells of the immune system and is involved in normal inflammatory and immune responses. TNF-α is also involved in a variety of cellular processes, including apoptosis, differentiation, and proliferation. Elevated levels of TNF-α are found in the synovial fluid of patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. TNF-α plays an important role in both the pathologic inflammation and the joint destruction that are characteristic of these diseases. TNF-α occurs both as a membrane bound (mTNF-α) form and a soluble form (sTNF-α). PF-06438179 binds to both the soluble and membrane bound forms. PF-06438179 functions primarily by binding and neutralizing and sequestering excess sTNF-α produced in local tissue sites in inflammatory disease states.

  Other possible clinically relevant PF-06438179 activities include mediating antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) towards mTNF-α-positive inflammatory T-cells or other cells associated with inflammatory disease. Additionally, PF-06438179 may induce "reverse signaling" in mTNF-α-positive cells or induce regulatory macrophages. These activities have been suggested to contribute to inflammatory bowel disease indications, although the significance of the contribution of any of these individual mechanisms not well established (based on literature review).

- Potency Assay: The potency assay measures neutralization of soluble TNF-α induced apoptosis in a human monocyte cell line that expresses TNF receptors (U937 cells). The assay measures relative caspase-3 and caspase-7 levels, which are proportional to the apoptosis of cells, using a luminescence detection method. PF-06438179 causes a dose-dependent loss in luminescence signal. This activity is reported as a percentage of the activity of the reference standard.

- Reference Materials: A well characterized primary reference standard was derived from a clinical batch manufactured by the to-be-commercialized manufacturing process. A working reference standard was also derived from the same batch. Pfizer plans to qualify a working reference standard against this primary reference standard. Qualification of future master or working reference standards will be submitted as prior approval supplements.

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

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

(b) (4)

- Container closure: (b) (4) .

- Dating period and storage conditions: The sponsor conducted real-time stability studies at (b) (4) °C for 3 clinical batches and 3 process validation batches. These data are also supported by accelerated and stressed stability and temperature cycling studies. These data support a dating period of (b) (4) months at (b) (4) °C in (b) (4)

D. Drug Product Quality Summary:

Table 4 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. See Table 2 for CQAs related to both the Drug Substance and Drug Product.

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

CQA (type)	Risk	Origin	Control Strategy	Other
Visible Particles	Safety	Product-related, derived from processing equipment, contamination	(b) (4)	
Appearance (lyophilized cake)	safety	Manufacturing process		
Appearance (before reconstitution)	safety	Manufacturing process		
Appearance (visible particulates)	safety	Manufacturing process		
Appearance (clarity and coloration)	safety	Manufacturing process		
Content uniformity	Control of dosing	Manufacturing process		
Sub-visible particles	Safety	Manufacturing process, product degradation		
Reconstitution time	Safety, efficacy	Manufacturing process, storage conditions		
Moisture content	Stability	Manufacturing process, loss of container closure integrity		
Osmolality	Safety, stability	Manufacturing process		
Extractable volume	Control of dosing	Manufacturing process		
Endotoxin	Safety	Contamination during the manufacturing process		
Bioburden	Safety	Contamination during the manufacturing process		
Sterility	Safety, Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced during manufacture or through a container closure integrity failure		PMC to repeat the capping validation using a dye ingress method shown to detect breaches of ≤ 20 µm PMC to perform 3 consecutive media fills simulating the DP manufacturing process using the specific PF-06438179 container closure system

- Potency: Potency of PF-06438179 is considered, for the purposes of this review, as the percent inhibition of TNF-α-induced apoptosis activity relative to the current reference standard. The potency assay is the same as those described in the Drug Substance section of this review.

- Strength: PF-06438179 is supplied as a 100 mg lyophilized solid in a single-use vial. The lyophilized powder in the vials is to be reconstituted in 10 mL sterile water for injection, yielding a 100 mg/10 mL solution. There is a (b) (4)% overfill to assure that 10 mL reconstituted solution can be withdrawn per the product labeling. Comparative data for protein concentration demonstrate that PF-06438179 (100 mg lyophilized solid in a single-use vial) has the same total usable content of therapeutic antibody and the same concentration of antibody upon reconstitution as US-licensed Remicade. The proposed PF-06438179 presentation (100 mg lyophilized solid in a single-use vial) meets the statutory same strength requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.

- Summary of Product Design: PF-06438179 will be supplied as a sterile, preservative-free lyophilized powder in 15 mL vials. The lyophilized powder is to be reconstituted in sterile water for injection and further diluted into 0.9% sodium chloride solution in an infusion bag. Because of the potential formation of visible particles, the draft labeling for PF-06438179 states that an in-line filter must be incorporated during infusion.

- List of Excipients: Excipients include disodium succinate hexahydratesuccinate, succinic acid, sucrose, and polysorbate 80. Except for the antibody itself, all ingredients meet compendial requirements (USP/NF, Ph. Eur. and/or JP) and are commonly used for formulation of biopharmaceuticals. No excipients are of human or animal origin.

- Reference Materials: The same reference standard is used for Drug Product as for Drug Substance. Refer to the Drug Substance reference standard section above.

- Manufacturing process summary: The manufacturing process for Drug Product includes the following steps: (b) (4)

  Three Drug Product batches at the commercial scale were manufactured and analyzed to validate the manufacturing process. Manufacturing process parameters were within pre-specified parameters, and product quality attributes were within specification limits. These data support a well controlled process that will consistently produce a high quality product and that is adequate from a product quality review perspective. Microbial control was also assessed for these validation batches, and media fill simulations were also performed. The review of the microbiology data by the Division of Microbiology Assessment concluded that these data are adequate to assure product sterility. Additionally, four clinical batches were also successfully manufactured at commercial scale, providing additional data supporting a reproducible, controlled process.

- Container closure: The primary packaging material for PF-06438179 Drug Product consists of a clear and colorless 15 mL (b) (4) glass vial ((b) (4) stoppered with a 20 mm (b) (4) stopper (b) (4)

- Dating period and storage conditions: The sponsor conducted real-time, accelerated, and thermal-stressed stability studies on 3 commercial Drug Product lots and 3 clinical Drug Product lots. These data support a dating period of 42 months when stored at 2 to 8°C. The data also support storage for single period at a maximum temperature of 30°C for up to six months, but not exceeding the original expiration date.

- List of co-package components: none

E. Biopharmaceutics Considerations: None

F. Novel Approaches/Precedents: none

G. Any Special Product Quality Labeling Recommendations: none

H. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture, in-process control testing, release testing, DS storage, cell bank storage	(b) (4)		Inspect Facility ORA lead DMA and OBP participation	Pre-license inspection (b) (4) NAI	Approve facility
Cell bank manufacture and storage	Wyeth BioPharma Division of Wyeth Pharmaceuticals Inc. One Burtt Road Andover, MA 01810 USA	174350868/ 1222181	Inspect Facility OBP participation	Pre-license inspection Oct 10 – 12, 2017 NAI	Approve facility
Cell bank storage, release and stability testing	Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin, Dublin 22 Ireland	985586408/ 3004145594		waived	Approve facility
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture, release testing, DS storage, (b) (4) , primary packaging,	Pfizer Manufacturing Belgium NV Rijksweg 12 2870 Puurs Belgium	370156507/ 1000654629	Inspect Facility DIA lead	Pre-license inspection June 12 – 20, 2017 NAI	Approve facility

batch release, secondary packaging and labeling					
Release and stability testing	Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin, Dublin 22 Ireland	985586408/ 3004145594	Waive inspection	waived	Approve facility

I. Facilities: no approvability issues

J. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved: Stability protocol for the extension of shelf life, annual stability protocol, protocol for the preparation, qualification, and storage of renewal working cell banks
ii. Outstanding review issues/residual risk: To mitigate risk of drift in ADCC, there is a PMC to implement a release test for FcγRIIIa receptor binding, a biochemical attribute linked to ADCC activity.
iii. Future inspection points to consider: none

b. Drug Product

i. Protocols approved: Stability protocol for the extension of shelf life, annual stability protocol, Comparability protocol to implement (b) (4)
ii. Outstanding review issues/residual risk: none
iii. Future inspection points to consider: none

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: [fill in information]				
	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-NDA Agreements			x	
18.	SPOTS (special products on-line tracking system)			x	
19.	USAN assigned name			x	
20.	Other [fill in]		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 {fill-in}			x	

Christopher Downey

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Juhong Liu

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51,10903 New Hampshire Ave.
Silver Spring, MD 20993

To: Administrative File, STN 761072/0
From: Marion Michaelis, CSO, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
US License: 2060
Applicant: Pfizer, Inc.
Mfg Facility: **Drug Substance**: (b) (4)
FEI: (b) (4)
Drug Product: Pfizer Manufacturing Belgium NV, Puurs, Belgium
FEI: 1000654629
Product: Established/Proper Name: PF-06438179, a proposed biosimilar to Remicade®
Dosage: 100 mg of PF-06438179 in a 15 mL vial (lyophilized)
Indication: Same indications as the proposed product Remicade®

Due Date: 12/13/2017

RECOMMENDATION:

Approval is recommended from a facility perspective.

SUMMARY

Pfizer, Inc (Pfizer) submitted this new Biologics License Application (BLA) dated February 13, 2017 for PF-06438179 for intravenous infusion. The commercial PF-06438179 (also referred to as infliximab) drug product has been developed as a proposed biosimilar to the reference product, Remicade®. As part of this BLA there were three pre-license (PLI) inspections conducted for manufacturing which were the following:

- (b) (4)), FEI: (b) (4) – Drug Substance (DS) Manufacturing Inspection Conducted (b) (4) - Outcome Classified as VAI (CMS Work ID # (b) (4))
- Pfizer Manufacturing Belgium NV (Pfizer), FEI: 1000654629 – Drug Product (DP) Manufacturing Inspection Conducted 6/12-21/2017 – Outcome Classified as NAI for the PLI and VAI for GMP Surveillance (CMS Work ID #168818)
- Wyeth BioPharma Division of Wyeth Pharmaceuticals Inc. (FEI:1222181) - Cell bank manufacture and storage. Also responsible conducting the Bio-similarity assessment tests for this Biosimilar product. – PLI conducted October 6-12, 2017 Outcome Classified as NAI.

The scope of this review is primarily for equipment and facilities. Items documented as “reviewed on inspection” in this memo are discussed in the Establishment Inspection Report (EIR) associated with the individual PLI for this application.

From a facility perspective approval is recommended.

REVIEW:

Drug Substance Manufacturing

(b) (4)

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Zhihao Peter Qiu

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

BLA STN 761072
Product PF-06438179
Proposed Trade Name IXIFI
Manufacturer Pfizer Inc.

CMC - Product Quality Review of Drug Product, Analytical Methods, and Immunogenicity Assays

Nilou Sarah Arden, PhD, Product Quality Reviewer, OBP DBRR II

Christopher Downey, PhD, Application Technical Lead, OBP DBRR II

OBP CMC Review Data Sheet

1. BLA#: 761072

2. Review Date: October 2, 2017

3. Primary Review Team:

a. Medical Officer	Erika Torjusen/ Banu Karimi-shah, Nikolay Nikolov
b. Pharm/Tox	Matthew Whittaker/ Tim Robinson
c. Product Quality Team	Yanming An (DS quality, analytical similarity) Nilou Sarah Arden (DP quality, analytical method validation, immunogenicity) Christopher Downey (Application Technical Lead) Kathleen Jones (DS microbiology) Aimee Cunningham (DP microbiology)
d. Facilities	Marion Michaelis/ Peter Qiu
e. Clinical Pharmacology	Manuela Grimstein/ Anshu Marathe
f. Statistics	Yongman Kim (End 06/07/2017) William Koh/ Greg Levin Meiyu Shen/ Yu-Ting Weng (CMC Stats)
g. OBP Labeling	Vicky Borders-Hemphill
h. RBPM	Sadaf Nabavian Christine Ford (End 08/18/2017) Kelly Ballard (OPQ) Keith Olin (OPQ)

4. Major GRMP Deadlines:

a. Filing Meeting	March 20, 2017
b. Mid-cycle meeting	July 17, 2017
c. Wrap-up meeting	October 31, 2.17
d. Primary review due	November 9, 2017
e. Secondary review due	November 16, 2017
f. PDUFA action date.	December 13, 2017

5. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request (DMA)	March 07, 2017
Information Request (DIA)	March 16, 2017
OPQ Filing Review	April 14, 2017
Information Request (OBP I)	May 09, 2017
Information Request (DIA/OBP II)	May 18, 2017
Information Request (OBP III)	August 09, 2017
Information Request (DMA)	September 19, 2017
Information Request (OBP IV)	September 29, 2017

Information Request (DIA/DMA)	October 12, 2017

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
761072/0001	February 13, 2017	
761072/0009 (OBP IR I response)	May 22, 2017	Yes
761072/0011	June 13, 2017	Yes
761072/0014 (OBP IR III response)	August 18, 2017	Yes
761072/0015 (OBP IR III response)	August 28, 2017	Yes
761072/0017 (OBP IR III response)	September 11, 2017	Yes
761072/0018 (OBP IR III response)	September 20, 2017	Yes
761072/0020 (OBP IR IV response)	October 06, 2017	

7. Drug Product Name/Code/Type:

a. Proprietary Name PF-06438179
b. Trade Name IXIFI (proposed)
c. Non-Proprietary Name/USAN infliximab-qbtx (proposed)
d. CAS Name: 170277-31-3
e. Common Name:
f. INN Name To be determined
g. Compendial Name not applicable
h. OBP systematic name (refer to OPQ-SOP-OBP-3006)
MAB CHIMERIC (IGG1) ANTI P01375 (TNFA_HUMAN) [PF-06438179]

8. Pharmacological Category: Therapeutic recombinant human monoclonal antibody

9. Dosage Form: 100 mg lyophilized solid in a single-use 15 mL vial to be reconstituted with 10 mL sterile water for injection

10. Strength/Potency:

(i): The concentration/strength of the Drug Product
100 mg of lyophilized infliximab in a 15 mL single-vial, to be reconstituted with 10 mL sterile water for injection
(ii): Type of potency assay(s) Cell-based bioassay

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	DMF is current and will comply with all
			Yes	

(b) (4)		statements made in it.
	Yes	
	Yes	
	Yes	

13. Inspectional Activities:

Refer to the Drug Substance review by Yanming An for a description of inspectional activities associated with Drug Substance manufacture.

A PAI was conducted on the Drug Product Manufacturing facility from June 12, 2017 to June 20, 2017. Information about the facility and FDA personnel involved is described below:

Firm: Pfizer Manufacturing Belgium NV
Location: Puurs 2870, Belgium
FEI: 1000654629
Dates of inspection: June 12-16 & 19-21/2017
Days in the facility: 7
FDA Participants: Marion Michaelis CDER/OPQ/OPF/DMA

This pre-license inspection of the drug substance manufacturing facility at Pfizer Manufacturing Belgium NV was conducted on 6/12-16 and 19-21/2017 following a request by Division of Microbiology Assessment, Office of Process and Facilities, Office of Pharmaceutical Quality, CDER. The inspection was conducted to support the approval of Pfizer's biosimilar BLA STN761072/0 for PF-06438179. This inspection covered a comprehensive scope of Quality, Facilities and Equipment, Materials, Production and Laboratory Controls. This inspection was limited to the manufacturing of PF-06438179 drug product. No refusals were encountered during the inspection. No sample collection was needed.
Four observations were made and presented to the firm's management via Form 483 at the conclusion of the inspection on 06/21/2017.

14. Consults Requested by OBP: N/A

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:

Summary of Quality Assessments

I. **Primary Reviewer Summary Recommendation:**

We recommend approval of the BLA. The data submitted in this Biologics License Application support the conclusion that the manufacture of PF-06438179 is well controlled and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. It is recommended that PF-06438179 be approved for human use (under conditions specified in the package insert).

We recommend an expiration dating period of 42 months for PF-06438179 drug product when stored at 2 to 8°C. Unopened PF-06438179 vials may also be stored at temperatures up to a maximum of 30ºC for a single period of up to 6 months but not exceeding the original expiration date.

Refer to the OBP Drug Substance Review by Yanming An for recommendations on Drug Substance expiry dating.

We recommend approval of the proposed release and shelf-life specifications for PF-06438179 Drug Product.

II. **List of Deficiencies to be Communicated:** None

III. **List of Post-Marketing Commitments/Requirements:** refer to Drug Substance Review by Yanming An

IV. **Review of Common Technical Document- Quality Module 1:**

A. Environmental Assessment of Claim of Categorical Exclusion

Pfizer Inc. claims a categorical exclusion to the environmental assessment requirements in compliance with the categorical exclusion criteria 21 CFR Part 25.31 (b): Action on an NDA: the estimated concentration of the substance(s) at the point of entry into the aquatic environment will be below 1 part per billion. Pfizer Inc. claims that to our knowledge, no extraordinary circumstances.

V. **Primary Container Labeling Review:**
The primary container labeling was reviewed separately by Vicky Borders-Hemphill with concurrence by Yanming An, Nilou Sarah Arden and Christopher Downey.

VI. **Review of Common Technical Document - Quality Module 3.2:**
CTD Modules 3.2.P, 3.2.S.4.3, 3.2.S.2.5 and the Comparability Protocol contained in 3.2.R are reviewed in this document. Modules 3.2.S, 3.2.R, and 3.2.A were reviewed separately by Yanming An and Christopher Downey.

VII. **Review of Immunogenicity Assays:** Module 5.3.1.4 is reviewed in this document.

P. DRUG PRODUCT

P.1 Description and Composition of the Drug Product

The PF-06438179 drug product (DP) is supplied as a lyophilized concentrate for injection in a dosage strength of 100 mg/vial. After reconstitution with 10 mL of Sterile Water for Injection (SWFI), the DP concentration is 10 mg/mL that is further diluted with 0.9% sodium chloride. DP is supplied with no preservatives for single use in a 15 mL glass vial sealed with a stopper and an aluminum seal with flip-off plastic cap. The composition of the DP is shown in Table 3.2.P.1-1 below. The formulation includes (b) (4) succinate buffer, 2.5% sucrose and 0.005% polysorbate 80 at pH 6. An overfill of (b) (4) % ensures that the nominal dose can be delivered.

Table 3.2.P.1-1. Composition of PF-06438179 Drug Product, 100 mg/vial

Name of Ingredients	Reference to Standard	Function	Unit Formula (mg/vial)
PF-06438179	In-house specification	Active ingredient	100
Disodium succinate hexahydrate	In-house specification	(b) (4)	12.1
Succinic acid	NF		0.6
Sucrose	Ph. Eur., NF, JP		250
Polysorbate 80	Ph. Eur., NF, JP		0.5

P.2 Pharmaceutical Development

P.2.1 Components of the Drug Product

(b) (4)

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Memorandum: Immunogenicity Review

STN:	BLA 761072
Type:	351(k)
Subject:	Immunogenicity review
Submission Date:	February 13, 2017
Review/Revision Date:	June 9, 2017/October 20, 2017
Primary Reviewer:	Nilou Sarah Arden, Ph.D. Product Quality Reviewer, CDER/OPQ, OBP, DBRR II
Secondary Reviewer:	Chris Downey, Ph.D. Product Quality Team Leader, CDER/OPQ, OBP, DBRR II
Assigned RPM:	Anita Brown CDER/OPQ/OPRO
Applicant:	Pfizer
Product:	PF-06438179 (proposed biosimilar to US-licensed Remicade)
Indication(s):	Rheumatoid Arthritis, Crohn's Disease

EXECUTIVE SUMMARY

The assays submitted to assess the immunogenicity of the PF-06438179, US-licensed Remicade, and EU-approved Remicade products were adequately validated. The sponsor validated and used two electrochemiluminescence (ECL) screening assays to evaluate anti-drug antibodies (ADA) for one of two clinical studies, B5371001; one assay used Remicade-derived reagents and the other used PF-06438179-derived reagents. Due to data demonstrating cross-reactivity between the two assays for ADA-positive sera, the sponsor elected to use the validated ECL ADA assay using PF-06438179-derived reagents for the second clinical study, B5371002. Likewise, the sponsor validated and used two cell based assays to evaluate neutralizing antibodies (NAbs) for the first study, B5371001 and again, due to demonstrating cross-reactivity across the two platforms, the sponsor elected to use a single validated cell based assay (the PF-06438179 platform) for the second study, B5371002. The validation reports for all four assays were reviewed here and are acceptable. A suite of validation exercises were performed to demonstrate and ensure the ability of the assays to reliably quantify levels of ADA and NAbs. The screening assays demonstrated adequate sensitivity and precision. Of note, the validated drug tolerance for the screening assays ranged from 0.5 – 5.0 μg/mL when challenging high and low positive control antibody concentrations. The impact of on-board drug on the assay sensitivity will be the same when testing sera from patients treated with either PF-06438179 or Remicade. The drug tolerance study results were discussed with the clinical pharmacology team, and it was concluded that the C_{trough} levels of PF-06438179 or Remicade at the relevant timepoints in the clinical efficacy study were within the levels demonstrated to be tolerated by the assay validation study. Thus, the data are sufficient to support that the assay is sensitive to ADA in the relevant clinical samples, and the screening assay is suitable for assessing and comparing ADA levels between PF-06438179 and EU-approved or US-licensed Remicade. The validation data support that the NAb assays are adequate to sensitively determine the level of neutralizing activity of confirmed ADA positive patient sera.

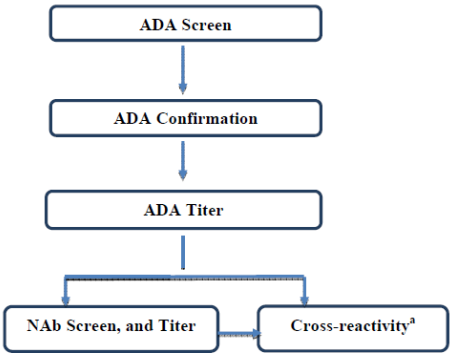
TABLE OF CONTENTS

I. Summary of Immunogenicity Assays

A. INTRODUCTION AND OVERVIEW

A tiered approach (screening assay, confirmatory assay, titering assay, NAb assay) was used to analyze patient ADA samples (See Figure 1 below). Confirmed ADA positive samples were analyzed for neutralizing antibodies using validated cell based NAb assays. ADA measurement was achieved using electrochemiluminescence (ECL) and NAb measurement was achieved using a cell based assay.

Figure 1. Tiered Testing Approach for Assessing Immunogenicity



a. Only applicable to Study B5371001

A cut point value is the antibody measurement (in relative light units (RLU)) which serves as the threshold to distinguish anti-Remicade antibody positive from antibody negative samples. Antibody titers are reported as log base 10 values and are defined as the reciprocal dilution of the sample that generates an RLU equal to the cut point value. Validation studies included: inter-assay variability of the positive control maximum RLU and cut point values, inter- and intra-day variability of the positive control log titer, inter and intra run variability of the cut point and matrix effects were assessed for normal, rheumatoid arthritis (RA), or Crohn's patients.

B. IMMUNOGENICITY STUDY SAMPLE ANALYSIS STRATEGY

Two ADA assay methods (validation numbers B5377001 and B5377002) were used to support ADA analysis of a "Phase I" Study B5371001 which included normal healthy subjects. Serum samples from Study B5371001 were analyzed for anti-Remicade antibodies (B5377001) or anti-PF-06438179 antibodies (B5377002). Cross-reactivity sample analysis was performed on study samples that tested positive for the administered study drug using the alternate assay with titer and confirmatory analysis. ADA assay method validation was performed by (b) (4) a contract research organization (CRO).

Two NAb assays methods (validation numbers B5377003 and B5377004) were used to support Study B5371001 NAb analysis based on the drug treatments. ADA positive samples were analyzed for neutralizing anti-Remicade antibodies (method B5377004) or neutralizing anti-PF-06438179 antibodies (method B5377003) using the validated drug-specific assay with a tiered approach. Cross-reactivity analysis was only performed for samples that tested NAb positive in the assay for the administered study drug using the alternate assay with titration. NAb assay method validation was performed by (b) (4) a CRO.

Based on significant cross-reactivity between the two ADA assay methods (>80% for positive samples and >100% for negative samples), the sponsor elected to use a single ADA method (B5377002) for

analyzing ADA and a single NAb method (B5377004) for analyzing NAb from a "Phase III" Study B5371002. Both of these methods use PF-06438179 to probe for ADA and neutralizing ADA.

Reviewer Comment: *Data demonstrating high cross-reactivity for ADA positive samples between the two assay methods B5377001 and B5377002 are provided in Module 5.3.3.1, B5371001 Report Body Table 16.2.8.5.4.1. Cross reactivity sample analysis was conducted on samples testing positive for the study drug using the alternate assay with a subset of negative samples from each assay also assessed in the alternate assay. Cross-reactivity was observed for both sets of assays leading to an adjustment from having two validated assays each for ADA and NAb profiling for the B5371001 healthy subjects study to having a single assay for ADA profiling and a single assay for NAb profiling for the B5371002 RA subjects study. These data were reviewed and the Reviewer is in agreement with the Sponsor's findings that the assays are cross-reactive. The Sponsor selected their PF-06438179-based assay platforms to probe for antibodies against their product and US-licensed and EU-approved Remicade. This approach of testing all samples using an assay format with reagents derived from the proposed similar is consistent with our expectations for ADA assessment for biosimilar products and is acceptable.*

C. ADA ASSAY METHOLODOGY OVERVIEW (ECL)

Two parallel ADA assays were validated using the following parameters; precision, specificity, matrix selectivity, assay sensitivity, drug tolerance, dilution linearity, tested stability and positive control (PC) cross-reactivity. Each assay established cut points for normal and disease (RA) populations.

To validate the anti-Remicade antibodies in human serum, samples were collected from 50 lots of naïve normal human serum, 25 lots of naïve RA human serum and 25 lots of naïve Crohn's human serum to determine the screening and confirmatory cut point values. To validate the anti-PF-06438179 antibodies in human serum, samples were collected from 50 lots of naïve normal human serum and 25 lots of naïve RA human serum to determine the screening and confirmatory cut point values.

Cut points were statistically determined with outlier exclusion and normalization as described in detail in the ADA validation reports B5377001 and B5377002. After validation of each of the methods, PC cross-reactivity was demonstrated. The screening cut point was determined at 95th percentile and the confirmatory cut point was determined at the 99th percentile.

A summary of the ECL ADA validation parameters are shown in Table 2 below.

