

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761118Orig1s000

PRODUCT QUALITY REVIEW(S)

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First Approval for Indication/First Biosimilar/Expedited or Breakthrough Review: No

Recommendation: Approval

BLA/NDA Number: 761118

Review Number: 1

Review Date: 8/8/2019

Drug Name/Dosage Form	ABRILADA, Adalimumab-afzb
Strength/Potency	Prefilled Syringes: 40 mg/0.8 mL, 20 mg/0.4 mL and 10 mg/0.2 mL Prefilled Pen: 40 mg/0.8 mL Vial: 40 mg/0.8 mL
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps), Juvenile idiopathic arthritis (JIA) in patients 4 years of age and older
Applicant	Pfizer

Product Overview:

Quality Review Team:

Discipline	Reviewer	Branch/Division
Drug Substance (DS)	Nailing Zhang	Division of Biotechnology Review and Research (DBRR) IV
Drug Product (DP)	Nailing Zhang	DBRR IV
Immunogenicity	Nailing Zhang	DBRR IV
Labeling	Vicky Borders-Hemphill	Office of Biotechnology Products (OBP)
Facility	Amy Devlin	Division of Inspectional Assessment (DIA)
Facility Team Lead	Thuy Thanh Nguyen	DIA
Microbiology	Aimee Cunningham	Division of Microbiology Assessment (DMA)
Microbiology Team Lead	Maria (Reyes) Candau-Chacon	DMA
Application Team Lead	Haoheng Yan	DBRR IV
RBPM	Anh-thy, Ly	Office of Program and Regulatory Operations (OPRO)

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Colette Jackson	DPARP
Cross-disciplinary Team Lead	Rachel Glaser	DPARP
Medical Officer	Jin Chen	DPARP

Pharmacology/Toxicology	Xiaochun Chen	DPARP
Clinical Pharmacology	Jianmeng Chen	DCPII
Statistics	William Koh	DBII
CMC Statistics	Tianjiao Dai	DBIV

Names:

- a. Proprietary Name: ABRILADA
- b. Trade Name: ABRILADA™
- c. Non-Proprietary Name/USAN: Adalimumab-afzb
- d. CAS Registry Number: 331731-18-1
- e. Common Name: Not applicable.
- f. INN Name: Adalimumab-afzb
- g. Compendial Name: Not applicable.
- h. OBP Systematic Name: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [PF06410293]
- i. Other Name(s): PF-06410293 (company code)

Submissions Reviewed:

Submission(s) Reviewed	Document Date
STN 761118/SN 0001,	11/16/2018
STN 761118/SN 0008,	02/22/2019
STN 761118/SN 0012,	04/30/2019
STN 761118/SN 0013	05/15/2019
STN 761118/SN 0014	05/24/2019
STN 761118/SN 0017,	06/25/2019
STN 761118/SN 0018,	07/08/2019
STN 761118/SN 0020,	07/12/2019
STN 761118/SN 0021,	07/31/2019

Quality Review Data Sheet:

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	7/2/2019	None
	III			3	Adequate	7/2/2019	None
	III			3	Adequate	7/2/2019	None
	III			3	Adequate	7/2/2019	None
	III			3	Adequate	7/2/2019	None
	III			3	Adequate	7/2/2019	None
	III			3	Adequate	7/2/2019	None
	III			3	Adequate	7/2/2019	None
	V			3	Adequate	7/2/2019	None

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

2. Action codes for Status column: 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: IND114729

3. Consults:

Discipline/Topic	Date Requested	Status	Recommendation	Reviewer
CDRH ODE/OC	12/04/2018	Complete	Approval.	Rumi Young/Sarah Mollo/ Stevens Alan

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Biotechnology Products, OPQ, CDER, recommends approval of STN 761118 for ABRILADA manufactured by Pfizer Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of ABRILADA is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

- Manufacturing location:

- Drug Substance:

Wyeth BioPharma, Division of Wyeth Pharmaceuticals LLC
One Burtt Road, Andover Massachusetts 01810, USA
FEI: 1222181

- Drug Product:

(b) (4)
[Redacted]

FEI: (b) (4)

(b) (4)
[Redacted]

FEI: (b) (4)

- Fill size and dosage form:

- Prefilled Syringes (PFS): 40 mg/0.8 mL, 20 mg/0.4 mL and 10 mg/0.2 mL
- Prefilled Pen (PFP): 40 mg/0.8 mL
- Vial: 40 mg/0.8 mL

- Dating period:

- Drug Product: 36 months at $5 \pm 3^\circ\text{C}$. This dating period may include a single period up to 30 days at a maximum of 30°C . The start date of the dating period is the date of manufacture which shall be defined as the date of final sterile filtration of the formulated drug product.
- Drug Substance: (b) (4) months at (b) (4) $^\circ\text{C}$
- Stability:
 - For stability protocols: we have approved the stability protocol(s) 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, ABRILADA is a specified product and exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

PF-06410293 is a proposed biosimilar to US-Humira Pfizer seeking licensure for the following indications: Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps), Juvenile idiopathic arthritis (JIA) in patients 4 years of age and older, for which US-Humira is licensed.