Table 2. Validation Parameter Summaries of the ADA ECL Methods

Validation Parameter	Assay Against Remicade	Assay Against PF-06438179
Relative Mass-based Assay Sensitivity (ng/mL)	15.4[a]/58.4[b]	54.8[a]/234[b]
Plate Cut Point Factor for Screening	1.11 (NS) 1.23 (RA)	1.34 (NS) 1.52 (RA)
Confirmatory Cut Point (%)	EU: 54.4 (NS)/59.7 (RA) US: 55.5 (NS)/57.4 (RA)	53.6 (NS)/53.6 (RA)
Drug Tolerance at LPC (320 ng/mL)	Infliximab-US: tolerate up to 1 ug/mL Infliximab-EU: tolerate up to 0.5 ug/mL	PF-06438179: tolerate up to 0.5 ug/mL
Drug Tolerance at HPC (2560 ng/mL)	Infliximab-US: tolerate up to 5 ug/mL Infliximab-EU: tolerate up to 1 ug/mL	PF-06438179: tolerate up to 5 ug/mL
Target Interference	Tolerate up to 5000 pg/mL	Tolerate up to 5000 pg/mL
Inter-Day (run) PC Precision (%CV)	6.50	2.36
Inter-Day (run) NC Precision (%CV)	6.79	20.0
Confirmatory assay Precision (HPC) (%CV)	< 0.377	< 0.0597
Room Temp Stability	25 hrs	24 hrs
Freeze/Thaw Cycle Stability	6 Cycle at -70°C	7 Cycle at -70°C
Matrix Recovery (Selectivity)	NS: 10/10 lots passed RA: 9/10 lots passed	NS: 10/10 lots passed RA: 14/20 lots passed
PC dilution linearity	180x	180x

Source: Module 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies; Assays B5377001 and B5377002

[a] from PC against Remicade (affinity purified rabbit polyclonal antibody)

[b] from PC against PF-06438179 (affinity purified mouse monoclonal antibody)

Abbreviations: CV=Coefficient of variation; EU= European Union; HPC=High positive control; LPC=Low positive control; NC=Negative control ;NS=normal (healthy subjects) serum; PC=Positive control; RA=rheumatoid arthritis serum; US=United States

D. NEUTRALIZING ANTIBODY ASSAY METHODOLOGY OVERVIEW (CELL-BASED)

Two cell based NAb assays were developed and validated for Remicade (US-licensed and EU-approved) and Pfizer PF-06438179 by assessing the following parameters; precision, specificity, matrix selectivity, assay sensitivity, drug tolerance, tested stability and PC cross-reactivity. A screening cut point factor was also established for normal and RA disease populations.

A summary of the NAb assay validation parameters are shown in Table 3 below.

Table 3. Validation Parameter Summaries of Cell-based NAb Methods

Validation Parameter	Assay Against Remicade	Assay Against PF-06438179
Relative Mass-based Assay Sensitivity (ng/mL)	1212[a]/402[b]	1436[a]/846[b]
Plate Cut Point Factor for Screening	0.62 (NS) 0.54 (RA)	0.54 (NS) 0.48 (RA)
Drug Tolerance at HPC (2500 ng/mL)	Remicade: tolerate up to 0.5 ug/mL	PF-06438179: tolerate up to 0.1 ug/mL
Target Interference	Tolerate up to 5000 pg/mL (PC)	
Inter-Day (run) PC Precision (%CV)	12.7	10.8
Minimal TNF-α blocking Rate (%)	66.7	67.0
Room Temp Stability	24 hours	24 hours
Freeze/Thaw Cycle stability	5 cycles at -70°C	5 cycles at -70°C
Matrix Recovery (Selectivity)	NS: 90% lots passed RA: 100% lots passed	NS: 90% lots passed RA: 100% lots passed
Cell line passage Stability	18 passages	18 passages

Source: Module 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies: Assays B5377003 and B5377004

[a] from PC against infliximab (affinity purified rabbit polyclonal antibody)

[b] from PC against PF-06438179 (affinity purified mouse monoclonal antibody)

Abbreviations: CV=Coefficient of variation; EU=European Union; HPC=High positive control; LPC=Low positive control; NAb=neutralizing antibody; NS=normal (healthy subjects) serum; PC=Positive control; RA=rheumatoid arthritis serum; TNF-α=Tumor necrosis factor alpha; US=United States

II. Review of Validation of ADA and NAb Assays

A. ADA Assay Validation (B5377001 and B5377002)

1. SCREENING ASSAY VALIDATION OVERVIEW

In both assays, antibodies against both US-licensed and EU-approved Remicade were measured in human serum using an ECL immunoassay method. Samples (including PC and NC) were diluted 1:5 in Diluent Buffer and loaded into wells of a polypropylene plate. The samples were acidified by an equal volume of 0.8% Acetic Acid in Diluent Buffer followed by incubation. The samples were then neutralized by the addition of an equal volume of 2X Master Mix (a 0.250 ug/mL concentration of Ruthenylated (Sulfo-tagged) Remicade and a 0.100 ug/mL concentration of Biotinylated Remicade labels) resulting in a final serum concentration of 5%. Samples were incubated on the transfer plate where anti-Remicade antibodies bound to Sulfo-tagged and Biotinylated Remicade to form an antibody complex bridge. Samples were then transferred to a streptavidin coated MSD assay plate and incubated to allow streptavidin to bind to the Biotinylated Remicade. The unbound material was washed and only samples containing antibody bound to both Biotinylated Remicade and Sulfo-tagged Remicade generated an ECL signal.

2. SCREENING ASSAY (B5377001, anti-Remicade ADA)

Two ECL assays were validated for use in detecting ADA directed against Remicade or PF-06438179 in human serum. As noted above, the method validations evaluated assay performance based on precision, specificity, dilution linearity, sensitivity, drug tolerance and stability. The validations also established screening and confirmatory cut point factors for normal, RA and Crohn's populations. The validation summary below presents the relevant information for this assay.

Pfizer Validation Number	B5377001
Pfizer Sponsor Location	Groton, CT
Pfizer Principal Contact	Chun-Hua (Sherry) Cai
Bioanalytical Laboratory	(b) (4)
Bioanalytical Laboratory Job Reference	
Notebook Reference	
Principal Bioanalytical Investigator	
Method Description Matrix Anticoagulant Sample Storage Temperature	 Human serum none -70°C
Source of Control Matrix	Biochemed
Response Detection	ECLA
Sample Aliquot Volume	Screen: not less than 10 µL Confirm : not less than 10 µL Titer: not less than 10 µL
Positive Control(s)	Affinity purified rabbit IgG RA-23008-A.01 (polyclonal)
Positive Control (PC) Concentrations	1.17 to 2560 ng/mL for PC titration curve; LPC = 320 ng/mL, HPC = 2560 ng/mL
Critical Reagents	Remicade-Biotin labeled Remicade-STAG2 (Ruthenium (SulfoTag™)) labeled
Assay MRD	1:20
Detection Instrument	MSD Sector Imager 2400
Analytical System Software and Version	Bio-Tek Gen5 Secure, Meso Scale Discovery WorkBench software
Plate Cut Point Factor (CPF) for screening	1.11 for normal human serum 1.23 for Rheumatoid Arthritis (RA) patient serum 2.26 for Crohns patient serum
Confirmatory assay cut point *	54.4% Infliximab-EU in normal human serum 55.5% Infliximab-US in normal human serum 59.7% Infliximab-EU in RA serum 57.4% Infliximab-US in RA serum Note: Confirmatory assay cut points were not established in Crohns serum.

Inter-Day Precision (NC, %CV of NC RLU):	6.79% (normal human serum)
Inter-Day Precision (PC, %CV of End Point Log_{10} Titer) (using CPF 1.11):	6.50% (normal human serum)
Intra-Day Precision (NC, %CV of NC RLU)	3.70% (normal human serum)
Intra-Day Precision (PC, %CV of End Point Log_{10} Titer) (using CPF 1.11)	4.90% (normal human serum)
Intra-Run Precision (PC, %CV of End Point Log_{10} Titer) (using CPF 1.11)	1.30% - 4.66% (normal human serum)
PC End Point Log_{10} Titer Range (using CPF 1.11)	3.08 – 4.58 (normal human serum)
Drug Tolerance	HPC (2560 ng/mL) tolerated up to 5.00 µg/mL Infliximab-US or 1.00 µg/mL Infliximab-EU. LPC (320 ng/mL) tolerated up to 1.00 µg/mL Infliximab-US or 0.500 µg/mL Infliximab-EU.
Target Interference (TNF-α)	HPC and LPC both tolerate up to 5000 pg/mL
PC linearity of dilution	Dilution linearity observed with 20X, 60X, and 180X from PC 100 µg/mL.
PC freeze/thaw stability	At least 6 cycles at -70°C
PC ambient stability	At least 25 hours at room temperature
Relative Mass-based sensitivity for PC in human serum	15.4 ng/mL
Matrix Recovery (normal/disease)	Normal human serum spiked at high PC and low PC: 100% lots tested have recovery between 75% and 125%. RA patient serum spiked at high PC: 100% lots tested have recovery between 75% and 125%. RA patient serum spiked at low PC: 90% lots tested have recovery between 75% and 125%. Crohns patient serum spiked at high PC: 80% lots tested have recovery between 75% and 125%. Crohns patient serum spiked at low PC: 90% lots tested have recovery between 75% and 125%.
Assay robustness	Assay robustness was demonstrated by 62 validation runs on different days performed by two different analysts.

The table presents the assay validation acceptance criteria applied by the sponsor.

Reviewer Comments: *Floating cut points were determined and cut point factors for normal human serum and for RA patient serum were used to calculate the reported screening cut points reported.*

Targeted Assay Validation Acceptance Criteria	
PC log titer (endpoint titer (log_{10}))	Within a log of the PC serial dilution factor (i.e. $log_{10}3 = 0.48$).
Precision (CV) of PC response values above the assay cut point	≤ 25%
Precision (CV) of mean NC response values and plate cut point value	≤ 25%
Response value of the mean NC for each run	Acceptance criteria will be established for the NC from all acceptable validation runs.
Response value of the mean maximum positive control for each run	Within ± 3*SD of mean inter-run maximum response value
PC freeze/ thaw stability	Difference of PC log titer values are within a Log of the PC serial dilution factor when compared to cycle 1
PC Room Temperature stability	Difference of PC log titer values are within a Log of the PC serial dilution factor when compared to unexposed to room temperature sample
Linearity of PC sample	PC log titer values at various dilutions for the samples that are expected to generate a value above the cut point should be within a Log of the PC serial dilution factor
Matrix Specificity (recovery)	At least 2/3 of the lots spiked with low or high PC should have recovery between 75-125%.
Assay Robustness	Difference of PC log titer values are within a Log of the PC serial dilution factor when comparing the different conditions evaluated.

A drug tolerance range of 1 -5 µg/mL (boxed in red above) was validated which overlaps with the range of concentrations in the pharmacokinetic (PK) similarity studies and efficacy studies. B5377002 had a similar drug tolerance of 0.5 - 5 µg/mL PF-06438179 in the analogous study (reviewed below). The most likely risk suggested by the validated drug tolerance being similar to the range of the drug concentrations present in clinical samples is that the drug interference may lead to false-negative results, in which case the rate of ADA positive subjects may be underestimated. There is little risk that the assay sensitivity or drug tolerance would be different between patients treated with PF-06438179, US-licensed or EU-approved Remicade. Thus, the results of ADA testing for clinical samples can still be reliably compared between these products. We discussed the drug tolerance results with our clinical pharmacology colleagues in DCP and clinical colleagues in DPARP. The team agreed that the trough levels of drug was at or below the validated tolerance at the relevant timepoints for evaluating the rates of immunogenicity between the products. Consequently, we conclude that the assay is suitable for its intended use.

Negative controls (NC) and primary positive controls (PC) were analyzed for each plate. The negative control (NC) comprises pooled human serum. A primary PC was prepared in normal human serum spiked with affinity purified rabbit IgG RA-23008-A.01 at 100,000 ng/mL in the pooled human serum (NC) followed by 8 dilutions as shown in the Table below from Module 5.3.1.4 Appendix E.

20X Positive Control Calibrator Preparation

Stock Identity	Concentration (ng/mL)	Volume of Working Stock (µL)	Volume of 100% Matrix (µL)	Dilutions for EPLog$_{10}$
A	100,000	10.0 of Purified Rabbit IgG RA-23008-A.01	220	-
S1	2560	128 of A	4872	1/20
S2	853*	1500 of S1	3000	1/60
S3	284*	1500 of S2	3000	1/180
S4	94.8*	1500 of S3	3000	1/540
S5	31.6*	1500 of S4	3000	1/1620
S6	10.5*	1500 of S5	3000	1/4860
S7	3.51*	1500 of S6	3000	1/14580
S8	1.17*	1500 of S7	3000	1/43740

*Calculations based on unrounded values but rounded values are presented.

3. LINEARITY (B5377001, anti-Remicade ADA)

The positive control (PC) linearity assessment was performed using a series of dilutions to demonstrate that the assay can detect antibodies in samples over a range of titers (log base 10 titer values). The PC log titer values at the various dilutions are expected to generate a value above the cut point and remain within a log of the PC serial dilution factor of 0.48. Each dilution was analyzed on a separate plate in triplicate. One deviation was observed wherein the linearity assessment dilution of 1:20 did not meet the acceptance criteria (AC) of ±0.48 (the log of 1 dilution factor) because the difference of the normalized mean end point log titer from the mean end point log titer was determined to be -0.500. However, the PC performed as expected throughout the assay validation studies. Table 12.16 below from Section 5.3.1.4 demonstrates the PC linearity.

12.16. Positive Control Linearity for the Infliximab Antibody Assay for Human Serum

Cut Point Factor Applied: 1.11						
Positive Control Dilution^	**Plate**	**End Point Log$_{10}$ Titer**	**End Point Log$_{10}$ Titer (Normalized to Positive Control)**			**Diff [a]**
20	**62**	3.62 3.57 3.86	4.92 4.87 5.16	**Mean** **SD** **%CV**	4.98 0.155 3.11	-0.500
60	**54**	4.00 3.65 3.54	5.78 5.43 5.32	**Mean** **SD** **%CV**	5.51 0.240 4.36	0.0300
180	**55**	3.67 3.80 3.62	5.93 6.06 5.88	**Mean** **SD** **%CV**	5.96 0.0929 1.56	0.480
n **Mean^^** **SD** **%CV**					3 5.48 0.491 8.96	

[a]Diff = Normalized Mean End Point Log10 Titer of the Dilution Sample - Mean End Point Log10 Titer^^ (±0.48)
Endpoint Log$_{10}$ Titer Normalized to PC = Endpoint Log$_{10}$ Titer + Log$_{10}$ (PC Dilution^)

Reviewer Comment: *The Sponsor has noted the PC 1:20 dilution failure to meet the AC of ±0.48 (log of 1 dilution factor) for linearity. However, the PC performed as expected throughout the assay validation at the 1:20 dilution. This justification provides reasoning for the low risk to integrity, reliability or data quality despite the excursion from AC. This is acceptable.*

4. DRUG TOLERANCE (B5377001, anti-Remicade ADA)

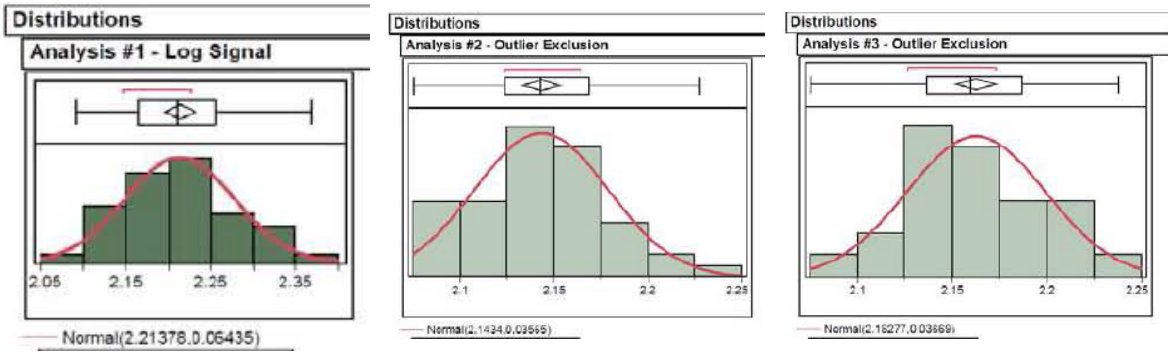
Assay interference may be caused by samples containing PF-06438179 due to competition for anti-PF-06438179 antibodies between free PF-06438179 in the sample and labeled PF-06438179 within the assay platform. Drug tolerance of the PC was assessed with both the high positive control (HPC, 2560 ng/mL) and the low positive control (LPC, 320 ng/mL). Varying concentrations of either US-licensed Remicade or EU-approved Remicade ranging from concentrations of 1.00, 0.5, 0.1, to 0.00 µg/mL were spiked with either the HPC or the LPC. The mean RLU of pre-incubated samples in presence and absence of free drug were compared. Results demonstrate that the HPC tolerated up to 5.00 µg/mL US-licensed Remicade or 1.00 µg/mL EU-approved Remicade. The LPC tolerated up to 1.00 µg/mL US-licensed Remicade or 0.500 µg/mL EU-approved Remicade (See Table 12.17 and 12.18 of Section 5.3.1.4, B5377001 - The Validation of an ECLA Method for Detection of anti-Infliximab Antibodies in Human Serum - Amendment 2).

5. SCREENING CUT POINTS (B5377001, anti-Remicade ADA)

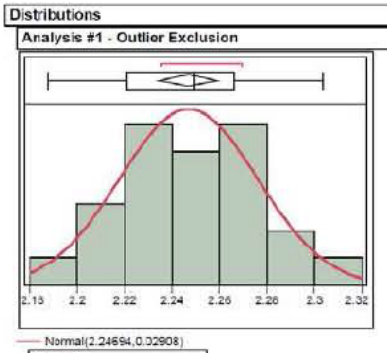
Each sample was analyzed in duplicate by three independent analyses. Data was log transformed and assessed for normality and outliers. The data was re-assessed for normality after excluding outliers. Subsequently, both the normal and RA samples were analyzed using a parametric approach while Crohn's samples were analyzed using both parametric and non-parametric approaches.

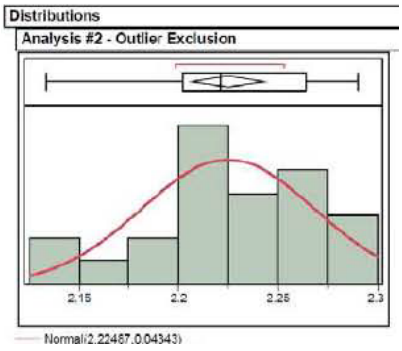
Reviewer Comment: *Information for the cut point analysis was sourced from Module 5.3.1.4 Appendix F: Cut Point Determination.*

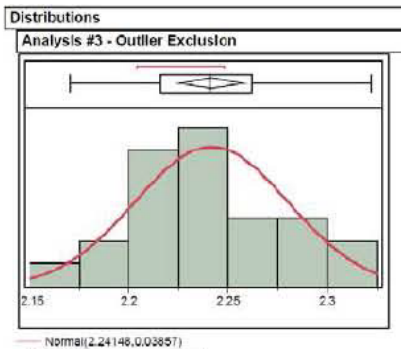
Normal serum cut point results (applicable to both anti-Remicade and anti-PF-06438719 antibodies) are shown for each of the three independent analyses 1-3 in the Figures below and result in the overall cut point factor of 1.11 which is the normalization factor that is then multiplied by the mean negative control value to derive the floating cut point.



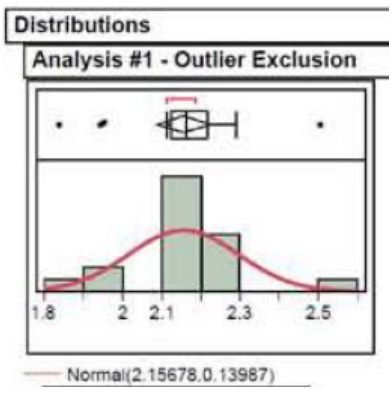
RA serum cut point results (applicable to both anti-Remicade and anti-PF-06438719 antibodies) are shown for each of the three independent analyses 1-3 in the Figures below and result in the overall cut point factor of 1.23.

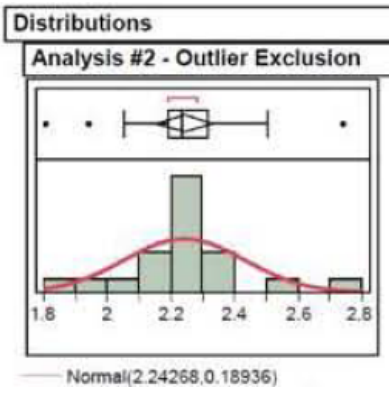


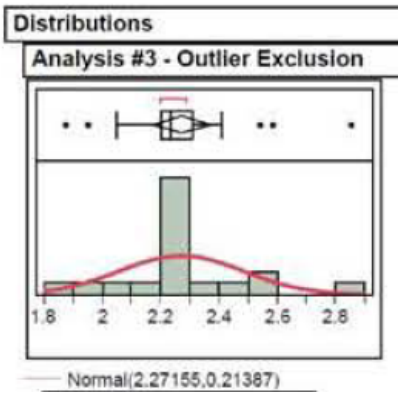




Crohn's serum cut point results (applicable to anti-Remicade antibody detection) are shown for each of the three independent analyses 1-3 in the Figures below and result in the overall cut point factor of 2.48.







A non-parametric analysis of Crohn's serum was also performed and tabulated in Module 5.3.1.4 Appendix F Table 7 with an overall cut point factor of 2.26.

6. SCREENING ASSAY (B5377002, anti-PF-06438179 ADA)

This validation study evaluated the ECL immunoassay for detection of anti-drug antibodies directed against PF-06438179 in human serum. The method validation evaluated assay performance parameters including; precision, specificity, dilution linearity, sensitivity, drug tolerance and stability. Validation also established screening and confirmatory cut points for normal and RA populations.

The tables below present validation details and targeted assay validation criteria.

Pfizer Validation Number	B5377002
Pfizer Sponsor Location	Groton, CT
Pfizer Principal Contact	Chun-Hua (Sherry) Cai
Bioanalytical Laboratory	(b) (4)
Bioanalytical Laboratory Job Reference	
Notebook Reference	
Principal Bioanalytical Investigator	
Method Description Matrix Anticoagulant Sample Storage Temperature	 Human serum none -70°C
Source of Control Matrix	Biochemed
Response Detection	ECLA
Sample Aliquot Volume	Screen: not less than 10 µL Confirm : not less than 10 µL Titer: not less than 10 µL
Positive Control(s)	Affinity purified rabbit IgG RA-23008-A.01 (polyclonal)
Positive Control (PC) Concentrations	1.17 to 2560 ng/mL for PC titration curve; LPC = 320 ng/mL, HPC = 2560 ng/mL
Critical Reagents	PF-06438179-Biotin labeled at (b) (4) PF-06438179-STAG (Ruthenium (SulfoTag™)) labeled at (b) (4)
Assay MRD	1:20
Detection Instrument	MSD Sector Imager 2400
Analytical System Software and Version	Bio-Tek Gen5 Secure, Meso Scale Discovery WorkBench software
Plate Cut Point Factor (CPF) for screening	1.34 for normal human serum 1.52 for Rheumatoid Arthritis (RA) patient serum
Confirmatory assay cut point	53.6% PF-06438179 in normal human serum 53.6% PF-06438179 in RA serum

Inter-Day Precision (NC, %CV of NC RLU):	20.0% (normal human serum)
Inter-Day Precision (PC, %CV of End Point Log_{10} Titer) (using CPF 1.34):	2.36% (normal human serum)
Intra-Day Precision (NC, %CV of NC RLU)	12.4% (normal human serum)
Intra-Day Precision (PC, %CV of End Point Log_{10} Titer) (using CPF 1.34)	3.46% (normal human serum)
Intra-Run Precision (PC, %CV of End Point Log_{10} Titer) (using CPF 1.34)	0.994% - 3.70% (normal human serum)
PC End Point Log_{10} Titer Range (using CPF 1.34)	2.87 – 3.31 (normal human serum)
Drug Tolerance	HPC (2560 ng/mL) tolerated up to 5.00 µg/mL PF-06438179. LPC (320 ng/mL) tolerated up to 0.500 µg/mL PF-06438179
Target Interference (TNF-α)	HPC and LPC both tolerate up to 5000 pg/mL
PC linearity of dilution	Dilution linearity observed with 20X, 60X, and 180X from PC 100 µg/mL.
PC freeze/thaw stability	At least 7 cycles at -70°C
PC ambient stability	At least 24 hours at room temperature
Relative Mass-based sensitivity for PC in human serum	54.8 ng/mL
Matrix Recovery (normal/disease)	Normal human serum spiked at high PC and low PC: 100% lots tested have recovery between 75% and 125%. RA patient serum spiked at high PC and low PC: 70% lots tested have recovery between 75% and 125%.
Assay robustness	Assay robustness was demonstrated by 37 validation runs on different days performed by two different analysts.

Targeted Assay Validation Acceptance Criteria	
PC log titer (endpoint titer (log_{10}))	Within ± 3*SD from inter-run precision.
Precision (CV) of PC response values above the assay cut point	≤ 25%
Precision (CV) of mean NC response values and plate cut point value	≤ 25%
Response value of the mean NC for each run	Acceptance criteria will be established for the NC from all acceptable validation runs.
Response value of the mean maximum positive control for each run	Within ± 3*SD of mean inter-run maximum response value
PC freeze/ thaw stability	Difference of PC log titer values are within a Log of the PC serial dilution factor when compared to cycle 1
PC Room Temperature stability	Difference of PC log titer values are within a Log of the PC serial dilution factor when compared to unexposed to room temperature sample
Linearity of PC sample	PC log titer values at various dilutions for the samples that are expected to generate a value above the cut point should be within a Log of the PC serial dilution factor
Matrix Specificity (recovery)	At least 2/3 of the lots spiked with low or high PC should have recovery between 75-125%.
Assay Robustness	Difference of PC log titer values are within a Log of the PC serial dilution factor when comparing the different conditions evaluated.

7. LINEARITY (B5377002, anti-PF-06438179 ADA)

A dilution linearity test was conducted to assess the positive control (PC). The PC (2.30 mg/mL) was diluted to demonstrate that the assay detects antibody in samples across a range of titers. Three samples were prepared for the PC at dilutions of 1:20, 1:60 and 1:180. Each dilution was analyzed on separate plates in triplicate. The difference between the PC endpoint log titer values at the various dilutions are expected to generate values above the cut point within the log of the PC serial dilution factor of 3 which is 0.48. Results indicated that no non-linear trends were observed.

8. DRUG TOLERANCE (B5377002, anti-PF-06438179 ADA)

Assay interference may be caused by samples containing PF-06438179 due to competition for anti-PF-06438179 antibodies between free PF-06438179 in the sample and labeled PF-06438179 within the assay platform. Drug tolerance of the PC was assessed with both the high positive control (HPC, 2560 ng/mL) and the low positive control (LPC, 320 ng/mL). Varying concentrations of PF-06438179 ranging from 50.0, 25.0, 10.0, 5.00, 1.00, 0.5, 0.1, to 0.00 µg/mL were spiked with either the HPC or the LPC. The mean RLU of samples in presence and absence of free drug were compared. Results demonstrate that the HPC tolerated up to 5.00 µg/mL PF-06438179. The LPC tolerated up to 0.500 µg/mL PF-0643817 (See Table 12.12 of Section 5.3.1.4, B5377002 - The Validation of an ECLA Method for Detection of anti-Infliximab Antibodies in Human Serum - Amendment 1).

9. SCREENING CUT POINTS (B5377002, anti-PF-06438179 ADA)

To validate the detection of anti-PF-06438179 antibodies in human serum, 50 individual lots of normal human serum and 25 individual lots of RA human serum were analyzed for screening cut point assessments.

Each sample was analyzed in duplicate in three independent analyses. The means were log transformed and each analysis was assessed for normality and outliers. If outliers were identified, these were removed and the data was re-assessed for normality. Both normal and RA samples were found to be normal and therefore, parametric analysis was suitable for cut point factor determination which are used as normalization factors due to the variation in mean response of negative control samples across plates.

Plate cut point factors for screening	
Normal	1.34
RA	1.52

10. CONFIRMATORY CUT POINTS (B5377001, anti-Remicade ADA)

Fifty individual lots of normal human serum and 25 individual lots each of RA and Crohns human serum were evaluated for cut points in the confirmatory assays. All individual lots were analyzed with and without a spike of 25.0 µg/mL US-licensed Remicade or 25.0 µg/mL EU-approved Remicade. All confirmatory assay cut points were calculated from the percent signal inhibition in the presence of the spike versus no spike. Confirmatory assay cut points for normal human serum were determined to be; 55.5% for US-licensed Remicade (See Section 5.3.1.4 b5377001 Table 12.5) and 54.4% for EU-approved Remicade (See Section 5.3.1.4 b5377001 Table 12.6). The confirmatory assay cut points for RA human serum were determined to be 57.4% for US-licensed Remicade and 59.7% for EU-approved Remicade (See Section 5.3.1.4 b5377001 Tables 12.7 and 12.8). The Sponsor decided not to use a confirmatory cut point in Crohn's human serum as disclosed in Study Binder #179242 (See Section 5.3.1.4 b5377001 Tables 12.9 and 12.10). A 1% false positive rate was targeted. The sponsor did not submit clinical trial data from Crohn's patients in this BLA. Each sample was analyzed in duplicate by three independent analyses. Data was log transformed and assessed for normality and outliers. The data was re-assessed for normality after excluding outliers.

Reviewer Comment: *Information for the cut point analysis was sourced from Module 5.3.1.4 Appendix F: Cut Point Determination.*

Normal serum cut point results are shown for each of the three independent analyses 1-3 in the Figures below.

For ease of review, the following table is a reviewer summary for the results of the confirmatory assay cut points.

Confirmatory cut points (% signal inhibition)		
Normal	US-licensed Remicade	55.5
	EU-approved Remicade	54.4
RA	US-licensed Remicade	57.4
	EU-approved Remicade	59.7
Crohns	US-licensed Remicade	99.4
	EU-approved Remicade	100

Reviewer Comment: *Confirmatory assay cut points for the normal and RA samples show comparable results, while the Crohn's samples are not being used by the Sponsor. As the results show in the table above, the Crohn's cut point values are so high for sera without ADA that they do not give useful information about whether ADA binding competition would impact the results. The Sponsor recited that a*

study on the Crohns results may be undertaken in the future. No clinical data from Crohn's patients was submitted in this BLA.

Overall confirmatory assay precision by DS inhibition of ADA assay signal is ≤16.0%. This was demonstrated using HPC spiked with drug vs. HPC spiked without drug over multiple runs (See Section 5.3.1.4 B5377001 Tables 12.11).

11. CONFIRMATORY CUT POINTS (B5377002)

Fifty (50) individual lots of normal human serum and 25 individual lots of RA human serum were evaluated for confirmatory cut point assessments. Each sample was spiked with either buffer or excess drug (PF-06438179) and analyzed in duplicate in three independent analyses. Based on the removal of outliers and log normalization, a parametric assessment resulted in the confirmatory cut points shown in the reviewer summary table below. The confirmatory cut point of 53.6% will be used for both validation assessments and in-study sample analysis.

Confirmatory cut points (% signal inhibition)	
Normal	53.6
RA	53.6

Reviewer Comment: *Parametric assessment of confirmatory cut points results were identified at a signal inhibition of 53.6% for normal serum and 53.6% for RA serum.*

12. SENSITIVITY (B5371001 AND B5371002)

Relative assay sensitivity was determined at the concentration for which the PCs produced a response equal to the cut points for the assays. This is reported as the 95% confidence internal value from inter-run precision data. The relative mass assay sensitivity of anti-ID MAb PC were analyzed on multiple days and two different analysts to assess inter-day precision of the values and log titers. The sensitivity for the PC associated with the first validated ADA screening assay (B5377001) is 15.4ng/mL PC (See Section 5.3.1.4, Amendment 2, Table 12.13). The sensitivity for the PC associated with the second validated ADA screening assay (B5371002) is 54.8 ng/mL (See Section 5.3.1.4, Amendment 1, Table 12.8).
Reviewer Comment: *There is a discrepancy in the numbers wherein the text cites 55.4 ng/mL and the referenced table cites 54.8 ng/mL. This is attributed to a typographical error in the text and is confirmed based on statistical data presented in the table providing evidence that the reported 54.8 ng/mL sensitivity is the correct value. Because this is understood by the reviewer to be the correct value, the typographical error has no impact on the review or assessment of sensitivity of the assay.*

Reviewer Comment: *The sensitivity of the anti-Remicade assay (B5371001) was 15.4 ng/mL of PC. The sensitivity of the anti-PF-06438179 assay (B5371002) was 54.8 ng/mL of PC. Both assays demonstrate sensitivity well within the current FDA recommendation for sensitivity of at least 100 ng/mL. This is appropriate.*

B. Neutralizing Antibody Assay Validation (B5377003 and B5377004)

1. NEUTRALIZING ANTIBODY (NAB) ASSAY (B5377003) (anti-PF-06438279 NAbs)

A semi-quantitative cell based immunogenicity assay to detect the presence of neutralizing anti-PF-06438179 antibodies in human serum samples was validated. For validation, 50 normal, 25 Crohn's and 25 RA human serum samples were used. The cut point factor of 0.54 from normal human serum was used to process PC data reduction in all validation runs.

The analytical method including parameters and parameter values used in the validation runs are shown below.

5.3. Analytical Method

Parameter	Value of Parameter
General:	
Analyte	Neutralizing Anti-PF-06438179 antibody
Matrix	Human Serum
Control Concentrations	NC: pooled normal human serum PC: rabbit anti-Infliximab polyclonal antibody (5 µg/mL)
Minimum Required Dilution (MRD)	5
Sample Volume	44 µL for screening 100 µL for selectivity 100 µL for titration
Assay Procedure Summary	In this homogenous assay, samples / negative controls / positive controls are mixed with PF-06438179, TNF-α and Actinomycine D, then add into WEHI-13VAR cell-seed plate. The mixture is incubated at 37°C for 20±2 hours to initiate the TNF-α induced cytotoxicity. CellTiter Glo™ is used to generate the signal by the quantitation of the ATP present, an indicator of metabolically active cell. The presence of a neutralizing antibody inhibits the function of PF-06438179 and results in a lower chemiluminescent signal.
Data Acquisition:	
Equipment	Molecular Devices Spectra max L plate reader
Program	SoftMax Pro 5.2
Analysis and Reporting:	
Program	Watson 7.4.1 with Immune Response Module or Microsoft Excel
Precision for Reporting	3 Significant digit for RU, 3 decimal places for $\log_{10}$ titer

The validation reports disclose that high individual matrix variations were observed from both Crohn's disease and RA populations on each plate from three independent validation runs performed on different days. Plate NC EPT and various NC and TNF-α blocking rates for each run were within AC. The %CV of each plate was greater than 30%, which resulted in screening cut point factor close to zero (or negative) when data was normally distributed according to the initial validation protocol. A non-parametric approach was used to calculate the plate screening cut point factor for both Crohn's disease and RA populations regardless of the data distribution normally or non-normally distributed.

Three validation runs were performed to evaluate: (1) the screening cut points for RA, Crohn's populations, (2) the PC cross-reactivity, and (3) PC EPT range. Controls consisted of pooled normal human serum as the NC and rabbit anti-Remicade (PF-06438179 biosimilar of Remicade) polyclonal antibody as the primary PC. The PC stock B was prepared at 5 µg/mL in human serum. Results were provided in the Addendums for the Pfizer Validation Study No. B5377003.

Precision was measured as the coefficient of variation (%CV) from analyzing replicates of PC 5000 ng/mL. The Sponsor states that the assay is considered precise if the %CV of PC end point log titers from each set of (intra-run) PC and all accepted (inter-run) runs are less than 30%. Intra-run precision was determined from 4 sets of rabbit anti-Remicade polyclonal antibody PC on each of the 6 intra-run plates. Inter-run precision was determined from the 30 accepted analytical runs. Given the CPF 0.54, the %CV for inter-assay precision of mean RU at maximal PC, PC end point titer and end point log titer are 49.6%, 13.1%. and 4.4%, respectively. Both intra-run and inter-run PC end point log titer precisions met the sponsor's validation AC.

2. CELL-BASED NAB ASSAY CUT POINT (B5377003) (anti-PF-06438279 NAb)

The cell-based NAb cut point factor was determined from the mean response of NC of each plate after removal of any outliers. Cut point determination included 40 RA and 40 Crohn's disease samples using a 99.9% upper confidence limit. The average calculated plate cut point factors for the screening runs of normal, Crohn's, and RA human serum yielded values of 0.54, 0.21, and 0.83, respectively. The cut point factor of 0.54 established from normal human serum was used to process PC data reduction for all validation runs.

Reviewer Comment: *Note that, per Draft FDA Guidance: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products, a 1% false-positive rate is advised rather than a 0.1% false-positive rate. However, because most (around 80%) ADA positive patient samples also test positive for Nabs, a more conservative cut point is unlikely to impact outcomes or the ability to compare the biosimilar and the reference product.*

3. MATRIX INTERFERENCE/DRUG TOLERANCE (B5377003) (anti-PF-06438279 NAb)

The PF-06438179 concentration that inhibits the ability to detect PC was assessed using 5µg/mL PC pre-incubated with PF-06438179 at different concentrations: 0.00, 0.10, 0.25, 0.50, and 1.00 µg/mL. The lowest concentration of PC yields either positive results or is less than the plate cut point for each level of PF-06438179 (See Table 14 of Section 5.3.1.4, B5377003 Amendment 1).

4. SENSITIVITY AND SELECTIVITY (B5377003) (anti-PF-06438279 NAb)

The mass based assay sensitivity to detect neutralizing anti-PF-06438179 antibody is 1358 ng/mL based on the surrogate rabbit anti-Remicade polyclonal antibody (See Table 15 of Section 5.3.1.4, B5377003 – Amendment 1). The assay is capable of detecting the presence of neutralizing anti-Remicade antibody and neutralizing anti-PF-06438179 antibody.

Matrix selectivity (recovery) was determined by analyzing 10 individual lots of pooled normal and diseased human serum spiked with and without PC sera at 2.5 µg/mL. Results demonstrate that 9 of 10 Crohn's and 10 of 10 normal showed recovery between 75-125% (See Tables 10-12 of Section 5.3.1.4, b5377003 – Amendment 1).

5. NEUTRALIZING ANTIBODY (NAB) ASSAY (B5377004) (anti-Remicade NAb)

A semi-quantitative cell based immunogenicity assay to detect the presence of neutralizing anti-US licensed Remicade and anti-EU approved Remicade antibodies in human serum samples was validated. The cut point factor of 0.54 from normal human serum was used to process PC data reduction in all validation runs.

6. CELL-BASED NAB ASSAY CUT POINT (B5377004) (anti-Remicade NAb)

The cell-based NAb cut point factor was determined from the mean response of NC of each plate after removal of any outliers. Cut point determination included 50 normal, 25 RA and 25 Crohn's disease samples using a 99.0% upper confidence limit. The average calculated plate cut point factors for the screening runs of normal, Crohn's, and RA human serum yielded values of 0.62, 0.65 and 0.45, respectively (See Tables 4-6 of Section 5.3.1.4, B5377004, Addendum 1). The cut point factor of 0.62 established from normal human serum was used to process PC data reduction for all validation runs.

Reviewer Comment: *The Sponsor indicated that the cut point factor established from normal human serum samples will be used in future analyses, while the RA and Crohn's samples will be re-assessed. The Sponsor's justification for the re-assessment is that cut point factors for Crohn's (0.65) and RA (0.45) are different from the Remicade NAb assay for the biosimilar product, PF-06438179 (0.21 and 0.83), respectively as shown in Pfizer study report B5377003 (anti-PF-06438179 NAb) and above in this review. This is acceptable.*

7. MATRIX INTERFERENCE/DRUG TOLERANCE (B5377004) (anti-Remicade NAb)

The Remicade concentration that inhibits the ability to detect PC was assessed using 5 µg/mL PC pre-incubated with Remicade at different concentrations: 0.00, 0.10, 0.20, 0.50, and 1.00 µg/mL. The lowest PC concentration retains a positive or greater signal than the plate cut point at each Remicade concentration tested (See Table 14 of Section 5.3.1.4, B5377004).

8. SENSITIVITY AND SELECTIVITY (B5377004) (anti-Remicade NAb)

The mass based sensitivity is the concentration of anti-Remicade antibodies in human serum that will result in a signal that is equal to the plate cut point. The assay sensitivity for rabbit anti-Remicade polyclonal antibody is 1215 ng/mL of anti-Remicade antibody. See Table 15 of Section 5.3.1.4, B5377004. The assay is capable of detecting the presence of neutralizing anti-Remicade antibody and neutralizing anti-PF-06438179 antibody.

Matrix selectivity (recovery) was determined by analyzing 10 individual lots of pooled normal and diseased human serum spiked with and without PC sera at 2.5 µg/mL. Results demonstrate that 9 of 10 of normal human serum and 10 of 10 Crohn's or RA showed recovery between 75-125% (See Tables 10-12 of Section 5.3.1.4, B5377004 – Addendum 1).

Reviewer Comment: *Drug tolerance, mass based sensitivity, and matrix selectivity were evaluated with results demonstrating that the anti-Remicade NAb and the anti-PF-06438179 NAb assays are capable of detecting and accurately quantifying NAb antibodies as intended.*

N. Sarah Arden

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Date: 11/09/2017 03:45:39PM
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Christopher Downey

Digitally signed by Christopher Downey
Date: 11/09/2017 04:19:34PM
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FDA U.S. FOOD & DRUG ADMINISTRATION

BLA STN 761072
Product PF-06438179
Proposed Trade Name IXIFI
Manufacturer Pfizer Inc.

Review of Drug Substance Product Quality and of the Analytical Similarity Assessment

Yanming An, Ph.D.
Drug Substance and Similarity Assessment Reviewer

Christopher Downey, Ph.D., ATL

Office of Biotechnology Products
Division of Biotechnology Review and Research II

OBP CMC Review Data Sheet

1. BLA#: 761072

2. Review Date: November 08, 2017

3. Primary Review Team:

a. Medical Officer	Erika Torjusen/ Banu Karimi-shah, Nikolay Nikolov
b. Pharm/Tox	Matthew Whittaker/ Tim Robinson
c. Product Quality Team	Yanming An (DS quality, Analytical Similarity) Sarah Arden Nilou (DP quality, analytical method validation, immunogenicity) Christopher Downey (Application Technical Lead) Kathleen Jones (DS microbiology) Aimee Cunningham (DP microbiology)
d. Facilities	Marion Michaelis/ Peter Qiu
e. Clinical Pharmacology	Manuela Grimstein/ Anshu Marathe
f. Statistics	Yongman Kim (End 06/07/2017) William Koh/ Greg Levin Meiyu Shen/ Yu-Ting Weng (CMC Stat)
g. OBP Labeling	Vicky Borders-Hemphill
h. RBPM	Sadaf Nabavian Christine Ford (End 08/18/2017) Kelly Ballard (OPQ) Keith Olin (OPQ)

4. Major GRMP Deadlines:

a. Filing Meeting	March 20, 2017
b. Mid-cycle meeting	July 17, 2017
c. Wrap-up meeting	October 31, 2.17
d. Primary review due	November 9, 2017
e. Secondary review due	November 16, 2017
f. PDUFA action date.	December 13, 2017

5. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request (DMA)	March 07, 2017
Information Request (DIA)	March 16, 2017
OPQ Filing Review	April 14, 2017
Information Request (OBP I)	May 09, 2017
Information Request (DIA/OBP II)	May 18, 2017
Information Request (OBP III)	August 09, 2017
Information Request (OBP IV)	September 29, 2017
Information Request (OBP V)	November 01, 2017

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
761072/0001	February 13, 2017	Yes
761072/0009 (OBP IR I response)	May 22, 2017	Yes
761072/0011	June 13, 2017	Yes
761072/0014 (OBP IR III response)	August 18, 2017	Yes
761072/0015 (OBP IR III response)	August 28, 2017	Yes
761072/0017 (OBP IR III response)	September 11, 2017	Yes
761072/0018 (OBP IR III response)	September 20, 2017	Yes
761072/0023	October 30, 2017	Yes
761072/0024 (OBP IR V response)	November 06, 2017	Yes

7. Drug Product Name/Code/Type:

a. Proprietary Name PF-06438179
b. Trade Name IXIFI (proposed)
c. Non-Proprietary Name/USAN infliximab- qbtx (proposed)
d. CAS Name: 170277-31-3
e. Common Name:
f. INN Name To be determined
g. Compendial Name not applicable
h. OBP systematic name (refer to OPQ-SOP-OBP-3006)
MAB CHIMERIC (IGG1) ANTI P01375 (TNFA_HUMAN) [PF-06438179]

8. Pharmacological Category: Therapeutic recombinant human monoclonal antibody

9. Dosage Form:100 mg lyophilized solid in a single-use 15 mL vial to be reconstituted with 10 mL sterile water for injection

10. Strength/Potency:

(i): The concentration/strength of the Drug Product
100 mg of lyophilized infliximab in a 15 mL single-use vial, to be reconstituted with 10 mL sterile water for injection
(ii): Type of potency assay(s) Cell-based bioassay

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	DMF is current and will comply with all statements made

[redacted] (b) (4)	Yes	in it.
	Yes	
	Yes	
	Yes	

13. Inspectional Activities:

A PAI was conducted from [redacted] (b) (4). Information about the facility and FDA personnel involved is described below:

Firm: [redacted] (b) (4)
FEI: [redacted] (b) (4)
Dates of inspection: [redacted] (b) (4)
Days in the facility:
FDA Participants: [redacted]

CDER/OPQ/OPF/DMA
CDER/OPQ/OPF/DMA
CDER/OPQ/OBP/DBRRII
CDER/OPQ/OBP/DBRRII

This pre-license inspection of the drug substance manufacturing facility at [redacted] (b) (4) was conducted on [redacted] (b) (4) following a request by Division of Microbiology Assessment, Office of Process and Facilities, Office of Pharmaceutical Quality, CDER. The inspection was conducted to support the approval of Pfizer's biosimilar BLA STN761072/0 for PF-06438179. This inspection covered a comprehensive scope of Quality, Facilities and Equipment, Materials, Production and Laboratory Controls. This inspection was limited to the manufacturing of PF-06438179 drug substance. No refusals were encountered during the inspection. No sample collection was needed.

Two verbal discussion items were brought to the attention of firm's management at the conclusion of the inspection on 0[redacted] (b) (4) concerning: [redacted] (b) (4) Management acknowledged the Discussion Items and promised corrections.

A PAI was conducted from October 10, 2017 through October 12, 2017. Information about the facility and FDA personnel involved is described below:

Firm: Pfizer Inc.
Location: Andover, MA

FEI:
Dates of inspection: October 10 to 12, 2017
Days in the facility: 3

FDA Participants:	Sean Marcsisin	ORA/OMPTO/OPQO/DPQOI/PQIBI
	Chris Downey	CDER/OPQ/OBP/DBRRII
	Yanming An	CDER/OPQ/OBP/DBRRII

This pre-license inspection of the drug substance cell bank manufacture and storage facility and similarity assessment laboratory at Pfizer Worldwide Research and Development (WRD), Andover, MA was conducted on 10/10-10/12/2017 following a request by Pharmaceutical Quality Investigation Branch I, Division of Pharmaceutical Quality Operations I, Office of Pharmaceutical Quality Operations, Office of Medical Products and Tobacco Operations, ORA. This inspection covered the cell bank manufacture and storage facility and the similarity assessment studies. This inspection was limited to the PF-06438179. No refusals were encountered during the inspection. No sample collection was needed. No observations were made to the firm.

Refer to the OBP Drug Product review by Sarah Arden for information regarding inspectional activities related to Drug Product.

14. Consults Requested by OBP: N/A

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:

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation

We recommend approval of the BLA. The data submitted in this Biologics License Application support the conclusion that the manufacture of PF-06438179 is well controlled and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product

has been manufactured from multiple production runs. It is recommended that PF-06438179 be approved for human use (under conditions specified in the package insert).

We recommend an expiration dating period of (b) (4) months for PF-06438179 Drug Substance when stored at (b) (4) °C in (b) (4). (b) (4)

Refer to the OBP Drug Product Review by Sarah Arden for recommendations on Drug Product expiry dating.

We recommend approval of the proposed release and shelf-life specifications for PF-06438179 Drug Substance.

The analytical similarity assessment performed supports that:

- PF-06438179 is highly similar to US-licensed Remicade notwithstanding minor differences in clinically inactive components:
- A sufficiently robust analytical bridge was established to support the use of EU-approved Remicade as a comparator in the clinical study.

II. List of Deficiencies to be Communicated

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

III. List of Post-Marketing Commitments/Requirements

There are one Product Quality-related Post-Marketing Commitment, which will include due dates negotiated with the sponsor:

1) Implement an assay assessing binding to FcγRIIIa into the Drug Substance release specification. Submit the proposed release specification as a prior approval supplement described under 21 CFR 601.12 (b).

IV. Review of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion

Pfizer Inc. claims a categorical exclusion to the environmental assessment requirements in compliance with the categorical exclusion criteria 21 CFR Part 25.31 (b): Action on an NDA: the estimated concentration of the substance(s) at the point of entry into the aquatic environment will be below 1 part per billion. Pfizer Inc. claims that to our knowledge, no extraordinary circumstances.

Reviewer note: The sponsor's environmental analysis and claim of categorical exclusion are adequate.

V. Primary Container Labeling Review

The primary container labeling was reviewed separately by Vicky Borders-Hemphill with concurrence by Yanming An and Christopher Downey.

VI. Review of Common Technical Document- Quality Module 3.2

CTD Modules 3.2.S, 3.2.R, and 3.2.A are reviewed in this document. Modules 3.2.P, 3.2.S.4.3, and the Comparability Protocol in 3.2.R.4 were reviewed separately by Nilou Sarah Arden and Christopher Downey.

VII. Review of Immunogenicity Assays- Module 5.3.1.4

The immunogenicity assays were reviewed separately by Nilou Sarah Arden and Christopher Downey.

Description of Drug Substance

S. Drug Substance

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

Information on the nomenclature of PF-06438179, the proposed Pfizer biosimilar to Remicade® (infliximab) is provided in Table 3.2.S.1.1-1.

Table 3.2.S.1.1-1. Nomenclature of PF-06438179 Drug Substance

Name/code	Description
International Nonproprietary Name (INN) for Reference Product	infliximab
International Nonproprietary Name (INN) for PF-06438179	To be determined
Chemical Name (IUPAC)	Not applicable
Internal Company or Laboratory Code (Pfizer)	PF-06438179 or infliximab-Pfizer
CAS Registry Number for infliximab	170277-31-3

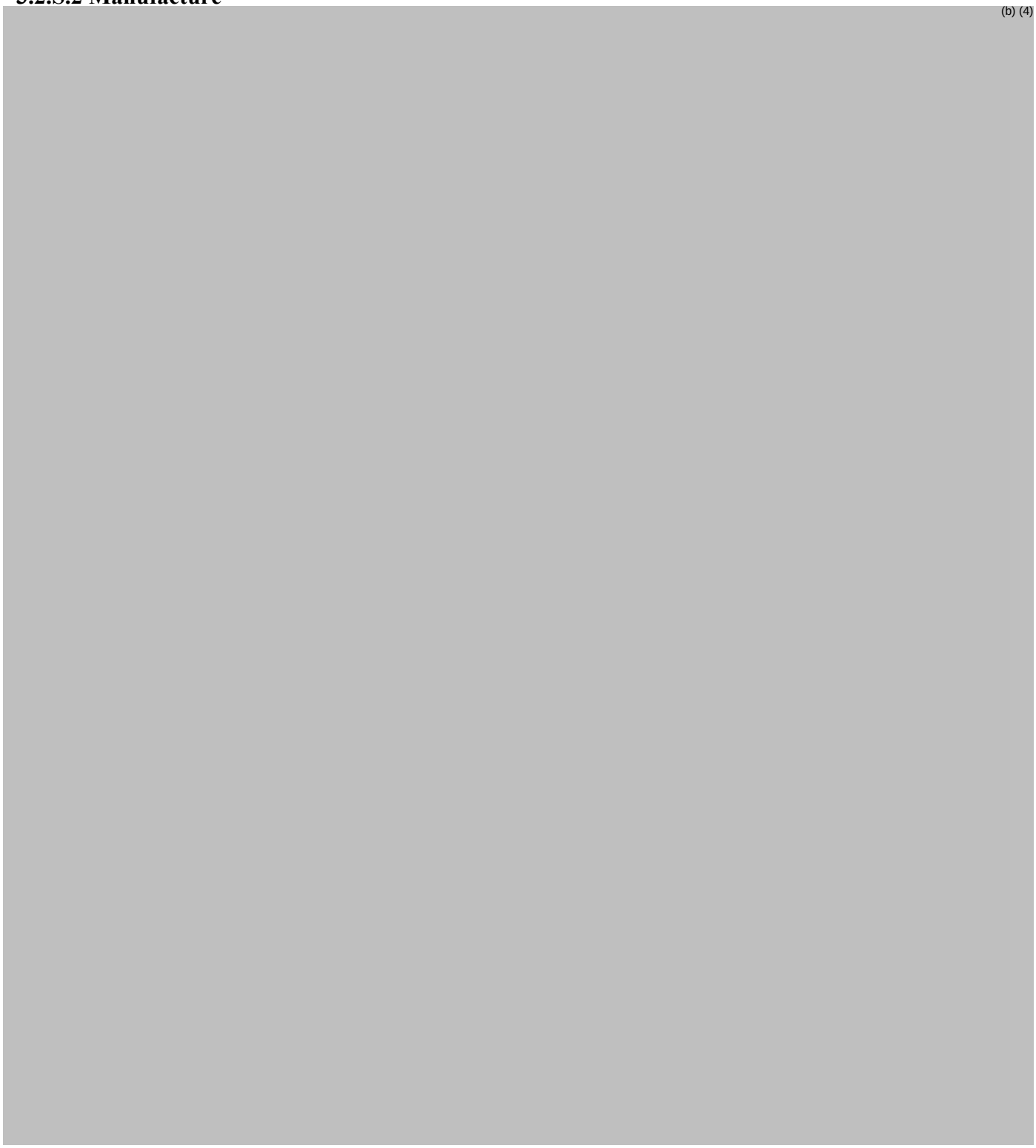
3.2.S.1.2 Structure

PF-06438179 is a recombinant chimeric IgG1 kappa monoclonal antibody (mAb) composed of complementarity-determining regions derived from mouse anti-human tumor necrosis factor alpha monoclonal antibody and framework and constant regions derived from human IgG1. PF-06438179 has two identical heavy (H) chains and two identical light (L) chains, covalently linked with four inter-chain disulfide bonds.