The data submitted support the demonstration that PF-06410293 is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components (refer to Section II of this memo for further details and discussion of the differences observed).

The assessment of manufacturing information provided in the application has concluded that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The drug substance manufacturing process is robust for removal and control of adventitious agents.

The DMA assessor concluded that the microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective.

The DIA assessor recommends approval of Wyeth BioPharma, Division of Wyeth Pharmaceuticals LLC FEI # 1222181, for commercial manufacture of PF-06410293 DS and (b) (4) FEI# (b) (4) for commercial manufacture of DP (vial and PFS).

CDRH Office of Compliance and Office of Device Evaluation provided evaluations of the device component of the product and the PFP assembly site at (b) (4) FEI# (b) (4); no approvability issues were identified from a device component perspective.

Individual assessments for each discipline, (1) drug substance and drug product quality, and immunogenicity assays [OBP], (2) analytical similarity assessment [OBP] (3) microbiological control of drug substance and drug product [DMA], (4) facilities evaluation [DIA], (5) device evaluation [CDRH/ODE] and (6) labeling [OBP] are located as separate documents in Panorama or ICCR salesforce.

D. Recommendation on Phase 4 (Post-Marketing) Commitments

Draft Language:

PMC#1 Develop and implement a control strategy for the FC-domain-mediated effector functions of Abrilada, including antibody-dependent cell mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

Final report submission date: September 30, 2020

PMC#2 Include (b) (4) syringes and vials as positive controls for routine container closure integrity testing.

Final report submission date: May 31, 2020

PMC#3 Submit data supporting capping and crimping parameters (minimal, nominal, and maximum pressures) using a dye ingress container closure integrity test that includes (b) (4) positive control vials.

Final report submission date: May 31, 2020

PMC#4 Provide the polysorbate 80 (PS80) test method (drug product release method) and method transfer report to commercial laboratory.

Final report submission date: September 30, 2020

II. Comparative Analytical Assessment and Evaluation of the Analytical Component of the Scientific Bridge

I. Analytical Assessment Overview and Conclusions

Pfizer performed a comparative analytical assessment using 68 US-Humira DP lots (40 mg/0.8 mL PFS or PFP), 77 EU-Humira DP lots (40 mg/0.8 mL PFS or PFP) and 10 independent PF-06410293 lots which include 7 commercial scale DP lots (3 lots of 40 mg/0.8 mL PFS, 2 lots of 40 mg/0.8 mL vial and 1 lot each of 20 mg/0.4 mL and 10 mg/0.2 mL PFS), 2 commercial scale DS lots and 1 development DS lot. PF-06410293 in PFP was not included in the analytical assessment. This approach is acceptable because Pfizer provided adequate data to show that assembly of the PFS into the secondary packaging component of the PFP does not impact product quality attributes. The analytical assessment included:

- extensive comparative physicochemical and functional assessment of quality attributes,
- comparative assessment of the degradation profiles under forced degradation conditions.

Pfizer used a risk-based approach for statistical evaluation of analytical results. Highest-ranked risk attributes tested using quantitative assays were evaluated using equivalence testing. Moderate risk attributes tested using quantitative assays were evaluated using quality ranges, calculated to account for reference product manufacturing variability and assay variability. Low risk attributes or attributes tested using qualitative assays were evaluated using visual display comparisons. Results from method validation or qualification studies support the suitability of the methods used in the analytical assessment.

Based on our assessment of the PF-06410293 and US-Humira data, we determined that PF-06410293 is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components. PF-06410293 has the same strength, dosage forms, presentations, and route of administration as US-Humira, but has certain formulation differences. Pfizer used a comprehensive array of analytical methods that were suitable to evaluate critical quality attributes of PF-06410293 and US-Humira to support the demonstration that the products are highly similar. Numbers of lots tested and statistical analyses were appropriate to allow for a

meaningful evaluation of the results of the analytical studies. Observed differences do not preclude a determination that PF-06410293 and US-Humira are highly similar.