Reviewer notes: *The protein sequence of PF-06438179 is experimentally verified and it is the same as the biosimilar reference product, US-licensed Remicade.*

3.2.S.2 Manufacture

(b) (4)



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(b) (4)

[redacted]

ANALYTICAL SIMILARITY ASSESSMENT

Reviewer Comment:

The data from 3.2.R reviewed in the below sections of the memo support the following conclusions:

- *PF-06438179 is analytically highly similar to US-licensed Remicade.*
- *The data demonstrate an analytical bridge between US-licensed Remicade and EU-Approved Remicade.*
- *For attributes where minor potential differences between PF-06438179 and US-licensed Remicade are noted, the totality of the analytical data support that there are no impacts on function, activity, or stability in vitro. Therefore, the differences are not expected to be clinically meaningful.*
- *Method validation or qualification results for methods used in the analytical similarity assessment are adequate to support that the methods are scientifically sound and suitable to study the intended quality attributes.*
- *The sponsor's proposed quality ranges based on a 3 standard deviation range are appropriate acceptance criteria for each attribute evaluated with Tier 2 statistical test unless otherwise noted.*
- *The strength of U.S.-licensed Remicade is labeled in mass per vial. U.S.-licensed Remicade is 100 mg of lyophilized infliximab in a single-use vial to be reconstituted in 10 mL for intravenous infusion. Pfizer is seeking approval of PF-06438179 for the same strength as U.S.-licensed Remicade. Comparative in vitro potency, protein concentration upon reconstitution (mg/mL), and extractable volume (mL) data reviewed as part of the analytical similarity assessment were used to inform the assessment of whether the proposed presentation of PF-06438179 has the same strength as the presentation of U.S.-licensed Remicade. Based on these comparative data, the 100 mg of lyophilized PF-06438179 in a single-use vial for intravenous infusion has the same total content of drug substance in units of mass in a container as the presentation of U.S.-licensed Remicade. This presentation meets the statutory "same strength" requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.*

3.2.R.3 Comparative Physicochemical and Functional Assessment

3.2.R.3.1 Overall Strategy

The analytical similarity assessment consisted of three comparisons: PF-06438179 to US-licensed Remicade, PF-06438179 to EU-approved Remicade and EU-approved Remicade to US-licensed Remicade. With this approach, PF-06438179 could be demonstrated to be highly similar to the Remicade product approved in the US and EU, and support the use of EU-approved Remicade as the comparator in the comparative clinical study.

The comparative physicochemical and functional assessment includes:

- Comparative similarity characterization studies of the following quality attributes (QA).
    - Primary structure and posttranslational modifications
    - Biological activity
    - N-linked glycan structure
    - Charge heterogeneity
    - Product purity
    - Protein concentration
    - Disulfide bonds
    - Higher order structure
- Assessment of the similarity of the degradation mechanism resulting from forced degradation studies.

The sponsor ranked quality attributes related to similarity per their potential impact on activity, PK/PD, safety and immunogenicity. Attributes with the highest level of risk and significance to similarity that are evaluable by quantitative assays were assessed as using Tier 1 Statistical assessments[1]. Attributes having a moderate level of risk, high risk attributes present at low levels, or attributes orthogonal to those evaluates as Tier 1 are evaluated using Tier 2 statistical assessments, and the remaining attributes are assessed by Tier 3 methods. In addition, the method or assay used to measure a quality attribute was assessed to determine if the data produced is amendable to statistical analysis. Tier 1 statistical evaluation of assay results consists of equivalence testing. For Tier 2 assessments, results were evaluated by using quality ranges; analytical similarity for the attribute would meet Tier 2 criteria if 90% or greater of test values fall within the statistical quality range (3

[1] As defined in the 2017 Draft FDA Guidance *Statistical Approaches to Evaluate Analytical Similarity Guidance for Industry*

standard deviations of estimated mean of the comparator product). QAs evaluated in Tier 3 are assessed using side-by-side graphical comparisons of the raw data, and descriptive statistics were used for quantitative QAs.

A total of 53 drug product (DP) lots of US-Licensed Remicade and 60 DP lots of EU-approved Remicade were purchased and included as licensed infliximab produce in the similarity assessment. All US-licensed and EU-approved comparator lots were enrolled in the similarity assessment within the manufacturer's assigned expiry date, and were tested using the PF-06438179 release methods. Subsets of the licensed DP lots were also tested with additional characterization assays. A total of eleven drug substance (DS) batches, eight DP lots and two reference materials of PF-06438179 were included in the similarity assessment (see discussion of lot independence below). The PF-06438179 DS batches and DP lots were all produced at the commercial scale and commercial manufacturing sites.

Table 3.2.R.3-1: PF-06438179 DS and DP lots used for similarity assessment

DS Batch #	DS Date of manufacture	DP Lot #	DP Date of manufacture	Purpose of material
94200[a, b]	Aug 2012			Non-clinical
94000[b]	Oct 2012	Z09719[a]	Nov 2012	Clinical, stability
94001[b]	Oct 2012	A03038[a]	April 2013	Clinical, stability
94002[b]	Oct 2012	A02637[a]	April 2013	Clinical Inventory, Stability, Nonclinical study
		L07814	Nov 2014	Clinical
94003	Dec 2014	M01013[a, b]	May 2015	Clinical, PV, reference standard
94004	Dec 2014	M29852[a, b]	July 2015	Clinical inventory, PV, Stability
94005	Dec 2014	M29851[a, b]	Aug 2015	Clinical inventory, PV, stability
94003, 94004, 94005		M29853	Aug 2015	Clinical inventory, PV, stability
19200000[a, b]	May 2017	N/A	N/A	Intended for Commercial
19200001[a, b]	May 2017	N/A	N/A	Intended for Commercial
19210000[a, b]	May 2017	N/A	N/A	Intended for Commercial

19210001[a, b]	May 2017	N/A	N/A	Intended for Commercial

a. Defined as an independent lot and result used in the Tier 1 inhibition of staff-induced cell Apoptosis assay.
b. Defined as an independent lot and result used in the Tier 1 sTNF binding assay.

The sponsor used "independent" lots for the quality attributes (inhibition of Cell Apoptosis and Binding to sTNF) evaluated using Tier 1 equivalence testing. Independent lots refer to individual DS batches and DP lots made from different DS batches; a DS lot and the DP lot made from that DS lot are not independent from each other. Because not all DP lots were tested in both assays, lots were selected based on the following principles:

- First, independent DP lots tested in the assay were selected. In the situation where 2 DP lots were made for the clinical from a single DS batch, the DP lot enrolled in stability was selected for the similarity assessment.

- Second, DS batches that did not have a corresponding, tested DP lot were selected. This case applied for characterization assays that were not routinely applied to DP lot release testing but were performed at FDA request, for example the binding affinity to soluble TNFα measured by SPR assay. In such cases, the similarity data include a mix of DS and DP PF-06438179 lots.

Reviewer comments:

1. *The initial BLA submission included data for 7 independent lots of PF-06438179 drug substance and drug product in the analytical similarity assessment. On August 9, 2017 FDA requested that the sponsor provide, for both Tier 1 assays, all lot release tests data derived from all independent lots of PF-06438179 manufactured to date including lots manufactured since submission of the BLA. The sponsor provided the requested data from lots 19200000, 19200001, 19210000, and 19210001 in Amendment eCTD0018 (Sep 20, 2017). The data from the additional 4 lots were included in the two Tier 1 assays analyses.*

2. *To assure independence of the data points, it is acceptable to use results from available independent DS batches and DP lots manufactured solely from single DS lots. This is acceptable for attributes that depend primarily on the sequence, 3-dimensional structure, and glycosylation of the product, which is determined primarily by the DS manufacturing process. Such attributes include binding affinity to TNFα and Fc-mediated functions. We assess attributes such as aggregates or deamidated species that may be impacted by DP manufacture or long term storage either by only comparing drug product lots and/or by assessing whether the attribute was differs significantly between PF-06438179 DS and DP.*

3. *The OBP team participated in a pre-approval inspection at Pfizer Worldwide Research and Development located at Andover MA from Oct 10-12, 2017. During the inspection, we toured the analytical laboratories where most of the similarity assessment assays were performed.*

We reviewed their data management system, sample management, laboratory notebooks, instrumentation records, and SOPs. We audited the analytical similarity data of Tier 1 and Tier 2 bioassays and interviewed SMEs. We reviewed electronic notebooks of bioassays, including inhibition of apoptosis, sTNF SPR binding, FcγIIIα158V and 158F binding, NK cell ADCC, FcγRIIIαRGA, mTNF binding FACS, CDC assay, and C1q Binding ELISA, and cross-checked the data with those reported in the BLA. We requested the Analytical Test Reports (ATR) for all PF-06438179 and US-licensed Remicade, which include all the release test results for each sample. We cross-checked the data in these reports with those in BLA. No objectionable conditions were noted, and our assessment found that the similarity data and characterization assay descriptions presented in the BLA are accurate and representative of the raw data for PF-06438179, US-licensed Remicade, and EU-approved Remicade collected by the applicant.

A summary of the analytical similarity results prepared by the reviewer are presented in the following Table 3.2.R.3-2.

1. *The sponsor originally intended to analyze both DP lots and the same DS lots from which they were produced in its Tier 1 and Tier 2 statistical assessments. In the BPD Type 4 pre BLA meeting, FDA communicated that applicant should statistically assess independently manufactured lots to accurately represent the variability of its manufacturing process. Thus, Pfizer included only independent lots (i.e. DP lots made from unique DS lots and unique DS lots) in the Tier 1 assessments. For many of the Tier 2 quality range assessments, Pfizer included all its data from all DS and DP lots, including non-independent DP lots and the DS lots from which they were produced. The "Number of lots" column on the table below shows the total number of lots the sponsor tested, including DS and DP lots. Our conclusions of "pass/fail" for these Tier 2 assessments are based on looking at independent lots, with DP selected for Tier 2 analysis rather than its constituent DS when data from both were available.*

2. *The sponsor ranked the quality attributes (QAs) in the similarity assessment study. The two quantitative assays selected for evaluation by Tier 1 statistical method (equivalence test) reflect the known clinical mechanism of action (MoA), which is sTNF binding activity. The bioassays evaluated by Tier 2 method include assays that reflect the plausible MoA of Fc domain effector function and mTNF binding and reverse signal activities. The other QAs evaluated by the Tier 2 approach are relevant to drug quality and safety and are quantitative. Assays evaluated by Tier 3 either reflect same bioactivities as the bioassays evaluated by Tier 1 and Tier 2, or are relevant to the protein primary and higher order structure. Assays evaluated by Tier 3 are either qualitative or otherwise not amenable to statistical analysis or reflect less critical attributes. The assessment by Tier of statistical methods is consistent with our expectations and precedent for previous Remicade*

biosimilars, and we agree with the sponsor's evaluation. In some cases, we evaluated similarity using a different tier than the applicant and put the describe the Tier method we used in the table.

3. *As the commercial reference standard was not yet available at the time of assay development, the reference standard lot 128926-7 was used throughout the assay development work, including for the analytical similarity assessment. All relative values reported in the analytical similarity assessment were measured relative to reference standard 128926-7.*

4. *Regarding Tier 2 statistical assessments, Pfizer established quality ranges using the mean of the US-licensed Remicade ±3 standard deviations (SD). We evaluated the Pfizer established quality ranges for each assay. We concur with this range in all cases, and our conclusions of "pass/fail" are based these quality ranges we determined as suitable. The ranges for PF-06438179 in the table represent the range of minimum and maximum results.*

5. *A pairwise comparison was performed between PF-06438179, US-licensed Remicade and EU-approved Remicade. "Pass" means that the comparison met criteria of statistical equivalence test for quality attributes evaluated by Tier 1 statistics, statistical quality range test for attributes evaluated by Tier 2 statistics, and visual comparison for attributes evaluated by the Tier 3 approach. "Fail" means the comparison didn't meet the statistical or visual comparison criteria. The "fail" results are discussed in detail in the following sections of the review. A "fail" designation does not necessarily mean the product failed the overall assessment of similarity; similarity is determined by scientific evaluation of all the available evidence.*

Table 3.2.R.3-2. PF-06438179 Similarity Assessment Results

Category	Test		Analysis Tier	Number of Lots (PFE: US-licensed Remicade: EU-approved Remicade)	US-licensed Remicade Range or Quality Range[a]	PFE min – max Range	EU-approved Remicade Quality Range	US-licensed Remicade vs PFE / PFE vs EU-approved Remicade/ US-licensed Remicade vs EU-approved Remicade
Primary Structure and Post translational modifications (PTM)	Amino Acid Sequence	Edman degradation	3	1:1:1	Identical amino acid sequence for the variable and constant regions.	Identical amino acid sequence for the variable and constant regions for US-licensed Remicade	Identical amino acid sequence for the variable and constant regions for US-licensed Remicade	Pass/Pass/Pass
		LC-MS/MS with specialized bioinformatic	3	1:1:1	Identical amino acid sequence for the variable and constant regions.	Identical amino acid sequence for the variable and constant regions for US-licensed Remicade	Identical amino acid sequence for the variable and constant regions for US-licensed Remicade	Pass/Pass/Pass
	Molecular Mass	nanoESI-MS intact protein	3	1:1:1	Similar molecular mass and size	Similar molecular mass and size to US-licensed Remicade	Similar molecular mass and size to US-licensed Remicade	Pass/Pass/Pass
	Primary structure and PTM	LC/MS-subunit Analysis	3	1:1:1	Identical primary structure and high similar identity and locations of PTM at the subunit/domain level.	Identical primary structure and high similar identity and locations of PTM at the subunit/domain level to US-licensed Remicade	Identical primary structure and high similar identity and locations of PTM at the subunit/domain level to I US-licensed Remicade	Pass/Pass/Pass
		LC/MS and LC/UV-Peptide mapping (Trypsin or Lys-C treatment)	3	1:1:1	Identical primary structure and high similar identity and locations of PTM at the subunit/domain level.	Identical primary structure and high similar identity and locations of PTM at the subunit/domain level to US-licensed Remicade	Identical primary structure and high similar identity and locations of PTM at the subunit/domain level to US-licensed Remicade	Identical primary structure and high similar identity and locations of PTM at the subunit/domain level.

Category	Test		Analysis Tier	Number of Lots (PFE: US-licensed Remicade: EU-approved Remicade)	US-licensed Remicade Range or Quality Range[a]	PFE min – max Range	EU-approved Remicade Quality Range	US-licensed Remicade vs PFE / PFE vs EU-approved Remicade/ US-licensed Remicade vs EU-approved Remicade
Biological Activity—Proven MoA: TNF Binding to Fab Domain	Binding TNF	Inhibition of sTNF-induced cell Apoptosis	1	11:53:60	83-118%[a]	87-104%	77-122%[a]	Pass/Pass/Pass
		Binding to sTNF Target Antigen by Surface Plasmon Resonance	1	11:11:11	98-112%[a]	94-114%	93-107%[a]	Pass/Pass/Pass
		Binding to Cell Surface TNF Antigen on NS0 Cells by FACS	2	11:12:16	74-138%	90-117%	80-138%	Pass/Pass/Pass
		Reverse Signaling	2	7:10:10	86-120%	100-109%	86-122%	Pass/Pass/Pass
		Inhibition of TNF-induced ELAM-1 expression	3	8:7:7	91-107%[b]	91-104%	93-110%[b]	Pass/Pass/Pass

Category	Test		Tier	Number of Lots (PFE: US-licensed Remicade: EU-approved Remicade)	US-licensed Remicade Quality Range	PFE min – max Range	EU-approved Remicade Quality Range	US-licensed Remicade vs PFE / PFE vs EU-approved Remicade / US-licensed Remicade vs EU-approved Remicade
Biological Activity—Functional Characterization of Fc Domain	ADCC Activity	Primary NK Cell ADCC Assay	2	10:10:9	61-141%	65-110%	29-145%	Pass/Pass/Pass
		FcγRIIIa Reporter Gene Assay	2	12:11:11	85-136%	93-110%	83-129%	Pass/Pass/Pass
		Mixed Lymphocyte Reaction (MLR) Assay	3	5:5:5	Inhibit proliferation of T-cells in a dose-dependent manner	Similar dose-dependent response curve to US-licensed Remicade	Similar dose-dependent response curve to US-licensed Remicade	Pass/Pass/Pass
		Natural Killer (NK) Cell Binding Assay	3	5:5:5	Bound to primary NK cells in a dose-dependent manner	Similar dose-dependent response curve to US-licensed Remicade.	Similar dose-dependent response curve to US-licensed Remicade.	Pass/Pass/Pass
		Binding to FcγRIIIa 158V by SPR	2	10:11:10	64-103%	76-88%	65-103%	Pass/Pass/Pass
		Binding to FcγRIIIa 158F by SPR	2	10 11 10	59-103%	76-92%	60-104%	Pass/Pass/Pass

Category	Test		Tier	Number of Lots (PFE: US-licensed Remicade: EU-approved Remicade)	US-licensed Remicade Quality Range	PFE min – max Range	EU-approved Remicade Quality Range	US-licensed Remicade vs PFE / PFE vs EU-approved Remicade / US-licensed Remicade vs EU-approved Remicade
Biological Activity—Functional Characterization of Fc Domain	CDC Effector Function	CDC Assay	2	10:10:10	73-124%	97-106%	65-127%	Pass/Pass/Pass
		C1q Binding ELISA	2	13:12:13	68-111%	83-114%	72-116%	Fail/Pass/Pass
	Additional Fcγ Receptor Binding SPR Assay	Binding to FcγRI	3	10:11:10	85-119%	87-107%	93-111%	Pass/Fail/Pass
		Binding to FcγRIIa 131H	3	10:11:9	73-113%	85-106%	79-118%	Pass/Pass/Pass
		Binding to FcγRIIa 131R	3	10:11:10	Weak bonding K_D > 2500 nM	Weak bonding K_D > 2500 nM	Weak bonding K_D > 2500 nM	Pass/Pass/Pass
		Binding to FcγRIIIb	3	10:11:10	Weak bonding K_D > 2500 nM	Weak bonding K_D > 2500 nM	Weak bonding K_D > 2500 nM	Pass/Pass/Pass
Biological Activity—half-life		Binding to FcRn	2	15:10:10	85-123%	85-112%	85-124%	Pass/Pass/Pass

Category	Test		Tier	Number of Lots (PFE: US-licensed Remicade: EU-approved Remicade)	US-licensed Remicade Quality Range	PFE min – max Range	EU-approved Remicade Quality Range	US-licensed Remicade vs PFE / PFE vs EU-approved Remicade / US-licensed Remicade vs EU-approved Remicade
N-Linked Glycan Structure	N-Linked Glycan Profile Hydrophilic interaction liquid chromatography (HILIC)	% Total Afucosylation	2	8:52:60	3.7-10%	5.5-9.0%	2.9-10.4%	Pass/Pass/Pass
		% Terminal Galactosylation	2	8:52:60	20.3-53.2%	33.4-39.2%	15.9-62.5%	Pass/Pass/Pass
	N-Linked Glycan structure-Characterization	HILIC-MS Glycan Mapping	3	1:1:1	Similar N-Linked glycan distribution profile, structure, composition and glycosidic linkages	Similar N-Linked glycan distribution profile, structure, composition and glycosidic linkages to US-licensed Remicade	Similar N-Linked glycan distribution profile, structure, composition and glycosidic linkages to US-licensed Remicade	Pass/Pass/Pass
		Exoglycosidase Digestion/HILIC	3	1:1:1	Similar N-Linked glycan distribution profile, structure, composition and glycosidic linkages	Similar N-Linked glycan distribution profile, structure, composition and glycosidic linkages to US-licensed Remicade.	Similar N-Linked glycan distribution profile, structure, composition and glycosidic linkages to US-licensed Remicade	Pass/Pass/Pass
		Sialic Acid Form	3	1:1:1	Neu5Gc	Neu5Ac	Neu5Gc	Fail/Fail/Pass

Category	Test		Tier	Number of Lots (PFE: US-licensed Remicade: EU-approved Remicade)	US-licensed Remicade Quality Range	PFE min – max Range	EU-approved Remicade Quality Range	US-licensed Remicade vs PFE / PFE vs EU-approved Remicade / US-licensed Remicade vs EU-approved Remicade
Protein Concentration	UV 280 nm absorbance		2	8:53:60	8.8-10.6	9.6-10.3	9.1-10.1	Pass/Pass/Pass
Charge Heterogeneity	iCE	% Acidic Species	2	16:53:60	8.0-26.1%	21.5-23.2%	9.1-23.3%	Pass/Pass/Pass
		% Basic Species	2	16 53 60	30.2-61.4%	13.2-22.8%	33.9-58.7%	Fail/Fail/Pass Difference in C terminal lysine is not considered clinical relevant
	Characterization	Cation Exchange-HPLC profile characterized by MS	3	1:1:1	Similar major and minor charge isoforms	Similar major and minor charge isoforms to US-licensed Remicade	Similar major and minor charge isoforms to US-licensed Remicade	Pass/Pass/Pass Difference in C-terminal lysine is not considered clinical relevant.
		Carboxypeptidase B/ iCE	3	9:6:8	Similar major and minor charge isoforms	Similar major and minor charge isoforms to US-licensed Remicade	Similar major and minor charge isoforms to US-licensed Remicade	Pass/Pass/Pass

Category	Test		Tier	Number of Lots (PFE: US-licensed Remicade: EU-approved Remicade)	US-licensed Remicade Quality Range	PFE min – max Range	EU-approved Remicade Quality Range	US-licensed Remicade vs PFE / PFE vs EU-approved Remicade / US-licensed Remicade vs EU-approved Remicade
Product Purity	Size Exclusion HPLC	Monomer	2	16:53:60	99.4-99.9%	99.4-99.8%	99.4-100%	Pass/Pass/Pass
		HMMS	2	16:53:60	0.1-0.4%.	0.2-0.6%	0.1-0.4%	Pass/Pass/Pass
	CGE (reducing)	Fragment	2	16:53:60	0 -1.5%	1.0-1.9%	0.3-1.2%	Fail/Fail/Pass
		% HC+LC	2	16:53:60	98.0-100.0%	97.8-99%	98.4-100.0%	Fail/Fail/Pass
	SDS-PAGE	Total Protein staining and Western blotting	3	1:1:1	Similar banding pattern	Similar banding pattern to US-licensed Remicade.	Similar banding pattern to US-licensed Remicade	Pass/Pass/Pass
	Dissociation constants for self-association	Analytical ultracentrifugation equilibrium (AUC-SE)	3	1:1:1	Similar dissociation constant	Similar dissociation constant to US-licensed Remicade.	Similar dissociation constant to US-licensed Remicade	Pass/Pass/Pass

Category	Test		Tier	Number of Lots (PFE: US-licensed Remicade: EU-approved Remicade)	US-licensed Remicade Quality Range	PFE min – max Range	EU-approved Remicade Quality Range	US-licensed Remicade vs PFE / PFE vs EU-approved Remicade / US-licensed Remicade vs EU-approved Remicade
Disulfide Bonds	LC/MS Non-Reduced Peptide Mapping		3	1:1:1	Similar state of cysteines and disulfide bonds	Similar state of cysteines and disulfide bonds to US-licensed Remicade	Similar state of cysteines and disulfide bonds to US-licensed Remicade	Pass/Pass/Pass
	Sulfhydryl Analysis		3	1:1:1	Similar state of cysteines and disulfide bonds	Similar state of cysteines and disulfide bonds to US-licensed Remicade	Similar state of cysteines and disulfide bonds to US-licensed Remicade	Pass/Pass/Pass
Higher Order Structure	Secondary Structure	Far-UV CD	3	14:18:20	Similar secondary structure	Similar secondary structure to US-licensed Remicade	Similar secondary structure to US-licensed Remicade	Pass/Pass/Pass
		FTIR		5:7:7				
	Tertiary Structure	Near-UV CD	3	14:18:20	Similar tertiary structure	Similar tertiary structure to US-licensed Remicade	Similar tertiary structure to US-licensed Remicade	Pass/Pass/Pass
		Intrinsic Fluorescence		5:7:7				
		X-ray crystallography	3	1:1:1	Similar crystal structure	Similar crystal structure to US-licensed Remicade	Similar crystal structure to US-licensed Remicade	Pass/Pass/Pass

Category	Test		Tier	Number of Lots (PFE: US-licensed Remicade: EU-approved Remicade)	US-licensed Remicade min-max Range	PFE min – max Range	EU-approved Remicade min-max Range	US-licensed Remicade vs PFE / PFE vs EU-approved Remicade / US-licensed Remicade vs EU-approved Remicade
Forced Degradation - Drug product in lyophilized form held at 50°C for three months (Change from T=0)	HIAC	subvisible particles≥ 10 µm/mL	3	5:2:3	56-674	-2--15	1129-1541	Pass/Pass/Pass
		subvisible particles≥ 25 µm/mL	3	5:2:3	0-2	0-1	3-7	Pass/Pass/Pass
	UV spectroscopy (mg/mL)		3	5:2:3	-0.4 - -0.3	-0.4- -0.2	-0.5 - -0.2	Pass/Pass/Pass
	Cell-based bioassay		3	5:2:3	-13- 8	-12 - -1	0-4	Pass/Pass/Pass
	SE-HPLC	Monomer	3	5:2:3	-0.1 - 0	-0.4 - -0.3	-0.1 - 0	Pass/Pass/Pass
		HMMS	3	5:2:3	0.1	0.3-0.4	0-0.1	Pass/Pass/Pass
		LMMS	3	5:2:3	0	NA	0	Pass/Pass/Pass
	CGE (non-reducing)	IgG	3	5:2:3	-0.5 - -0.1	-0.7 - -0.4	-0.7 - -0.2	Pass/Pass/Pass
		Fragment	3	5:2:3	0.1-0.5	0.2-0.4	0.2-0.7	Pass/Pass/Pass
		other	3	5:2:3	NA	0.3	NA	Pass/Pass/Pass
	CGE (reducing)	HC + LC	3	5:2:3	0.9	0.7-0.9	0.4-1.1	Pass/Pass/Pass
		Fragment	3	5:2:3	-0.4	-0.1 - 0	-0.3- 0	Pass/Pass/Pass
		other	3	5:2:3	-0.5	-1 - -0.6	-0.7 - -0.4	Pass/Pass/Pass
	Lysyl endopeptidase limited proteolytic peptide map		3	5:2:3	0.8-0.9	0.1-0.6	0.5-1.1	Pass/Pass/Pass
	iCE	Acidic	3	5:2:3	-2.2 - -0.8	2.3-4.3	-1.1 - 0	Pass/Pass/Pass
		main	3		-4.0 - -3.1	-8.5 - -6.3	-4.6 - -3.4	Pass/Pass/Pass
		Basic	3		4.8-5.2	3.8-5.0	4.5-5.5	Pass/Pass/Pass

Category	Test		Tier	Number of Lots (PFE: US-licensed Remicade: EU-approved Remicade)	US-licensed Remicade min-max Range	PFE min – max Range	EU-approved Remicade min-max Range	US-licensed Remicade vs PFE / PFE vs EU-approved Remicade / US-licensed Remicade vs EU-approved Remicade
Forced Degradation - Drug product reconstitute held at 40°C for two months (Change from T=0)	HIAC	subvisible particles≥ 10 µm/mL	3	3:3:3	493-544	391-790	381-762	Pass/Pass/Pass
		subvisible particles≥ 25 µm/mL	3	3:3:3	23-35	36-74	34-105	Pass/Pass/Pass
	UV spectroscopy (mg/mL)		3	3:3:3	-0.1	-0.3- -0.1	-0.2 - -0.1	Pass/Pass/Pass
	Cell-based bioassay		3	3:3:3	-37 - -20	-49 - -10	-32 - -14	Pass/Pass/Pass
	SE-HPLC	Monomer	3	3:3:3	-5.4 - -5.0	-4.3 - -4.1	-5.2	Pass/Pass/Pass
		HMMS	3	3:3:3	0.3-0.6	0.2-0.3	0.4-0.6	Pass/Pass/Pass
		LMMS	3	3:3:3	4.6-4.9	3.8-4.1	4.7-4.8	Pass/Pass/Pass
	CGE (non-reducing)	IgG	3	3:3:3	-13.2 - -12.1	-4.3 - -2.9	-13.1 - -7.2	Pass/Pass/Pass
		Fragment	3	3:3:3	11.9-12.9	2.9-4.0	6.9-12.8	Pass/Pass/Pass
		other	3	3:3:3	0.3-0.4	0.3	0.3	Pass/Pass/Pass
	CGE (reducing)	HC + LC	3	3:3:3	-16.8 - -16.4	-3.9 - -3.2	-16.9 - -16.3	Pass/Pass/Pass
		Fragment	3	3:3:3	12.9-13.4	3.1-3.7	12.8-13.2	Pass/Pass/Pass
		other	3	3:3:3	3.3-3.6	0.2	3.6-4.1	Pass/Pass/Pass
	iCE	Acidic	3	3:3:3	39.8-42.9	22.9-24.0	42.3-44.9	Pass/Pass/Pass
		main	3	3:3:3	-30.5 - -16.9	-20.0 - -19.2	-27.2 - -25.8	Pass/Pass/Pass
		Basic	3	3:3:3	-23.2 - -15.6	-4.5 - -3.8	-18.0 - -16.5	Pass/Pass/Pass

Category	Test		Tier	Number of Lots (PFE: US-licensed Remicade: EU-approved Remicade)	US-licensed Remicade min-max Range	PFE min – max Range	EU-approved Remicade min-max Range	US-licensed Remicade vs PFE / PFE vs EU-approved Remicade / US-licensed Remicade vs EU-approved Remicade
Forced Degradation -Drug Product Reconstituted and exposed to light for 14 days at 25°C (Change from T=0)	Cell-based bioassay		3	1:1:1	9	-21.0	23	Pass/Pass/Pass
	SE-HPLC	Monomer	3	1:1:1	-7.4	-6.1	-6.4	Pass/Pass/Pass
		HMMS	3	1:1:1	7.0	5.7	6.1	Pass/Pass/Pass
		LMMS	3	1:1:1	0.4	0.4	0.3	Pass/Pass/Pass
	CGE (non-reducing)	IgG	3	1:1:1	-9.5	-7.5	-7.9	Pass/Pass/Pass
		Fragment	3	1:1:1	5.7	4.5	4.6	Pass/Pass/Pass
		other	3	1:1:1	3.8	3.0	3.3	Pass/Pass/Pass
	iCE	Acidic	3	1:1:1	10.1	8.3	11.2	Pass/Pass/Pass
		main	3	1:1:1	-1.0	-4.6	-3.7	Pass/Pass/Pass
		Basic	3	1:1:1	-9.1	-3.7	-7.4	Pass/Pass/Pass

Category	Test		Tier	Number of Lots (PFE: US-licensed Remicade: EU-approved Remicade)	US-licensed Remicade min-max Range	PFE min – max Range	EU-approved Remicade min-max Range	US-licensed Remicade vs PFE / PFE vs EU-approved Remicade / US-licensed Remicade vs EU-approved Remicade
Forced Degradation -Drug Product Reconstituted and diafiltered into 20 mM sodium phosphate, pH 8.0 for 14 days at 40°C (Change from T=0)	Cell-based bioassay		3	1:1:1	-25	-13	-17	Pass/Pass/Pass
	SE-HPLC	Monomer	3	1:1:1	-0.6	-0.9	-0.6	Pass/Pass/Pass
		HMMS	3	1:1:1	0.1	0.4	0.2	Pass/Pass/Pass
		LMMS	3	1:1:1	0.5	0.5	0.5	Pass/Pass/Pass
	CGE (non-reducing)	IgG	3	1:1:1	--3.8	-3.9	-3.8	Pass/Pass/Pass
		Fragment	3	1:1:1	3.8	3.9	3.8	Pass/Pass/Pass
		other	3	1:1:1	NA	NA	NA	Pass/Pass/Pass
	iCE (before CPB treatment	Acidic	3	1:1:1	46.0	56.7	50.4	Pass/Pass/Pass
		main	3	1:1:1	-16.5	-44.1	-27.5	Pass/Pass/Pass
		Basic	3	1:1:1	-29.5	-12.6	-22.9	Pass/Pass/Pass
	iCE (after CPB treatment)	Acidic	3	1:1:1	58.5	58.8	58.9	Pass/Pass/Pass
		Main	3	1:1:1	-59.1	-58.4	-60.4	Pass/Pass/Pass
		Basic	3	1:1:1	-0.6	-0.4	1.8	Pass/Pass/Pass

[a] For attributes assessed by Tier 1 and 3 statistics, the min - max range is shown. For attributes assessed by Tier 2 statistics, the statistical quality range is shown.

3.2.R.3.2 Characterization Data

3.2.R.3.2.1 Comparative Assessment for Assays evaluated by Tier 1 (Equivalence Test)

The blockade of TNF functionality by the binding of the Fab domain represents the primary MOA for PF-06438179.

3.2.R.3.2.1.1 Inhibition of [soluble TNFα-induced] Apoptosis Assay

Biological activity of PF-06438179, US-licensed Remicade, and EU-approved Remicade was assessed by an inhibition of cell apoptosis assay. This assay is the lot release assay for potency for PF-06438179. The assay measures the inhibition of TNF-induced cell apoptosis by PF-06438179 in U937 cells. Apoptosis is assayed via the luminescence of caspase-3 and caspase-7. This activity is determined against the activity of a reference standard tested at the same time.

The similarity assessment included the comparison of 11 PF-06438179 independent lots (1 drug substance (non-clinical) batch, 4 drug substance batches manufactured since BLA submission and 6 drug product (clinical) lots) to 53 US-licensed Remicade and 60 EU-approved Remicade drug product lots. Graphical presentation of the relative potency results is shown in Figure 3.2.R.3.2-1 (pasted below). A tier 1 equivalence test was performed for these assay results and summarized in Figure 3.2.R.3.2-2. Because the 90% confidence intervals fall within the corresponding equivalence acceptance limits, the sponsor concluded that PF-06438179 is like US-licensed Remicade and EU-approved Remicade in the inhibition of apoptosis potency assay. The results also demonstrate that EU-approved Remicade is similar to US-licensed Remicade with respect to the release assay for potency.

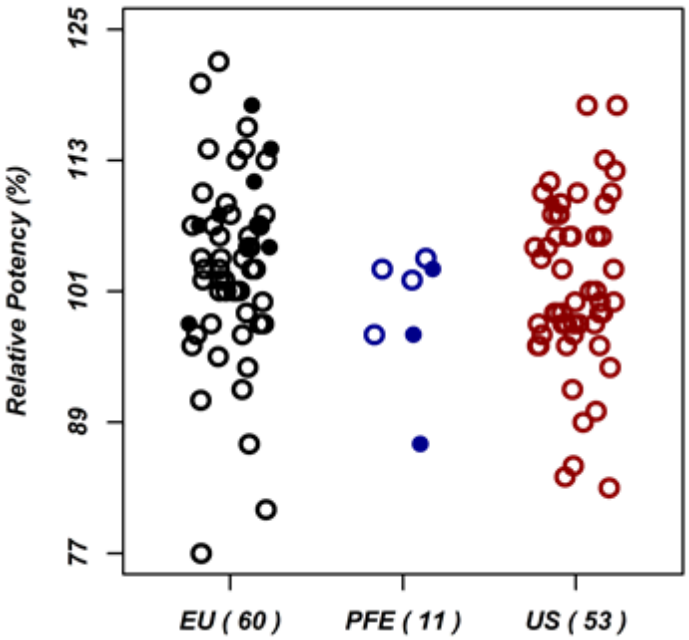


Figure 3.2.R.3.2-1 Inhibition of Apoptosis Activity of EU-approved Remicade, PF-06438179, and US-licensed Remicade.

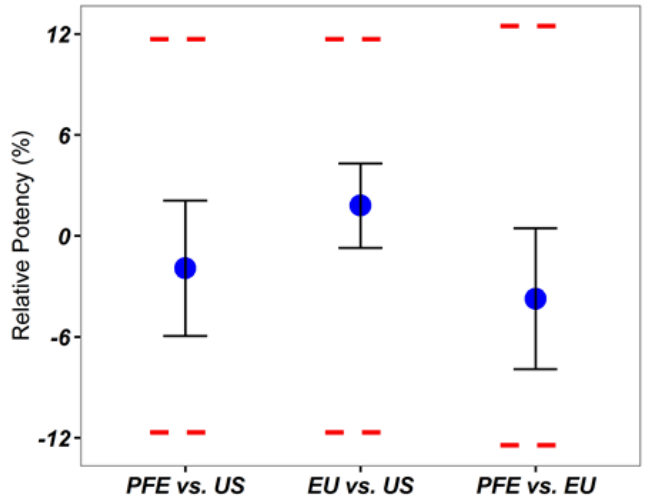


Figure 3.2.R.3.2-2 Statistical Analysis of Inhibition of Apoptosis Activity for US-licensed Remicade, PF-06438179 and EU-approved Remicade using an Equivalence Test. The solid circles represent the mean difference between the product to the left of "vs" and the product on the right. The (1-2α) confidence interval is represented by the error bars. The dashed lines represent the preset equivalence acceptance limits.

Assay qualification: Validation of the cell based assay was performed and determined that the assay is suitable for use.

This assay is a release test. Refer to section 3.2.S.4.3 Validation of Analytical Procedures.

Reviewer comment: *Figure 3.2.R.3.2-2 above showed the US and EU Equivalence Acceptance limits and the pairwise comparison results with 90% confidence interval. The products all have similar averages, and all PF-06438179 lots fall within the range of values measured for US-licensed Remicade. These data support similarity between all 3 products from a product quality perspective. Refer to the CMC stats review for assessment of whether this demonstrates a passing result for statistical equivalence testing.*

Originally, 7 PF-06438179 lots were included in this assessment. On 09 Aug., 2017, we sent an IR to request additional data for both tier 1 assays from all independent lots of PF- 06438179, and ask the sponsor to repeat equivalence testing using a 90% confidence level for all three pairwise comparisons for both attributes assigned to Tier 1 testing and report the results.

The sponsor submitted (in amendment eCTD0018) release test results from four DS batches which were manufactured after the original BLA submission. And they repeated the equivalence testing using 90% confidence level for three pairwise comparisons for both Tier 1 assays with the additional DS data. The data for all 11 DS lots are shown in the figures above and were analyzed by the CMC stats team.

3.2.R.3.2.1.2 Binding to sTNF Target Antigen by SPR

The binding kinetics and affinities of PF-06438179, US-licensed Remicade, and EU-approved Remicade to sTNF target antigen were evaluated using surface Plasmon resonance (SPR) technology. The similarity assessment included the comparison of 11 PF-06438179 independent lots (4 drug substance (non-clinical and clinical) batches, 4 drug substance manufactured since BLA submission and 3 drug product (clinical) lots) to 11 US-licensed Remicade and 11 EU-approved Remicade drug product lots. Graphical presentation of the ratio of the equilibrium dissociation constant K_D relative to the reference standard results is shown in Figure 3.2.R.3.2-3. A Tier 1 equivalence test was performed on the data. The results were summarized in Figure 3.2.R.3.2-4. Because the 90% confidence intervals fall within the corresponding equivalence acceptance limits, the sponsor concluded that PF-06438179 is similar to US-licensed Remicade and EU-approved Remicade for sTNF binding.

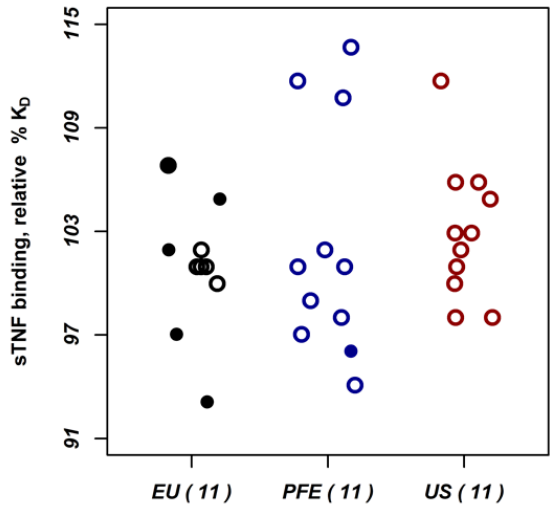


Figure 3.2.R.3.2-3 sTNF Binding Activity of EU-approved Remicade, PF-06438179 and US-licensed Remicade

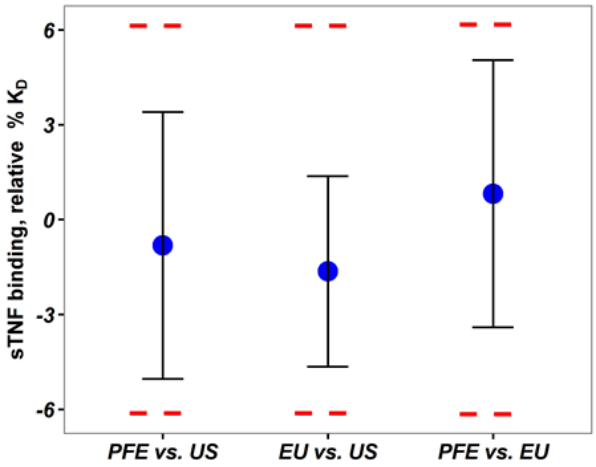


Figure 3.2.R.3.2-4 Statistical Analysis of Target Binding to sTNF for EU-approved Remicade, PF-06438179, and US-licensed Remicade using analyzed by equivalence testing. The solid circles represent the mean difference between the product to the left of "vs" and the product on the right. The confidence interval is represented by the error bars. The dashed lines represent the equivalence acceptance limits determined by the sponsor.

Assay qualification (INX100252521): The kinetics of infliximab binding to rhTNF-α was determined by surface plasmon resonance (SPR)-based measurements with a Biacore T200 instrument. The binding of a concentration range of sTNF (25.6 pM to 1.0 nM) to PF-06438179 and the Remicade products was analyzed for each data point. The equilibrium dissociation constant (K_D) for the reaction between sTNF and infliximab was calculated from the on and off rate constants measured at these concentrations. All samples were tested in four independent runs (n=4). PF-06438179 reference material was included in each run. Relative binding affinity (% K_D) was calculated by dividing K_D value of the reference material by K_D value of a test sample. The sponsor provided data evaluating method performance. The accuracy

and precision (%RSD) were demonstrated to be 103% and 6.7%, respectively. Injection of control samples demonstrated that sTNF binding SPR is specific for infliximab products.

Reviewer comment: *The accuracy, precision, and specificity of the assay were evaluated and the method is suitable for the intended purpose. The OBP team audited the data this assay and verified the raw data that went into the similarity assessment during the October 10 – 12, 2017 Inspection of the Pfizer Andover Facility. Refer to the CMC stats review for assessment of whether the results pass the statistical equivalence testing.*

On May 9, 2017, we sent an IR to ask the rationale for using much fewer Remicade lots (11 lots each from the US and EU markets) in the SPR binding assay than in the inhibition of apoptosis assay (>50 lots from both markets). The sponsor explained (amendment eCTD0009) that the sTNF binding SPR assay is not a release assay as the inhibition of apoptosis assay is. They used fewer Remicade lots for non-release assays. Pfizer did not intend to evaluate this using a Tier 1 method until advised to do so by FDA relatively late in development. The lot selection was based on availability of the materials at the time of testing and included clinical trial comparator EU lots.

From a product quality perspective, it is acceptable to use 11 lots each Remicade products in the similarity assessment. The lots selected are representative and do not appear to have been chosen in a manner that would bias the results. There are 11 independent PF-06438179 lots available for this assay. So, the sample sizes of the Remicade and PF-06438179 are the same. No sample size adjustment is needed in the statistical analysis.

In the May 9, 2017 IR, we also asked the rationale for testing three DS lots of PF-06438179 (94000, 94001, and 94002) instead of testing all DP lots for the sTNF binding assay. The sponsor explained that not all PF-06438179 DP lots were tested with this assay because it was not routinely used to test all lots throughout development like the PF-06438179 lot release assays were (e.g. the apoptosis assay). After the BPD Type 4 meeting with FDA in which we requested that the statistical analysis include only independent lots, they included independent DS lots for which they had data in the statistical analysis. It is acceptable to use independent DS lots data when the corresponding DP lots data are not available to assure the independence of the data points; this attribute is determined by the structure of the molecule and does not depend significantly on the DP manufacturing process.

Reviewer comment: *The attributes directly probing the primary mechanism of action are similar between PF-06438179 and US-licensed Remicade and EU-approved Remicade. The CMC Statistics reviewer concluded that the cell-based inhibition of apoptosis assay and the sTNF binding assay are statistically equivalent for pairwise comparisons. A sufficient number of US and EU lots were subjected for similarity analysis with the 11 independent PF-06438179 lots. The cell-based inhibition of apoptosis assay is also drug substance and drug product release test for identity and potency measurement, and was fully validated with PF-06438179 reference standard as a control. Assay accuracy, precision, and specificity were demonstrated.*

3.2.R.3.2.2 Similarity Assessment for Tier 2 (Quality Range Approach)

Quality attributes evaluated by Tier 2 are those of moderate to high risk for impact on quality for which quantitative data can be obtained. A quality range approach is used for the Tier 2 statistical analysis. Pfizer calculated the quality range as the estimated mean (of US-licensed Remicade) ± 3 standard deviations (SD). Analytical similarity would be established for the quality attribute if at least 90% of the lots of PF-06438179 or EU-approved Remicade are within the quality range of US-licensed Remicade.

3.2.R.3.2.2.1 Binding to mTNF Target Antigen on NS0 Cells

Flow cytometry (FACS) was employed to assess the binding of PF-06438179, US-licensed Remicade, and EU-approved Remicade to mTNF-expressing NS0 cells. Figure 3.2.R.3.2-5 shows a graphical presentation for relative EC50 values for all lots tested. Pfizer derived the statistical quality range of 74-138% relative EC50 for mTNF binding from the 12 US-licensed Remicade lots. 100% of PF-06438179 and EU-approved Remicade lots were within quality range for mTNF binding.

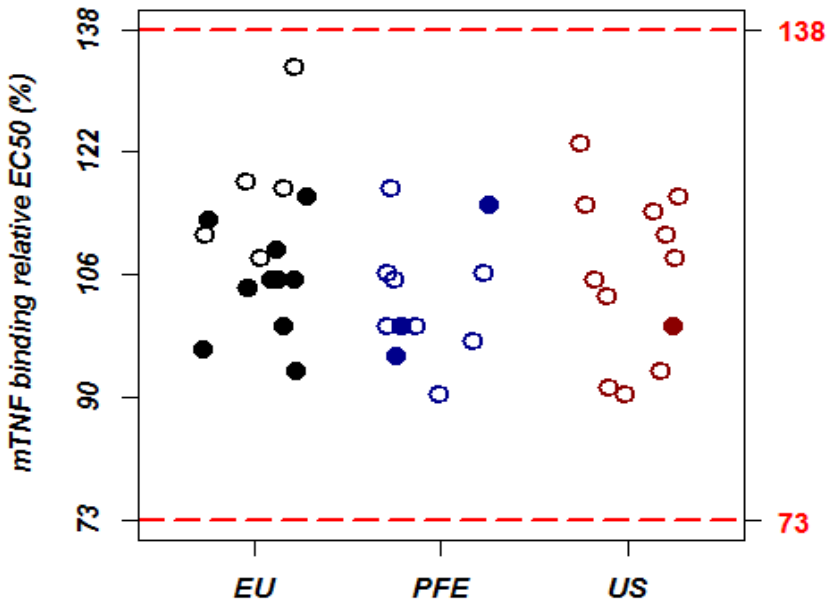


Figure 3.2.R.3.2-5 Statistical Quality Range for mTNF Binding Activity of EU-approved Remicade, PF-06438179, and US-licensed Remicade.

Assay Qualification (INX100250061): The mTNF binding assay was qualified, and its linear range is 50-150% relative potency (RP). The assay has an accuracy of 88% at target and an intermediate precision of 7% relative standard deviation (RSD). Specificity was demonstrated that no specific binding was measured with isotype control.

Reviewer comment: *The qualified assay is adequate to support the testing results. The SD of US-licensed Remicade mTNF binding results was 10.7%, reflecting method and lot to lot variability. The quality range is reasonable for similarity assessment. The infliximab binding to mTNF expressed on cell*

surface is similar for all pairwise comparisons between PF-06438179, US-licensed Remicade, and EU-approved Remicade.

3.2.R.3.2.2.2 Cell-based Reverse Signaling Assay

Reverse signaling is a likely mechanism of action for infliximab involving the binding of the Fab domain to mTNF on certain cell types. The infliximab/mTNF complex can initiate reverse signaling or outside-to-inside signaling in the TNF-producing cell and lead to cell apoptosis. In the reverse signaling cell-based assay, infliximab binds to mTNF expressed on the cell surface, resulting in signal transduction which initiates apoptotic events. A reagent is added that lyses the cells and enables luminescent detection of the apoptotic indicators, caspase 3 and caspase 7.

Reverse signaling activity was assessed for PF-06438179, US-licensed Remicade and EU-approved Remicade. Table 3.2.R.3-3 summarized the statistical analysis results. Pfizer derived the quality range of 86-120% relative EC50 using the mean ± 3 SD from the 10 US-licensed Remicade lots. All the lots of PF-06438179 and EU-approved Remicade were within the quality range.

Table 3.2.R.3.-3. Summary of Descriptive Statistics for Reverse Signaling Activity

Relative EC_{50} Ratio (%)						
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	10	104	6.1	5.8	97	115
Pfizer	7	105	3.9	3.7	100	109
US	10	103	5.7	5.6	91	110

N = sample size, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum, NA = Not Applicable

Assay qualification (INX100279419): The assay was qualified with a linear range of 50-150% relative potency (RP). The assay has an accuracy of 101% at target and an intermediate precision of 6% relative standard deviation (RSD).

Reviewer comment: *The qualified assay is adequate to support the testing results. The quality range of ±3 standard deviations is reasonable. Infliximab reverse signaling mediated by mTNF-α expressed on cell surface is similar for all pairwise comparisons between PF-06438179, US-licensed Remicade, and EU-approved Remicade.*

Fc-mediated effector functions

Remicade has moderate Fc domain effector function, antibody-dependent cell mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC). It has been proposed in the scientific literature that Fc-mediated effector functions may be a mechanism of action for IBD indications. Pfizer

used a group of in vitro bioassays for ADCC and CDC, evaluated by Tier 2 statistical assessment. The Fc glycosylation pattern can influence effector functions. Increase of terminal galactosylation can promote CDC activity by increasing C1q binding in vitro and has modest effects on ADCC. Decreases in core-fucose levels lead to an increase in ADCC via increased affinity of IgG1 for FcγRIIIa on immune cells.

3.2.R.3.2.2.3 Primary NK Cell ADCC Assay

ADCC activity requires Fab domain binding to mTNF followed by Fc domain binding to Fcγ receptors on an effector cell, leading to the lytic death of the mTNF-expressing target cell.

The applicant developed a "classical" ADCC assay using primary human NK cells as effector cells to measure antibody-dependent lysis of target cell death. In this assay, infliximab bound to mTNF-expressing target cells can bind simultaneously to FcγRIIIa receptors on primary NK cells from human donors. When cross-linking and clustering of receptors occurs, signaling pathways in the effector cells are activated and the activated effector cell mediates target cell killing. The ADCC assay quantifies this antibody-dependent target cell death.

10 lots of US-licensed Remicade, 9 lots of EU-approved Remicade and 10 (7 independent) lots of PF-06438179 with varied N-linked glycan profiles were tested with the Primary NK Cell ADCC Assay. Table 3.2.R.3-4 summarized the statistical analysis results.

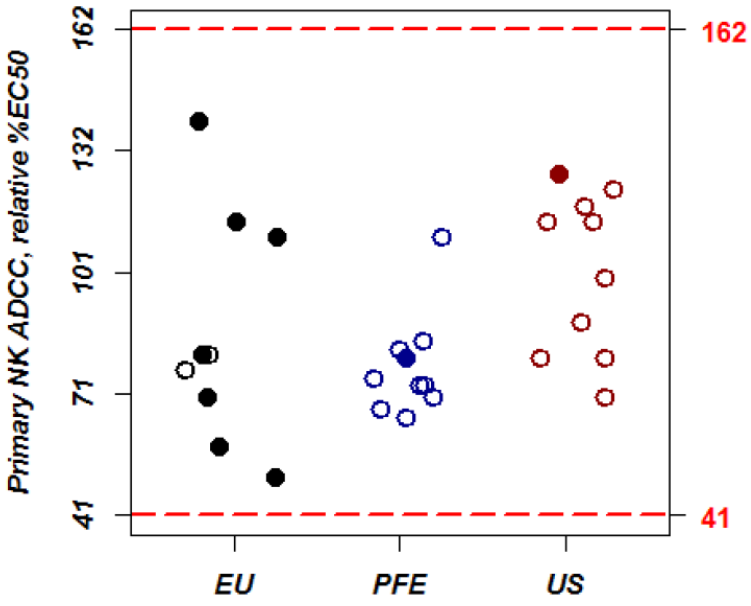


Figure 3.2.R.3.2.2-2. Scatter plot of primary NK cell-based ADCC results.

Table 3.2.R.3-4. Summary of Descriptive Statistics for ADCC Activity in the Primary NK Cell ADCC Assay

	Infliximab Relative EC50 (%)					
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	9	87	28.8	33.2	50	139
Pfizer	10	78	12.9	16.5	65	110
US	10	101	20.2	20.0	70	126

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

Pfizer derived the quality range using the mean ± 3SD from the 10 US-licensed Remicade lots, which is 41-162% relative potency (RP). The SD of US-licensed Remicade is 20.2%. This reflects the method variability across the linear range. Primary cells from multiple donors were used to complete all tests. Multiple donors heterogenicity increases the method variability. In addition, the variability of total afucosylation (5.0-9.5%) of the US-licensed Remicade added on some lot to lot variability.

Assay qualification (INX100257655): The primary NK cell ADCC assay was qualified with a linear range of 70-150% relative potency (RP). The assay performed with an accuracy of 102% at target and an intermediate precision of 4% RSD at target (100% RP), 26% RSD at 70% of target and 19% RSD at 150% of target.

Reviewer comment: *All pairwise comparisons passed the sponsor-established quality range analysis. All the ADCC activity measurements of PF-06438179 are within 2 standard deviations of the mean for US-licensed Remicade and EU-approved Remicade, and all PF-06438179 values are within the min – max range of the EU-approved Remicade lots. The assay qualification data support that this method is suitable for its intended use. The PF-06438179 lots tend slightly toward the lower end of the range for the US-approved Remicade, although still well within the quality range. This correlates with similar results for the reporter gene assay and SPR assay for FcγRIIIa binding; FcγRIIIa binding is part of the molecular mechanism of ADCC. See below for additional discussion. Thus, the ADCC assay appears to be sensitive to differences that can be detected by orthogonal methods. The data for the ADCC assay support similarity with respect to this activity.*

3.2.R.3.2.2.4 FcγRIIIa Reporter Gene Assay (FcγRIIIa RGA)

In this assay, the FcγRIIIa activation and signaling pathway were determined by the ability of the antibody to bind to mTNF on the transfected NS0 target cell and FcγRIIIa on engineered Jurkat cell, and lead to NFAT-driven reporter gene activation.

Twelve lots from PF-06438179 (both DS and DP, 7 independent), 11 lots of US-licensed Remicade and 11 lots of EU-approved Remicade were tested in the FcγRIIIa RGA. Tier 2 statistical analysis was

performed on this data. Pfizer derived the quality range of 85-136% relative EC50 from the 11 US-licensed Remicade lots. Figure 3.2.R.3.2-6 shows a graphical presentation for relative EC50 values for all lots tested. The results indicate that 100% of PF-06438179 and EU-approved Remicade lots were within the Pfizer's quality range meeting the tier 2 acceptance criteria.

Assay qualification (INX100250059): The FcγRIIIa RGA method was qualified with a linear range of 50-150% relative potency (RP). In linearity studies, the assay performed with an accuracy of 103% at target and an intermediate precision of 3% RSD at target (100% RP). Specificity was demonstrated with no response for alternate target cells.

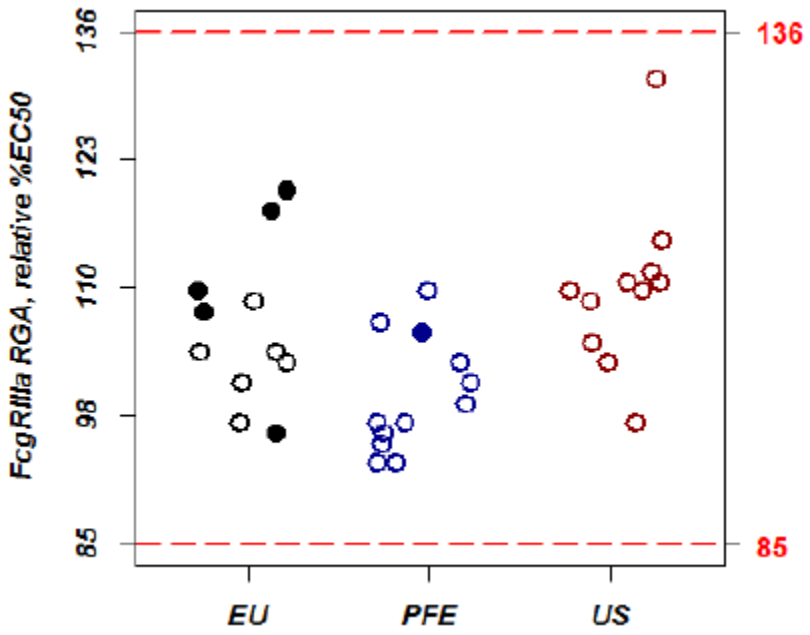


Figure 3.2.R.3.2-6 statistical Quality Range for FcγRIIIa RGA comparison of PF-06438179, US-licensed Remicade and EU-approved Remicade.

Reviewer comment: *Qualification data provided by the sponsor support that the assay is suitable for its intended use. The quality range of ±3SD is appropriate. The FcγRIIIa RGA measurement of PF-06438179 was within the US quality ranges, and the data support the conclusion that the results are similar for all pairwise comparisons between PF-06438179, US-licensed Remicade, and EU-approved Remicade. FcγRIIIa binding is an initiating step in ADCC, so this established similarity from the FcγRIIIa RGA assay suggests that ADCC activity is also similar.*

3.2.R.3.2.2.5 Binding to FcγRIIIa 158V and 158F by SPR

Binding of the antibody Fc domain to FcγRIIIa on effector cells is the first step in ADCC mechanism. FcγRIIIa 158V and 158F are two genetic variants of FcγRIIIa. SPR binding assays were employed to assess the binding affinity and kinetics of PF-06438179, US-licensed Remicade, and EU-approved

Remicade to FcγRIIIa 158V and 158F. In SPR assays, 10 lots (7 independent) of PF-06438179, 11 lots of US-licensed Remicade and 10 lots of EU-approved Remicade were tested.

Tier 2 statistical analysis was performed on the results. Figure 3.2.R.3.2-7 shows the quality range of 64-103% relative K_D for the FcγRIIIa 158V binding, which Pfizer derived from the 11 US-licensed Remicade lots. The results indicate that 100% of PF-06438179 and EU-approved Remicade lots were within the quality range meeting the tier 2 acceptance criteria.

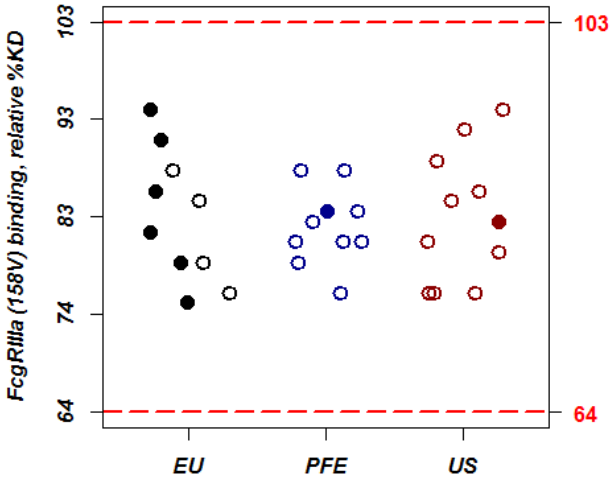


Figure 3.2.R.3.2-7 Statistical Quality Range for FcγRIIIa SPR (158V) Binding Activity Comparison.

Figure 3.2.R.3.2-8 shows the quality range of 59-103% relative K_D for the FcγRIIIa 158F binding, which Pfizer derived using the mean ± 3SD from the 11 US-licensed Remicade lots. The results indicate that 100% of PF-06438179 and EU-approved Remicade lots were within the quality range meeting the tier 2 acceptance criteria.

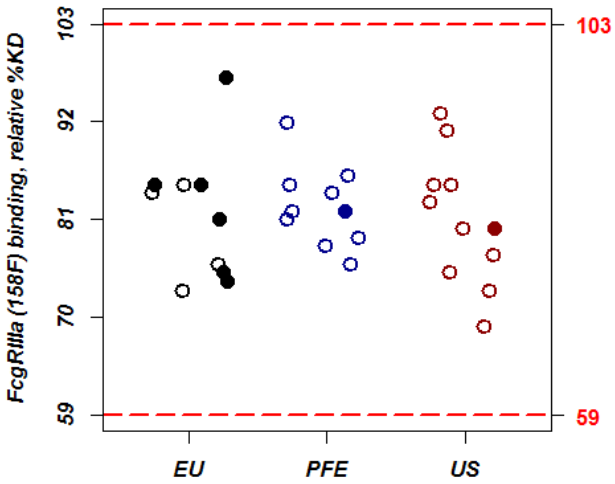


Figure 3.2.R.3.2-8 Statistical Quality Range for FcγRIIIa (158F) SPR Binding Activity Comparison.

Assay qualification (INX100252522): The SPR Binding Assays for FcγRIIIa (158V and 158F) were qualified for working range (31.25-1000 nM), precision (% RSD of KD: 7.4% for 158V and 8.5% for 158F).

Reviewer comment: *Qualification data for the assay are adequate to support the suitability of the assay. The quality ranges are appropriate. The SPR FcγRIIIa binding analysis of PF-06438179 was within the US quality ranges. All pairwise comparisons between PF-06438179, US-licensed Remicade, and EU-approved Remicade passed the Tier 2 statistical criteria for similarity. This established similarity on FcγRIIIa binding is indicative of similar ADCC activity between the products.*

During the inspection on Oct 10-12, 2017, we audited the similarity assessment data from the FcγIIIa 158V/F SPR binding assay. We found that the EU-approved Remicade batch 4RMA64902 FcγRIIIa 158V SPR binding result was "72% KD" in the electronic notebook entry for this lot, while this value was reported in BLA 3.2.R.3.5 Appendix as "82% KD". This discrepancy was discussed with the firm. The firm concluded that it was caused by a mistake during data transfer. The firm provided an updated statistical analysis with the correct 72% KD value in amendment eCTD0023 (Oct 30, 2017), and there is no impact on the outcome of the analysis.

3.2.R.3.2.2.6 FcRn Binding SPR Assay

FcRn binding was measured to complete the assessment of functional similarity between PF-06438179, US-licensed Remicade, and EU-approved Remicade because it is reported in the literature that IgG1 binding affinity to the FcRn can impact the half-life of an antibody. FcRn binding was measured by SPR. Results for FcRn binding activity in PF-06438179 DS and DP ranged from 85% to 112%, which was within the quality range of US-licensed Remicade (85-123%). All the results for EU-approved Remicade (96%-114%) also fell within the US-licensed Remicade quality range (Figure 3.2.R.3.2-9).

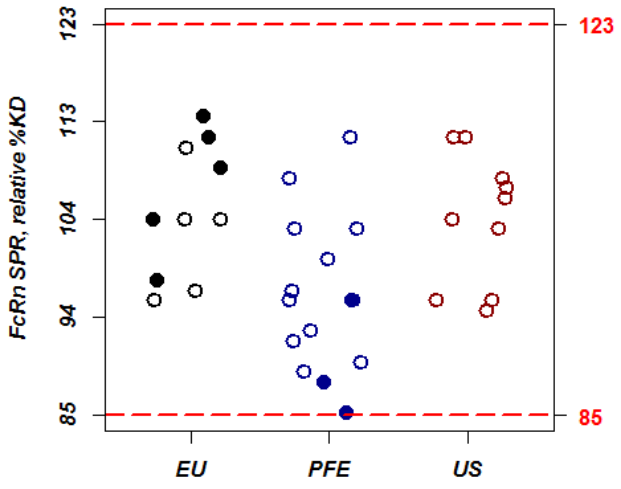


Figure 3.2.R.3.2-9 Statistical Quality Range for FcRn SPR Binding Activity of EU-approved Remicade, PF-06438179, and US-licensed Remicade.

Assay Qualification (INX100252703): The binding activity of the sample is compared to the binding activity of the reference standard and the result is reported as percent relative binding activity. The SPR Binding Assays for FcRn were qualified for working range (2.4-5000 nM), accuracy of 104% at target and an intermediate precision of 4.3% relative standard deviation (RSD) at target (100% RP) and specificity.

Reviewer comment: *FcRn is thought to be involved in the salvage pathway of IgG antibodies, and the most likely impact of FcRn differences between products would be the clearance of serum infliximab. The FcRn binding activities for all PF-06438179 lots and EU-approved Remicade lots were within the quality range of the US-licensed Remicade. The results support the conclusion that infliximab FcRn binding activity is similar for all pairwise comparisons between PF-06438179, US-licensed Remicade, and EU-approved Remicade. Of note, two of the PF-06438179 clinical lots FcRn results were at the lower end of the quality range. But, per the review by the clinical pharmacology team, the PK between these products is similar in the clinical studies, which suggests variation within the range observed here are not likely to clinical impact.*

3.2.R.3.2.2.7 Complement-dependent Cytotoxicity (CDC) Assay

CDC is an immune mechanism associated with the complement system. An IgG antibody first binds via its antigen-binding site to its specific target on a cell surface. Then, the Fc portion is recognized by C1q, a component of the complement complex. This interaction initiates the classical complement pathway; mediating formation of the membrane attack complex and consequent cell lysis.

10 lots (7 independent) of PF-06438179, 10 lots of US-licensed Remicade and 10 lots of EU-approved Remicade were evaluated in an in vitro CDC assay. Figure 3.2.R.3.2 -10 shows the statistical quality range of 73-124% relative EC50 for the CDC assay derived from 10 US-licensed Remicade lots. 100% of PF-06438179 and EU-approved Remicade lots fall within the quality range meeting the tier 2 acceptance criteria.

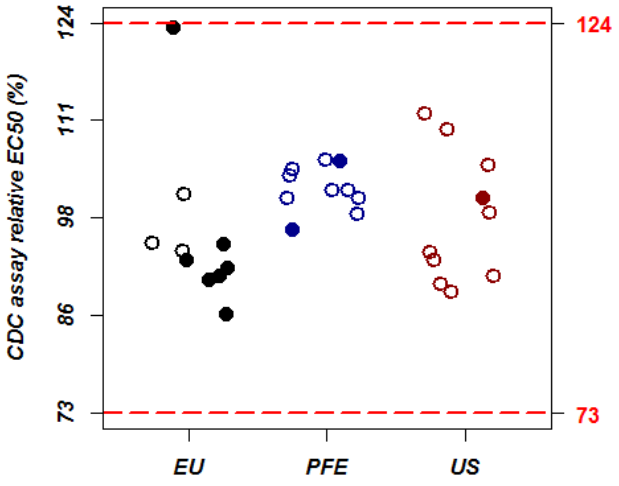


Figure 3.2.R.3.2-10 Statistical Quality Range for the CDC Comparison of EU-approved Remicade, PF-06438179, and US-licensed Remicade.

Assay Qualification (INX100251880): CDC activities were evaluated in an in vitro test in which the death of NS0 cells, transfected to overexpress mTNF, is measured after incubation with infliximab dilutions and human serum complement. This CDC assay was assessed for linearity (50-150%), accuracy of 102% at target and an intermediate precision of 4.4% relative standard deviation (RSD) at target (100% RP).

Reviewer comment: *Assay qualification data adequately demonstrated that the analytical procedure is suitable for measurement of relative CDC activity of PF-06438179. The quality range is appropriate. Results for CDC activity for all PF-06438179 and EU-approved Remicade are within the quality ranges of US-licensed Remicade. The data support similarity with respect to this biological activity.*

3.2.R.3.2.2.8 C1q Binding ELISA

The binding of the Fc region of target cell-bound antibodies to C1q protein of the human serum complement is the prerequisite first step in the complement cascade leading to CDC. Binding of human C1q to PF-06438179 was assessed by an ELISA binding assay. Figure 3.2.R.3.2.2-11 shows the statistical quality range of 68-111% RP for the C1q binding assay, and are derived from the 12 US-licensed Remicade lots. 92% EU-approved Remicade lots fall within quality range meeting the tier 2 acceptance criteria. One out of 7 independent lot of PF-06438179 fell out of the quality range.

Assay qualification (INX11835547): The objective of the qualification was to qualify the ELISA-based binding assay to measure the binding of infliximab to C1q. The results showed that linearity (50-150% RP), precision (intermediate precision: 7.7%RSD at target), accuracy (99% at Target).

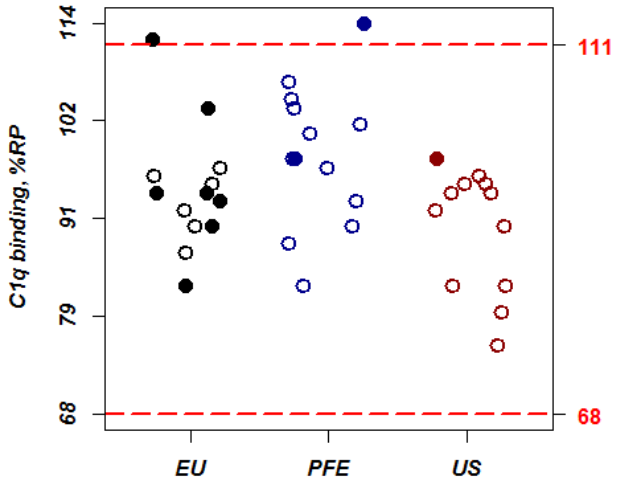


Figure 3.2.R.3.2-11 Statistical Quality Range for the C1q Binding Comparison.

Reviewer comment: *Assay qualification is adequately qualified demonstrating that the ELISA procedure is suitable for measurement of C1q binding activity of PF-06438179. The quality range of ±3SD is*

appropriate. One (DP lot M01013) out of 7 independent lot of PF-06438179 fell out of the quality ranges of US-licensed Remicade. Thus, PF-06438179 failed the quality range assessment for C1q binding ELISA. Note that the DS lot 94003, which is the constituent lot of M01013, was tested of 90% for the C1q binding. The Fc domain C1q binding activity is determined by protein structure and terminal galactosylation, therefore, is unlikely affected by filling/lyophilizing process. The difference between DS and DP likely reflects assay variability. In addition, PF-06438179 passes CDC assay (see above) and terminal galactosylation assay (see below) assessment. Considering the totality of the data, failure on the C1q binding assay to meet the 90% threshold for Tier 2 assessment does not impact on the conclusion of similarity between PF-06438179 and US-licensed Remicade for CDC activity. Note also that terminal galactosylation, which correlates to CDC activity, will be specifically controlled by a lot release test for commercial PF-06438179 lots. This will minimize the risk that attributes related to CDC will drift from the levels established to be similar to US-Remicade.

3.2.R.3.2.2.9 N-Linked Glycan Structure

The N-linked glycan assessment is important because of the possible impact on effector function activity, which is a potential MoA. The level of total afucosylation has been linked to ADCC (Shields et al. 2002, Mori et al. 2007) and the level of terminal galactosylation has been linked to CDC (Hodoniczky et al. 2005). Figure 3.2.R.3.2-12 and Figure 3.2.R.3.2-13 show the statistical quality range which Pfizer derived from 52 US-licensed Remicade lots. The results indicate that 100% of PF-06438179 lots fall within the quality range for total afucosylation and terminal galactosylation, meeting the acceptance criteria for similarity. For the EU-approved Remicade lots, 100% fall within the quality range for total afucosylation and 92% for terminal galactosylation, also meeting the acceptance criteria for similarity.

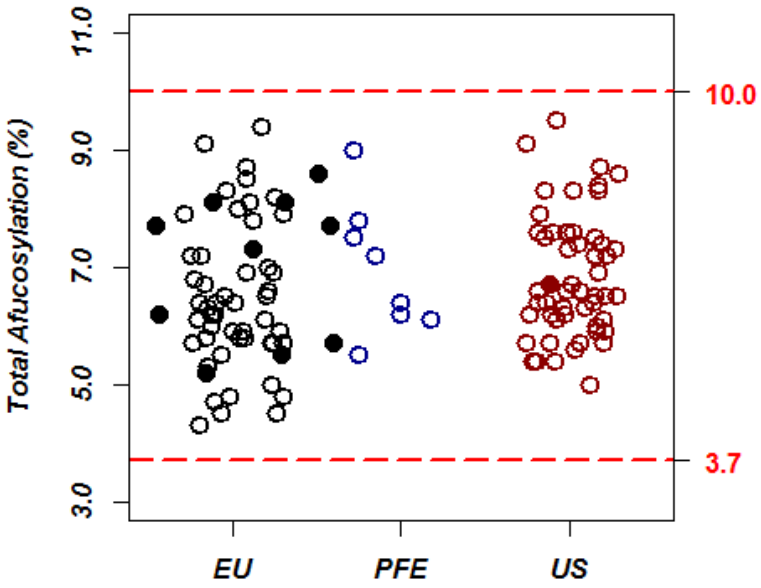


Figure 3.2.R.3.2-12 Statistical Quality Range and Individual Values for Total Afucosylation Determined by N-Linked Glycan Mapping for EU-approved Remicade, PF-06438179, and US-licensed Remicade lots.

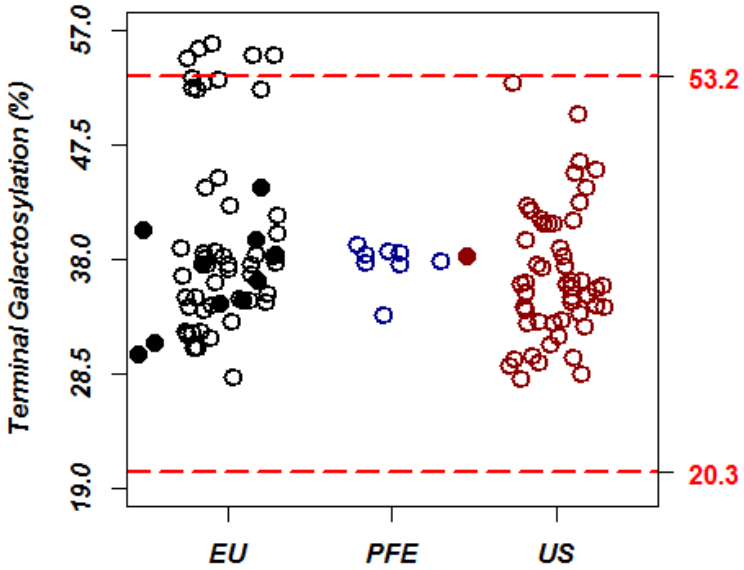


Figure 3.2.R.3.2-13 Statistical Quality Range and Individual Values for Total Terminal Galactosylation Determined by N-Linked Glycan Mapping for EU-approved Remicade, PF-06438179, and US-licensed Remicade lots.

Assay Qualification: Hydrophilic interaction liquid chromatography (HILIC) was validated for the content determination of each of the main N-linked glycan species in PF-06438179. The method is used as DS release assay to verify that the N-linked glycan content of the sample is comparable to that of the reference material. Refer to assay the review of assay validations in section 3.2.S.4.

Reviewer comment: *The HILIC assay is suitable for content determination of N-glycan species. The quality range is appropriate. The PF-06438179 level of the total afucosylation and total terminal galactosylation, which potentially has an impact on Fc effector function on ADCC and CDC, was within the quality ranges of US-licensed Remicade. The HILIC assay validation was reviewed in section 3.2.S.4.3 Validation of Analytical Procedures.*

During the inspection on Oct 10-12, 2017, we compared the data in release Analytical Test Reports (ATR) with those in BLA Appendix Table 3.2.R.3.5-1. For US-licensed Remicade lot CGD52015P1, the N-linked Glycan %Terminal galactosylation was 42.1% in the ATR, but it is 38.9% in the BLA table. We discussed this with the firm, who explained that the value reported in the BLA was generated after a correction to the chromatogram peak assignments for Remicade glycan analysis. The firm provided documentation of the characterization data that scientifically justified updating the chromatogram peak assignments, the resulting recalculation of peak areas, and the resulting values for N-glycan analysis. The results reported in the BLA were consistent with this primary data.

Reviewer notes: *The N-linked glycan structure characterization, including glycan distribution profile, composition and linkages and sialic acid assay were assessed as tier 3 attributes, and review details refer to section 3.2.R.3.2.3.2 N-linked Glycan Structure.*

3.2.R.3.2.2.10 Charge Heterogeneity

Product charge heterogeneity is important because of the possible impact on efficacy, safety, and immunogenicity. An imaged capillary electrophoresis (iCE) method was developed and applied for the analysis of charge heterogeneity. Tier 2 statistical analysis was performed on this data for both acidic and basic species. Figure 3.2.R.3.2-14 shows the statistical quality range of 8.0-26.1% for acidic species which Pfizer derived from the 53 US-licensed Remicade lots. The results indicate that 100% of the 7 independent[2] PF-06438179 and 100% of EU-approved Remicade lots fall within the established range, meeting the acceptance criteria for similarity.

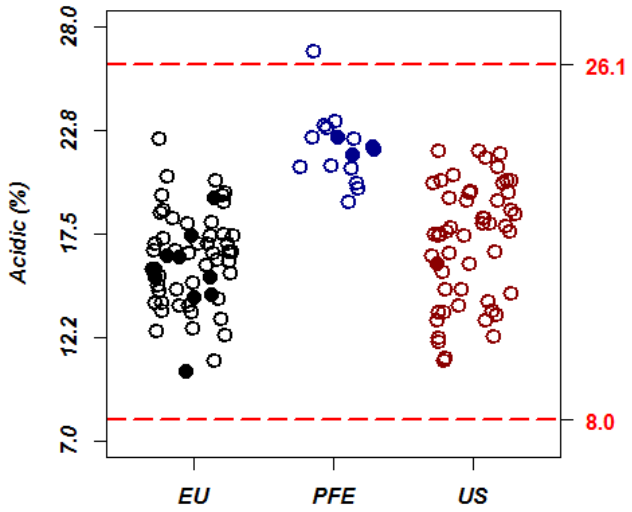


Figure 3.2.R.3.2-14 Statistical Quality Range and Individual Values for Acidic Peak Determined by iCE.

Figure 3.2.R.3.2-15 shows the statistical quality range for basic species which Pfizer derived from the 53 US-licensed Remicade lots. The results indicate that 100% of EU-approved Remicade lots fall within the established range, meeting the acceptance criteria for similarity; however, none of the PF-06438179 lots fall within this range.

[2]The outlying PF-06438179 data point in Figure 3.2.R.3.2-14 is a DS lot for which the DP lot also had data provided. In cases where data from both the DP and its constituent DS lot were available, I assessed the DP lot for the purposes of quality range testing. In this instance the DP lot fell within the quality range.

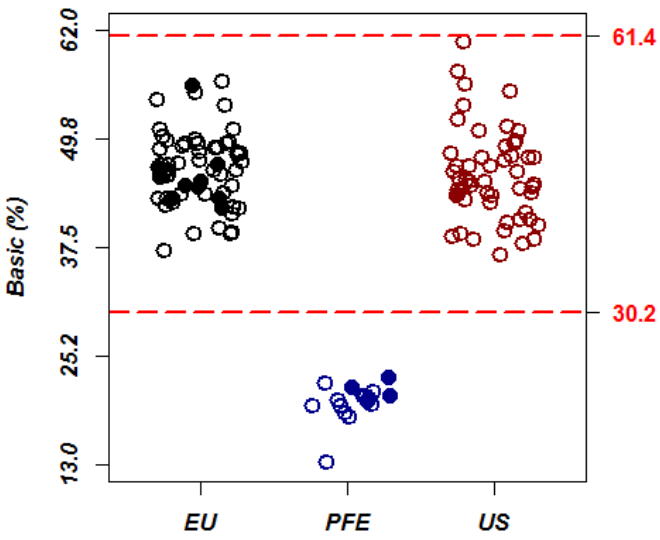


Figure 3.2.R.3.2-15 Statistical Quality Range and Individual Values for Basic Peak Determined by iCE.

US-licensed Remicade and EU-approved Remicade contain higher levels of basic species with a corresponding decrease in the main peak, when compared to PF-06438179. The major component of the basic species in PF-06438179, US-licensed Remicade, and EU-approved Remicade was identified as containing one or both heavy chains terminated with lysine. Once treated with carboxypeptidase B, which removes the C-terminal lysine, the predominant charge isoforms were similar between PF-06438179, US-licensed Remicade, and EU-approved Remicade (Section 3.2.R.3.2.3 Characterization).

The basic species identified in PF-06438179, US-licensed Remicade, and EU-approved Remicade (C-terminal lysine and amidated proline) are commonly observed structural features in the basic species of mAbs, therefore are not thought to impact safety or immunogenicity (Antes, B et al. 2007, Cai, B et al. 2011, Johnson KA et al. 2007). The C-terminal region of a mAb is not involved in target antigen binding and Fc-functions.

Assay Qualification: The iCE analytical procedure was validated as a quantitative method for determining the charge heterogeneity (percent acidic, main, and basic species) of PF-06438179 drug substance and drug product. The iCE procedure was validated.

Reviewer comment: *Pfizer used all PF-06438179 lots instead of independent lots for this analysis. When only considering independent lots, the % acidic species of all the 7 lots are within the quality range. The lot out of range is the reference standard lot 128926-7. The PF-06438179 and EU-approved Remicade pass the Tier 2 statistical test for % acidic species. The method is validated for use and the quality range is appropriate.*

The difference in basic species observed between PF-06438179 and the reference product was further characterized by characterizing structure and composition of each charge isoforms using CEX HPLC and mass spectrometry. The higher proportions of basic species observed in Remicade compared to PF-06438179 was attributed to a greater abundance of the 4-chain molecule containing C-terminal lysine.

After treatment with carboxypeptidase B, the iCE profile for PF-06438179 was similar to that of US-licensed Remicade and EU-approved Remicade (Figure 3.2.R.3.2-16). C-terminal Lysine is enzymatically cleaved in serum, and consequently the presence or absence of this lysine is not thought to affect in vivo performance. Scientific literature supports that proline amidation of the C-terminus of monoclonal antibody does not exert effect on the Fc region mediated effector function.

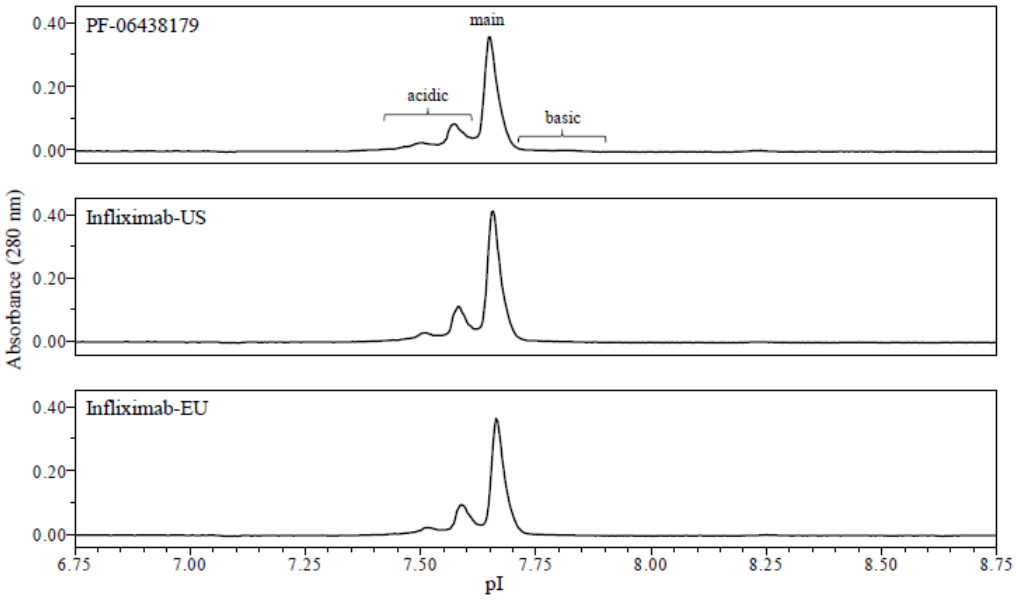


Figure 3.2.R.3.2-16 iCE profiles after carboxypeptidase B treatment

3.2.R.3.2.2.11 Product Purity-- Size-exclusion HPLC

Product purity is important because of the impact it may have on efficacy, safety, immunogenicity or PK. This size exclusion HPLC (SE-HPLC) procedure is validated for the quantitative determination of the monomer and high molecular mass species (HMMS) content of PF-06438179 drug substance and drug product. Tier 2 statistical analysis was performed on this data. Figure 3.2.R.3.2-17 and Figure 3.2.R.3.2-18 show the statistical quality ranges Pfizer derived from the 53 US-licensed Remicade lots for monomer and HMMS, respectively. 98% of EU-approved Remicade lots were within the established range, meeting the acceptance criteria for similarity. Pfizer used data from are all PF-06438179 lot instead of independent lots in this analysis. The out of range lot in both %monomer and % HMMS analysis is the reference material lot 128926-7 used during clinical development. This reference standard was derived from a pilot scale lot and is not necessarily representative of the commercial process. Considering only the 7 independent PF-06438179 lots in quality range assessment; 100% of these 7 independent lots are within the quality ranges for %monomer and %HMMS, meeting the quality range.

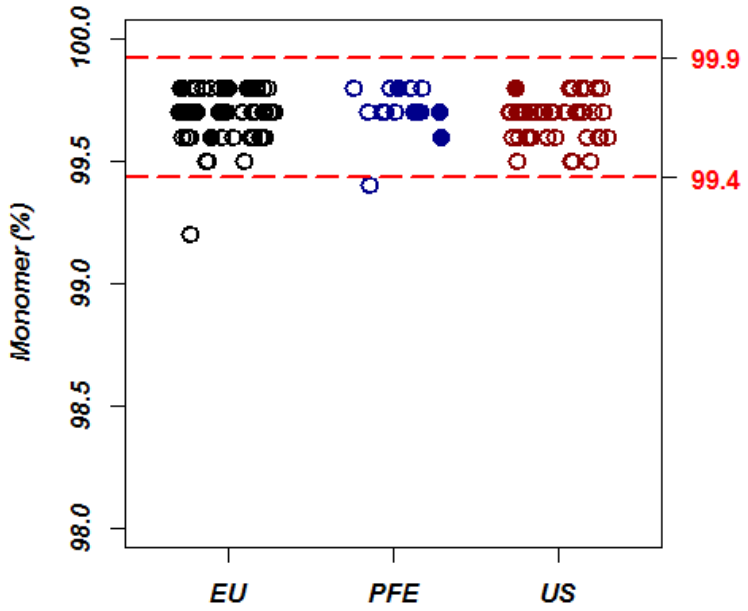


Figure 3.2.R.3.2-18 Statistical Quality Range and Individual Results for Monomer Levels Determined by SE-HPLC of EU-approved Remicade, PF-06438179, and US-licensed Remicade.

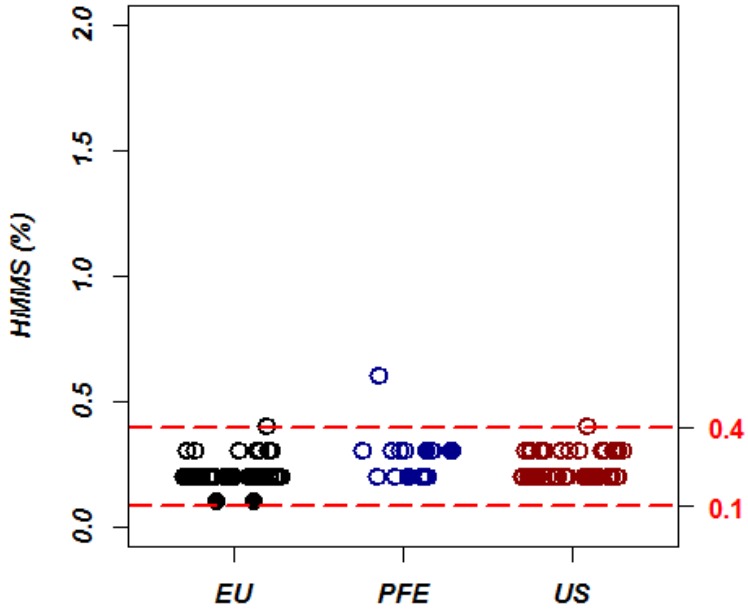


Figure 3.2.R.3.2-19 Statistical Quality Range and Individual Results for HMMS Levels Determined by SE-HPLC of EU-approved Remicade, PF-06438179, and US-licensed Remicade.

Assay Qualification: The SE-HPLC method was validated for quantifying monomer and HMMS and is used as release method for DS and DP.

Reviewer comment: *The assay is adequate to support the testing results. The SE-HPLC assay validation was reviewed in section 3.2.S.4.3 Validation of Analytical Procedures. The quality ranges are appropriate. All the independent lots of PF-06438179 were within the statistical quality range of the US-licensed Remicade. The lot that is out of the quality ranges is the reference material lot 128926-7(0.6%). The HMMS of 0.6% is very low and the difference is too small to be significant. These data support similarity with respect to monomeric forms and high molecular weight species.*

3.2.R.3.2.2.12 Protein Concentration

Protein concentration is a critical quality attribute which is directly linked to dosing and strength. The protein concentration of reconstituted PF-06438179 drug product lots and Remicade was determined by ultraviolet/visible spectroscopy (UV/VIS) at 280 nm. Protein concentration is assessed using the tier 2 statistical analysis. Figure 3.2.R.3.2-19 shows the statistical quality range of 8.8-10.6 mg/mL derived from the 53 US-licensed Remicade lots. The results indicate that all PF-06438179 and EU-approved Remicade lots are within the quality range meeting the tier 2 acceptance criteria for similarity.

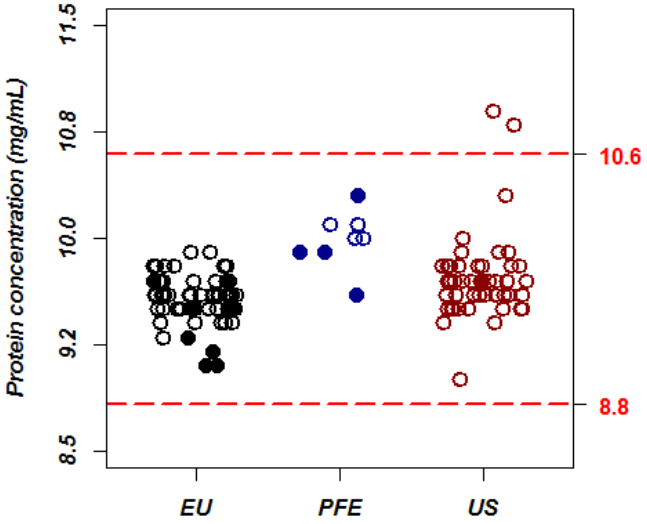


Figure 3.2.R.3.2-19 Statistical Quality Range for Protein Concentration Comparison.

Assay qualification: The ultraviolet (UV) spectroscopy procedure is validated as a quantitative method for the determination of the protein concentration of PF-06438179 drug substance and drug product.

Reviewer comments: *The UV spectroscopy procedure is validated for measuring the protein concentration for PF-06438179 DS and DP release. The protein concentration for all PF-06438179 lots and EU-approved Remicade lots were within the quality range of the US-licensed Remicade. The results support the conclusion that DP protein concentration is similar for all pairwise comparisons between PF-06438179, US-licensed Remicade, and EU-approved Remicade.*

Pfizer determined concentration for PF-06438179, US-licensed Remicade, and EU-approved Remicade by UV absorbance at 280 nm using an extinction coefficient of 1.39 $(mg/mL)^{-1}cm^{-1}$. The applicant

determined this value by measuring the absorbance of reconstituted US-licensed Remicade and EU-approved Remicade and calculating the extinction coefficient from the protein concentration, which they determined by dividing the nominal 100 mg of protein per vial by a measured solution volume of 10.4 mL. On May 09, 2017, we sent information request asking the applicant to explain how they experimentally determined the reconstituted volume and how many reference product lots they measured to determine the average extinction coefficient of 1.39 $(mg/mL)^{-1}cm^{-1}$. The applicant's response (May 22, 2017, amendment eCTD 0009) was that they determined the reconstituted volume by determining the difference in weight of vials after reconstitution and after subsequent rinsing and drying and calculating volume from the density of the solution. They measured absorbance and reconstituted volume and calculated and averaged the extinction coefficients for 8 lots each of US-licensed Remicade lots and EU-approved Remicade.

Reviewer comments: *Pfizer used the same extinction coefficient of 1.39 $(mg/mL)^{-1}cm^{-1}$ for all calculations of protein concentration throughout the similarity assessment. Thus, the calculation of concentration from raw 280 nm absorbance data is consistent throughout the analysis, allowing for meaningful comparison of concentration data between products for the analytical similarity assessment. The value of 1.39 $(mg/mL)^{-1}cm^{-1}$ derived from a combination of the nominal Remicade concentration and experimentally determined absorbance and reconstituted liquid volume agrees with the theoretical coefficient of 1.45 $(mg/mL)^{-1}cm^{-1}$ predicted by the amino acid sequence. The sequences of PF-06438179 and US-licensed Remicade are identical (see below). Pfizer's extinction coefficient is reasonable for use in the analytical similarity assessment and for use in routine determination of protein concentration in commercial manufacture and release.*

As described in eCTD module 3.2.P.2.2.1.1, PF-06438179 drug product includes an overfill to achieve the nominal reconstituted protein concentration of 10 mg/mL upon reconstitution. A target of 10 (b) (4) mg PF-06438179 are filled into the vials, and after reconstitution of the lyophilized powder with 10 mL of Sterile Water for Injection, the final volume of the solution is 10. (b) (4) mL. The applicant provided extractable volume data demonstrating that this volume is sufficient to extract at least 10 mL solution into a syringe (average extractable volume is 10.1 mL). -PF-06438179 drug product process validation data in module 3.2.P.3.5 demonstrated that the fill volume of PF-06438179 is tightly controlled during manufacture. Taken together, the similarity data, manufacturing control, and lot release controls support that PF-06438179 drug product will consistently yield a 10 mg/mL solution with a similar concentration to US-licensed Remicade in a volume sufficient to withdraw the 10 mL from the vial needed to prepare solution for infusion.

3.2.R.3.2.3 Similarity Assessment for Tier 3 Attributes (Raw Data/Graphical Comparison)

Quality attributes evaluated by Tier 3 include primary structure and post-translational modifications, N-linked glycan structure characterization, product purity, higher order structure, and additional biological activities. QAs in tier 3 were provided using side-by-side graphical comparisons of the raw data. In some cases, descriptive statistics were provided for quantitative QAs in this tier.

3.2.R.3.2.3.1 Primary Structure and Post-Translational Modifications

The characterization tests for the primary structure analyses of PF-06438179, US-licensed Remicade and EU-approved Remicade included:

- Amino acid sequencing using LC/MS/MS peptide mapping with bioinformatics and using Edman degradation
- Molecular mass determination by mass spectrometry (nanoESI-MS)
- Primary structure and post-translation modification by LC/MS subunit analysis and peptide mapping
- Identification of disulfide bonds and quantification of free sulfhydryl groups
- Analysis and quantification of PTMs included methionine oxidation (Met oxidation), deamidation, glycation as well as N- and C-terminal modifications

Study results showed that the PF-06438179 primary structure and amino acid sequence for the variable and constant regions is identical to those of US-licensed Remicade and EU-approved Remicade. The identity and locations of post-translational modifications of PF-06438179 and Remicade were similar.

The experimental results indicate that the disulfide bond connectivity are at the expected cysteines and are the same in PF-06438179, US-licensed Remicade and EU-approved Remicade, and the free sulfhydryl levels are very low and similar in all three products.

Reviewer comment: *The assays evaluated in Tier 3 and used in the studies were qualified, and the mass accuracy, sensitivity and resolution of instruments were confirmed before data acquisition. All the methods were suitable for their intended use. The characterization tests were performed using one lot each of PF-06438179, US-licensed Remicade and EU-approved Remicade. The primary structure and post-translational modifications of PF-06438179 is similar to US-licensed Remicade and EU-approved Remicade.*

3.2.R.3.2.3.2 N-linked Glycan Structure

N-linked glycan mapping by HILIC/MS supports that PF-06438179, US-licensed Remicade, and EU-approved Remicade are similar with respect to the most abundant N-linked glycan (G0F and G1F). Differences in minor (i.e. low abundance) glycan species are observed between PF-06438179 and US-licensed infliximab and EU-approved Remicade products. Figure 3.2.R.3.2-20 presents side-by-side comparison of the N-linked glycan profiles from PF-06438179, US-licensed Remicade and EU-approved Remicade.

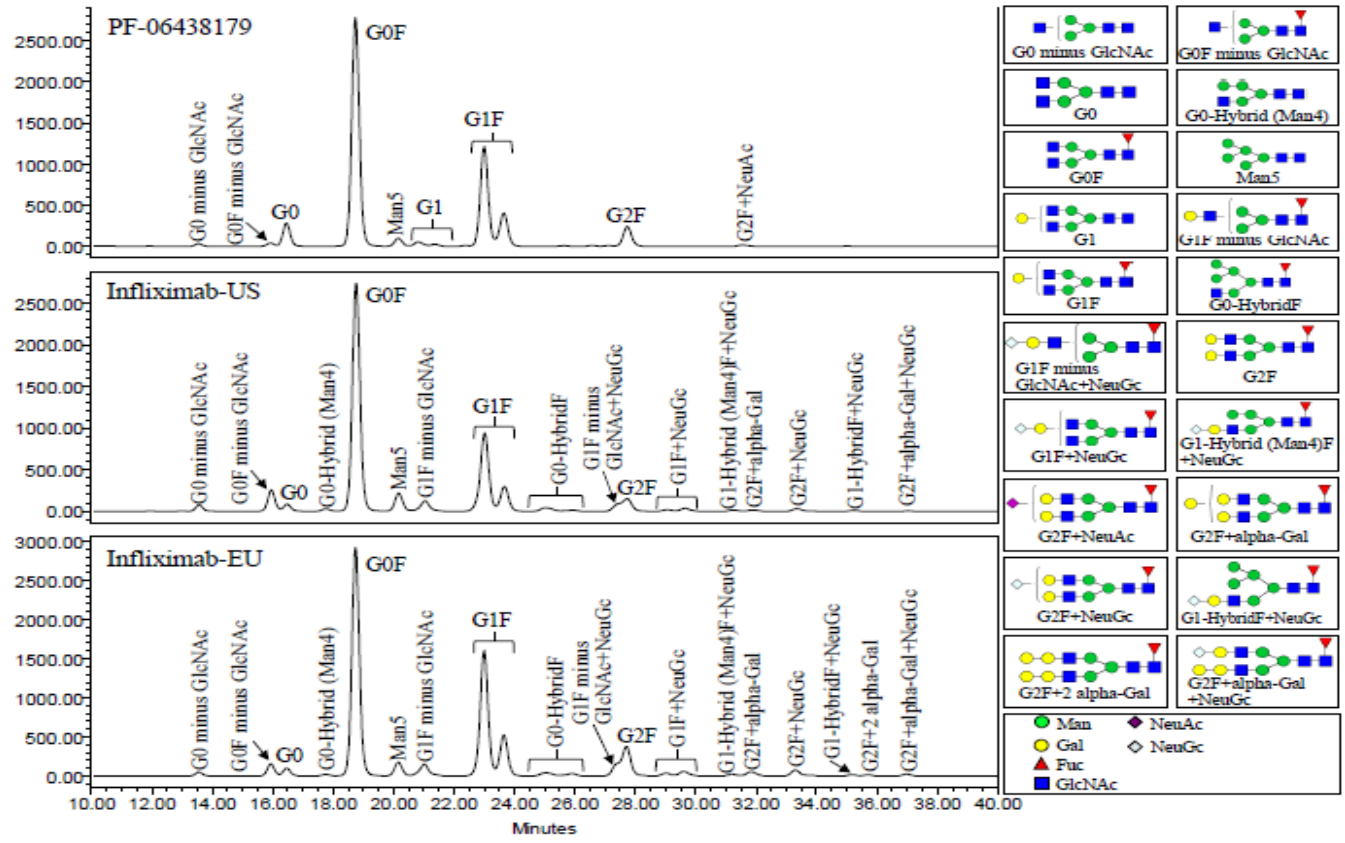


Figure 3.2.R.3.2-20 HILIC-MS N-Glycan Mapping

Reviewer comment: *Such differences in minor glycan species are unsurprising because PF-06438179 and the Remicade products are produced in* (b) (4) *cell lines, respectively. However, the major species are similar, and the total abundance of afucosylated and terminally galacosidated species are similar. The totality of the in vitro data, including Fc receptor binding affinities, C1q receptor affinity, and cell-based bioassays for ADCC, CDC, reverse signaling, and inhibition of regulatory macrophages, support that these minor differences in glycoforms do not significantly impact functions related to the mechanism of action of these products.*

The assignment of structures, monosaccharide composition, and specific glycosidic linkages to the N-linked glycan from infliximab was confirmed by sequential digestion of the total released pool of infliximab 2-AB labeled N-linked glycan with different linkage-specific exoglycosidases. All N-linked glycan are complex biantennary type with low levels of high mannose type of glycan. US-licensed Remicade and EU-approved Remicade N-linked glycan also include hybrid species.

N-acetylneuraminic acid (Neu5Ac) was the predominant sialic acid form in PF-06438179 (produced in (b) (4) cells) and N-glycolylneuraminic acid (Neu5Gc) was the predominant sialic acid form in US-licensed Remicade and EU-approved Remicade (produced in (b) (4) cells).

Reviewer comment: *Of note, the levels of sialylated glycan in PF-06438179 were shown to be at trace level (<3%). Literature studies have reported that the difference with respect to type of neuraminic acid (Ghaderi et al., 2010) or quantity of neuraminic acid (Wright & Morrison, 1998) is not considered clinically relevant.*

3.2.R.3.2.3.3 Capillary Gel Electrophoresis

The level of product-related fragment species present in PF-06438179, US-licensed Remicade, and EU-approved Remicade was analyzed by capillary gel electrophoresis (CGE) performed under reducing conditions. PF-06438179 and Remicade consist of two predominant peaks, which are the HC and LC. The products all have some trace level peaks as fragments. Pfizer performed Tier 3 descriptive statistical analysis on this data of % HC+LC and % fragments.

Reviewer comment: *The CGE (reduced) method was validated for DS and DP release tests. The %HC+LC and % fragment is controlled in the release test for purity of the product. Increased levels of fragment may pose a risk to impact potency. We performed a Tier 2 quality range analysis on the CGE (reduced) data. For % HC+LC data, the quality range derived from US-licensed Remicade is 98.0-100%. One out of the 7 independent PF-06438179 lots fell out of the range (DS 94200-97.8%). For % fragment, the quality range derived from US-licensed Remicade is 0-1.5%. One out of the 7 independent PF-06438179 lots fell out of the range (DPM01013-1.9%).*

The % HC+LC of DS lot 94200 is 0.2% less than the low limit of the US quality range. This difference had no impact on the measured bioactivity of PF-06438179. The %fragment of DP lot M01013 is 0.4% higher than the upper limit of US quality range. There is little risk that this minor difference in the low levels of fragments is clinically significant. This method is a PF-06438179 release test, which will ensure against drift in this attribute away from US-licensed Remicade.

SDS-PAGE (reducing conditions) was performed to compare the banding patterns and showed similar banding patterns for all three products. The analytical ultracentrifugation-sedimentation equilibrium (AUC-SE) technique was used to characterize the self-association of infliximab. The dissociation constant of all three products are in the same order of magnitude, indicating that under the same conditions the monomer-dimer self-association took place to a similar extent in these samples.

3.2.R.3.2.3.4 Higher Order Structure

The similarity of the higher order structure of PF-06438179, US-licensed Remicade and EU-approved Remicade were evaluated for orthogonal biophysical techniques. These techniques include far and near-UV circular dichroism (CD), intrinsic fluorescence, fourier transform infrared (FTIR), and X-rag crystallography.

Reviewer comment: *The sponsor conducted higher order structure analyses to assess the similarity between PF-06438179 and reference products. 14 lots of PF-06438179 (including DP lots and DS lots of the same lot genealogy), 18 lots for US-licensed Remicade and 20 lots for EU-approved Remicade*

were included for far-UV and Near-UV CD test. Five lots of PF-06438179, and 7 lots each for US-licensed Remicade and EU-approved Remicade were analyzed for FTIR and Intrinsic Fluorescence analysis. Data from the biophysical techniques support the conclusion that PF-06438179 is structurally like US-licensed Remicade and EU-approved Remicade.

3.2.R.3.2.3.5 Inhibition of ELAM-1 Expression Assay

PF-06438179 was shown to inhibit TNF-induced ELAM-1 (endothelial-leukocyte adhesion molecule 1 or E-Selectin) expression on human umbilical vein endothelial cells (HUVEC) (Thorp, K.M. et al. 1992, Hagi-Pavli, E. et al. 2003). Table 3.2.R.3-5 summarized the results for the inhibition of ELAM-1 expression assay of PF-06438179, US-licensed Remicade, and EU-approved Remicade.

Table 3.2.R.3-5. Summary of Descriptive Statistics for Inhibition of ELAM-1 Expression Activity of EU-approved Remicade, PF-06438179, and US-licensed Remicade

		Relative EC50 (%)				
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	7	100	5.2	5 1	93	110
Pfizer	8	96	4.3	4 5	91	104
US	7	98	5.5	5 7	91	107

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

Reviewer comment: *8 lots of PF-06438179 and 7 lots for US-licensed Remicade and EU-approved Remicade each were tested, the activity of PF-06438179 ranged from 91-104% with a mean of 96%, US-licensed Remicade ranged from 91-107% with a mean of 98%, and EU-approved Remicade ranged from 93-110% with a mean of 100%. The range of inhibition activity of PF-06438179 is similar to that of US-licensed Remicade and EU-approved Remicade. PF-06438179 is similar to US-licensed Remicade and EU-approved Remicade.*

3.2.R.3.2.3.6 Mixed Lymphocyte Reaction (MLR) Assay

Mechanisms other than TNF neutralization have been proposed to be important for management of CD (Mitoma et al., 2005). The mixed lymphocyte reaction (MLR) assay was used to evaluate effector function (Vos et al. 2011). The MLR assay employed here used peripheral blood mononuclear cells (PBMCs) from six genotype-matched donor pairs, and measured the dose-dependent inhibitory effect of infliximab on T-cell proliferation. As in ADCC effector function, both binding to mTNF and to Fc receptor are required to inhibit T-cell proliferation. The mechanism for inhibition of T cell proliferation is thought to occur via Fc-dependent, anti-TNF-induced generation of a population of macrophages with an immunosuppressive phenotype (Vos et 2011).

Five lots of each from PF-06438179, US-licensed Remicade, and EU-approved Remicade product were evaluated over the dose-response range for inhibition of T cell proliferation in MLR assays. All lots of

EU-approved Remicade, US-licensed Remicade, and PF-06438179 yielded qualitatively similar inhibition proliferation of T cells in a dose-dependent manner in the MLR, regardless of FcγRIIIa genotype. Figure 3.2.R.3.2-21 showed mean (±SD) absorbance (at 490 nm) for PF-06438179, US-licensed Remicade and EU-approved Remicade for all three FcγRIIIa genotypes.

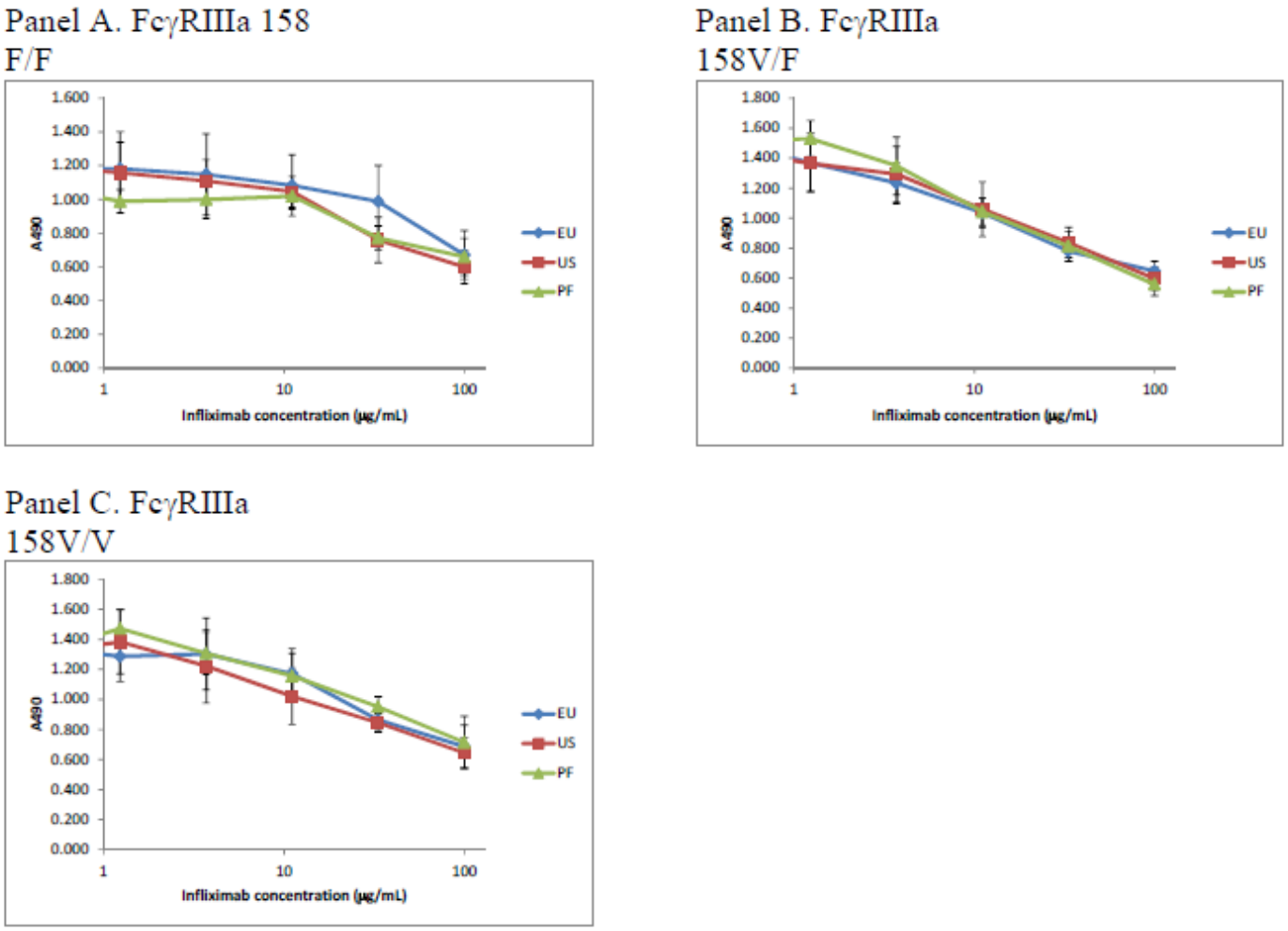


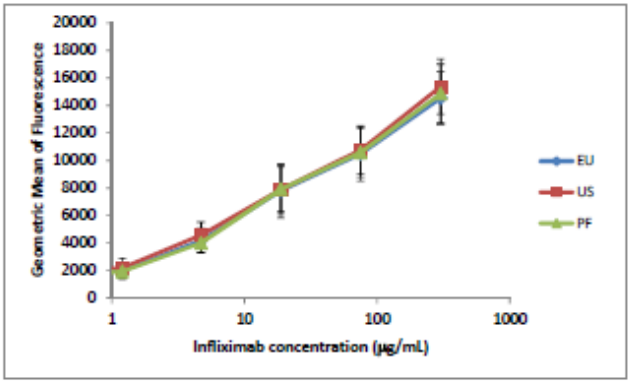
Figure 3.2.R.3.2-21 Mean Proliferation of Five Lots Each from PF-06438179, US-licensed Remicade, and EU-approved Remicade in the Mixed Lymphocyte Reaction (MLR) Assay.

Reviewer comment: *The T cell proliferation decreases with increased infliximab concentration in the assay. The three products showed inhibition activity of T cell proliferation regardless the FcγRIIIa genotype. The dose-response curves of the three products show similar down trend and sometimes overlapped to each other. The ranges of inhibition proliferation activity of five lots from each product at each concentration are close and overlapped. The graphic comparison of the data indicated that PF-06438179 has similar inhibition of T cell proliferation activity to US-licensed Remicade and EU-approved Remicade.*

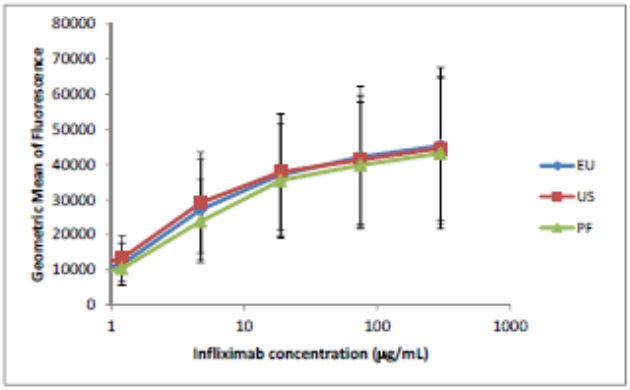
3.2.R.3.2.3.7 Natural Killer (NK) Cell Binding Assay

A cell-based binding assay was performed to evaluate the binding of PF-06438179, US-licensed Remicade, and EU-approved Remicade to the primary NK cells from donors with each of the three FcγRIIIa genotypes. Five lots each from the PF-06438179, US-licensed Remicade, and EU-approved Remicade were tested. All lots of PF-06438179, US-licensed Remicade, and EU-approved Remicade bound to primary NK cells in a qualitatively similar and dose-dependent manner regardless of FcγRIIIa genotype. Data shown in Figure 3.2.R.3.2-22 are the mean (± SD) of geometric mean fluorescence for five lots of each PF-06438179, US-licensed Remicade, and EU-approved Remicade for all three FcγRIIIa genotypes.

Panel A. FcγRIIIa 158 F/F



Panel B. FcγRIIIa 158V/F



Panel C. FcγRIIIa 158V/V

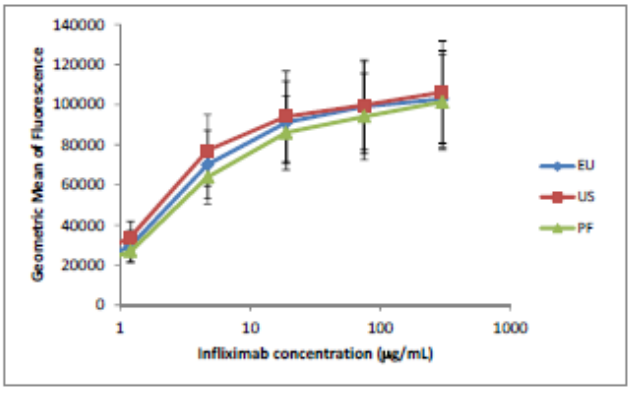


Figure 3.2.R.3.2-23 Mean Binding Activity of Five Lots Each from PF-06438179, US-licensed Remicade, and EU-approved Remicade in the NK Cell Binding Assay.

Reviewer comment: *NK cell binding dose-dependent curves of PF-06438179 and Remicade show similar up-trend and sometimes overlapped regardless the FcγRIIIa genotype. The ranges of geometric mean fluorescence of five lots from each product at each concentration are close and overlapped. The*

graphic comparison of the data indicated that PF-06438179 has similar NK cell binding activity to US-licensed Remicade and EU-approved Remicade.

3.2.R.3.2.3.8 Additional Fcγ Receptor Binding SPR Assays

Binding of PF-06438179, US-licensed Remicade, and EU-approved Remicade to Fcγ receptors, Fcγ RI, RIIa 131H, RIIa 131R and RIIIb was assessed by SPR.

Relative KD (% KD) values of PF-06438179, US-licensed Remicade, and EU-approved Remicade lots to the reference material were calculated for FcγRI and FcγRIIa 131H (Table 3.2.R.3-6 and Table 3.2.R.3-7). Relative % KD of PF-06438179 and US-licensed Remicade, EU-approved Remicade are overlapping within a very narrow range. The results indicate similar FcγRI and FcγRIIa 131H binding activity of PF-06438179, US-licensed Remicade, and EU-approved Remicade.

Table 3.2.R.3-6. Summary of Descriptive Statistics for FcγRI SPR Binding Activity of EU-approved Remicade, PF-06438179, and US-licensed Remicade

		Infliximab Relative K_D (%)				
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	10	102	3.0	2.9	97	109
Pfizer	10	97	5.9	6.1	87	107
US	11	102	5.7	5.6	95	116

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

Table 3.2.R.3-7. Summary of Descriptive Statistics for FcγRIIa 131H SPR Binding Activity of EU-approved Remicade, PF-06438179, and US-licensed Remicade

		Infliximab Relative K_D (%)				
Region	**N**	**Mean**	**SD**	**CV (%)**	**Min**	**Max**
EU	9	98	6.5	6.7	88	111
Pfizer	10	97	8.1	8.4	85	106
US	11	93	6.7	7.2	87	111

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

The SPR binding event for FcγRIIa 131R and FcγRIIIb did not achieve saturation at the highest experimental concentration. Consequently, reliable binding affinity values were not obtained. All lots tested from PF-06438179, US-licensed Remicade, and EU-approved Remicade were confirmed to have similar weak binding affinity, KD >2500 nM for FcγRIIa 131R and FcγRIIIb binding.

Reviewer comment: *We did statistical quality range analysis on these Fcγ receptor SPR binding data. For FcγRI binding, the quality range derived from US-licensed Remicade (mean±3SD) is 85-119% relative K_D. All the PF-06438179 and EU-approved Remicade lots are within the quality range. For FcγRIIa 131H binding, the quality range derived from US-licensed Remicade (mean±3SD) is 73-113%*

relative K_D. All the PF-06438179 and EU-approved Remicade lots are within the quality range. For the FcγRIIa 131R and FcγIIIb, the binding is too weak to be measured. PF-06438179 shows similar Fcγ receptor binding activity to US-licensed Remicade and EU-approved Remicade.

3.2.R.3.3 Comparative Forced Degradation Studies

Forced degradation studies were carried out to support similarity of PF-06438179, US-licensed Remicade, and EU-approved Remicade. The forced degradation studies included elevated temperature storage, light exposure and forced deamidation by incubating with phosphate buffer.

3.2.R.3.3.1 Comparative Forced Degradation Studies at Elevated Temperature

Two forced degradation studies at elevated temperature were performed using drug product lots of PF-06438179, US-licensed Remicade, and EU-approved Remicade: 1) drug product in lyophilized form was held at 50 °C for three months; 2) reconstituted drug product was held at 40 °C for two months. From these studies, the following quality attributes were measured:

- Protein concentration (UV spectroscopy)
- Relative potency (cell-based inhibition of apoptosis assay)
- Subvisible particles (HIAC)
- HMMS, LMMS (SE-HPLC)
- IgG, fragment (CGE non- reducing)
- HC+ LC, fragment (CGE reducing)
- Methionine oxidation (Lysyl endopeptidase limited proteolytic peptide map)
- Molecular charge (iCE)
- Identity of modified peptides (LC/MS-peptide mapping)

3.2.R.3.3.1.1 Comparative Study of Drug Product at Elevated Temperature in Lyophilized Form

Five lots of lyophilized PF-06438179 drug product, two lots of US-licensed Remicade and three lots of EU-approved Remicade were stored upright at 50 °C for three months. After three months' storage at 50 °C, samples were analyzed after storage to assess the product degradation pathway.

Reviewer comment: *Overall, I note only minor changes in attributes under these conditions*.

Subvisible particles increased after storage for all three products; however, Remicade increased more than PF-06438179; all results were below the USP acceptable range.

PF-06438179 samples HMMS increased (0.3 to 0.4%) more after storage when compared to Remicade (0.1% or less).

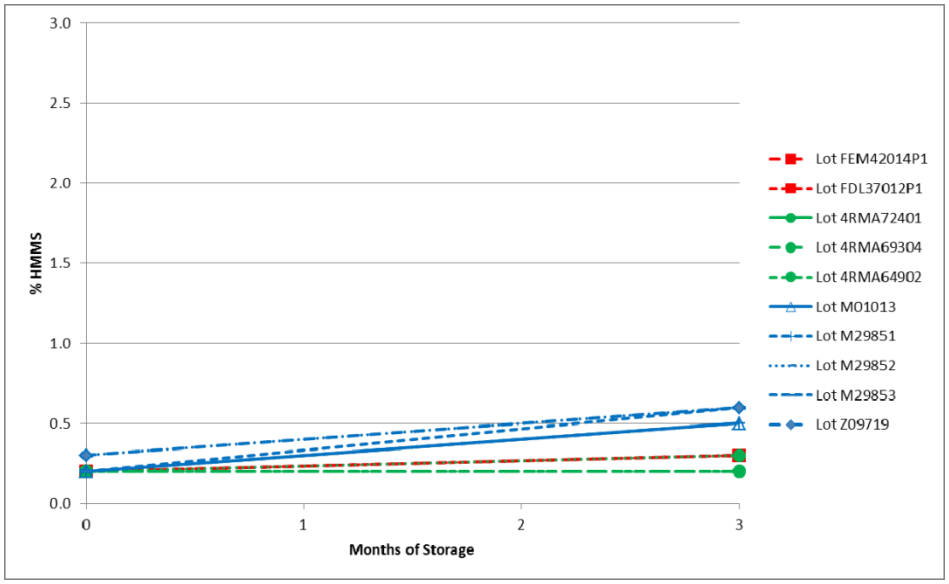


Figure 3.2.R.3.3-1 Percent HMMS by SE-HPLC after storage at 50°C for 3 months.

The abundance of acidic species increased in PF-06438179 (2 to 4%), while decreased in Remicade (0 to -2%) after storage at 50 °C for 3 months. These changes are within the variability of the method and the acidic peak profiles for all three products are similar.

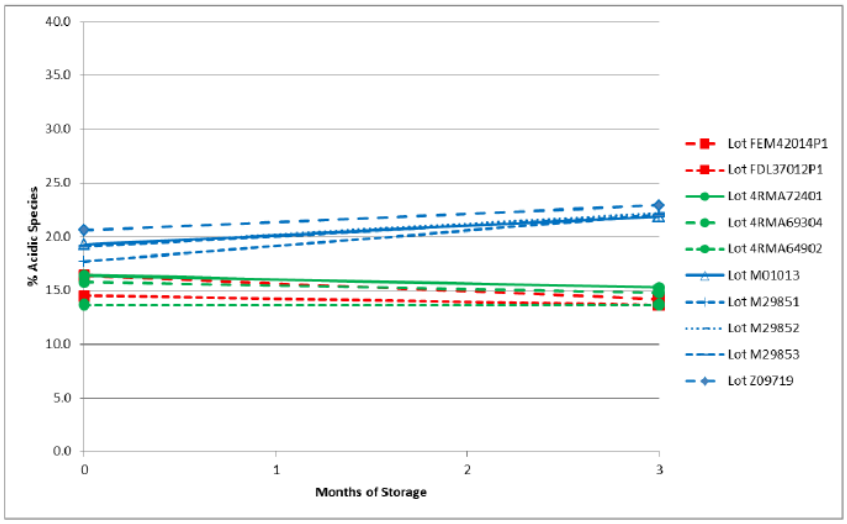


Figure 3.2.R.3.3-2 Percent Acidic Species by iCE for DPs stored at 50°C for 3 months.

There were no significant differences in the other quality attributes between the PF-06438179 DP lots and US-licensed Remicade and EU-approved Remicade lots analyzed in this study.

Reviewer comments: *The subvisible particles of PF-06438179 increased less than US Remicade and EU Remicade after 3 months' storage at 50°C, which is favorable for quality and stability of PF-*

06438179. The HMMS of PF-06438179 increased more than Remicade under the degradation conditions with the same trend. The same trend indicated similar degradation pathway in terms of aggregation. The total amount of HMMS is low and the difference is not significant. The acidic species in PF-06438179 increased while decreased in Remicade. The charge heterogeneity of PF-06438179 showed difference from Remicade such as higher main peak and acidic species and less basic species. The different trends of acidic species probably reflect the difference in charge variants and there may be a potential different degradation pathway due to the difference in charge variants, formulation or both. But the acidic species change of PF-06438179 is small and agrees with the stability results, and the forced deamidation study indicated that the deamidation trend are similar between PF-06438179 and Remicade. The acidic species degradation difference under 50°C is not significant.

3.2.R.3.3.1.2 Comparative Study of Reconstituted Drug Product at Elevated Temperature

Drug products were reconstituted with 10 mL of Sterile Water for Injection (SWFI), pooled, and filled into 2 mL vials under aseptic conditions at a volume of 1mL each and stored at 40 °C. After two months of storage at 40 °C, these reconstituted samples were analyzed for potential degradation.

The relative percent fragment of PF-06438179 increased (3-4%) less than Remicade (12-14%), in CGE (reduced and non-reduced). The iCE profiles of all three products after two-month storage at 40 °C were not sufficiently recognizable due to degradation. Therefore, one month samples were assessed. The acidic species increase and the main species decrease for all products; however, the changes of PF-06438179 were less than the Remicade products.

Similar variability trends in subvisible particles, HMMS, and relative potency for all three after storage at 40 °C for 2 months in reconstituted form.

LC/MS – peptide mapping showed that deamidation increased for the H7, H16, H24 and H38 peptides in all three products in similar abundances with slightly higher levels of H7 deamidation in Remicade.

Reviewer comments: *The reconstituted drug products show similar degradation trends in the stability-indicating attributes after storage at 40°C for 2 months. PF-06438179 showed less degradation than Remicade for fragment and charge variants, which may relate to the initial charge profile and formulation.*

All the testing results under elevated temperature conditions are all within the sponsor's predetermined criteria. The different changes in some of the stability-indicating attributes, including acidic species by iCE and fragment by CGE, are not significant. The testing results of the quality attributes are similar between PF-06438179 and US-licensed Remicade and EU Remicade.

3.2.R.3.3.2. Comparative Forced Degradation Study by Light Exposure (Photodegradation)

One lot of PF-06438179, US-licensed Remicade, and EU-approved Remicade were used in this study. All three products were reconstituted with 10 mL of Sterile Water for Injection (SWFI), placed in a light chamber and exposed to approximately 8.0 klux of light for 14 days at 25 °C. The drug product samples

were characterized at T=0 and T=14 days using the following analytical techniques: iCE, SE-HPLC, CGE (non-reducing), cell-based inhibition of apoptosis assay, and LC/MS-peptide mapping.

The PF-06438179, US-licensed Remicade and EU-approved Remicade degraded in a similar manner when exposed to 8.0 klux of light for 14 days at 25 °C. The results suggested that the predominant routes of degradation include increase in HMMS, increase in acidic species and decrease in basic species and increase in fragments. Light exposure didn't show any effect on biological activity.

LC/MS – peptide mapping showed that increase in oxidation on the Fc region peptides, H22 and H42, in the T=14 day samples from all three products with similar abundances.

In summary, no new degraded species or other changes were observed in the PF-06438179 when compared to US-licensed Remicade and EU-approved Remicade after reconstitution and significant light exposure. All drug product lots degraded in a similar manner.

3.2.R.3.3.3. Comparative Forced Deamidation Study by Phosphate Buffer Incubation

One lot each of PF-06438179 (Z09719), US-licensed Remicade (BEM34013P1), and EU-approved Remicade (1RMA64104) were used in this study. The reconstituted drug products were diafiltered into 20 mM sodium phosphate, pH 8.0 and incubated for 14 days at 40 °C. The drug products were characterized at T=0 and T=14 days using the following analytical techniques, iCE, SE-HPLC, CGE (non-reducing), cell-based inhibition of apoptosis assay, LC/MS-peptide mapping).

The results suggest that the predominant routes of degradation include changes in the charge profile, increase in acidic peak content, and decreases in main and basic peak content. The iCE profiles for PF-06438179, US-licensed Remicade and EU-approved Remicade after phosphate incubation show similar degraded species and a similar increase in acidic species levels.

All products have minor increases in HMMS, LMMS and fragment, and a small decrease in relative potency. LC/MS – peptide mapping indicated that deamidation increased on the H7, H16, and H38 peptides for all three products in similar abundances.

In summary, similar degradation profiles and levels are observed in the PF-06438179 drug product when compared to US-licensed Remicade and EU-approved Remicade after incubation for 14 days in phosphate buffer.

Reviewer comment: *The sponsor provided forced degradation comparison study data with PF-06438179 and Remicade DP lots under elevated temperature, light exposure and forced deamidation by phosphate buffer incubation. Forced degradation studies revealed all the drug products degrade in a similar manner. The results support the conclusion that PF-06438179 and US-licensed Remicade and EU-approved Remicade shared similar stability profiles and degradation pathway.*

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