In addition, three-way pairwise comparisons of PF-06410293, US-Humira, and EU-Humira were used to establish the analytical component of the three-way scientific bridge between PF-06410293, US-Humira, and EU-Humira to support the relevance of the data generated from studies using EU-Humira as the comparator to the assessment of biosimilarity.

Based on our review of the data, we conclude that Pfizer established the analytical portion of the scientific bridge between PF-06410293, US-Humira, and EU-Humira, using the same methods and statistical approaches used to evaluate high similarity between US-Humira and PF-06410293. The analytical portion of the scientific bridge was established to support the relevance of the data generated from studies using EU-Humira as the comparator to the assessment of biosimilarity.

II. Results of Comparative Analytical Assessment

Table A. Quality Attributes Analyzed to Support a Determination of Highly Similar

Comparative Analytical Attributes			
Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
Primary Structure	Amino acid sequence	Yes	Yes
	Disulfide mapping	Yes	Yes
	Free sulfhydryl group quantification	Yes	Yes
N-Linked glycan	Total afucosylation	Yes*	Yes*
	Terminal galactosylation	Yes*	Yes*
	Total high mannose	Yes*	Yes*
	Total sialylation	Yes*	Yes*
Purity and product related variants or impurities	HMW species	Yes	Yes
	Antibody fragments	Yes*	Yes*
	Monomer, Intact IgG	Yes	Yes
	Charged variants	Yes*	Yes*
High Order Structure	Secondary Structure	Yes	Yes
	Tertiary structure	Yes	Yes
	Melting Temperature	Yes	Yes
Bioactivity	Soluble Tumor neutralizing factor-alpha (TNF α) binding and neutralization	Yes	Yes
	Binding to membrane bound TNF α	Yes	Yes
	Reverse Signaling	Yes	Yes
	Antibody-dependent cell-mediated cytotoxicity (ADCC)	Yes	Yes

Comparative Analytical Attributes			
Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
	Binding to FcγIIIa Receptor	Yes*	Yes*
	Complement Dependent cytotoxicity (CDC)	Yes	Yes
	Binding to other Fcγ Receptors (FcγRI, FcγRIIa and FcγRIIb)	Yes	Yes
	Neonatal Fc receptor (FcRn) binding	Yes	Yes
Drug Product Attributes	Protein content	Yes	Yes

“Yes”: Differences were noted, but do not preclude a determination of highly similar or the establishment of the analytical component of the scientific bridge and will be discussed further below.*

The comparative assessment of the degradation profiles of PF-06410293, US-Humira and EU-Humira under forced degradation conditions, including stressed temperature storage, light exposure, forced deamidation and forced oxidation, show minor differences attributable to the differences in formulation, and therefore, these differences do not preclude a determination that PF-06410293 is highly similar to US-Humira.

III. Comparative Analytical Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

The clinical development of PF-06410293 included two pivotal clinical studies:

- Study B5381007: a randomized, double blind, three-arm, parallel group, single-dose study to compare the PK, safety/tolerability and immunogenicity of a single 40 mg administration of each PF-06410293, US-Humira, and EU-Humira in healthy subjects.
- Study B5381002: a randomized, double-blind, two-arm, parallel-group, multiple dose study to evaluate the efficacy, safety, tolerability, PK, and immunogenicity of PF-06410293 compared to EU-Humira in subjects with moderate to severe RA who had an inadequate response to methotrexate (MTX) therapy.

EU-Humira was used as a comparator to PF-06410293 in study B5381002. To support the relevance of the clinical comparative data generated using EU-Humira as a comparator product, Pfizer performed a three-way analytical assessment of PF-06410293, US-Humira, and EU-Humira using a comprehensive array of analytical methods. The analytical component of the three-way scientific bridge included comparison of PF-06410293 to US-Humira, PF-06410293 to EU-Humira, and EU-Humira to US-Humira. The same analytical methods used for the assessment of high similarity between PF-06410293 and US-Humira were used for comparison of PF-06410293 and EU-Humira and US-Humira and EU-Humira. The differences observed in the analytical studies do not preclude a determination that the three-way analytical component of the scientific bridge is acceptable. See section IV below. The results of the assessment establish a robust analytical component of the three-way scientific bridge.

IV. Assessment of Comparative Analytical Study Results

Comparative analytical acceptance criteria were met for all attributes evaluated with quality ranges with the following exceptions:

1. N-linked total afucosylation: 3 out of 10 PF-06410293 batches (5.5-7.5%) were below the quality ranges of US-Humira (5.9-10.9%), but within the quality range of EU-Humira (5.5-11.1%). Afucosylation positively correlate with binding affinity to FcγRIIIa. Binding to FcγRIIIa is the primary mechanism that can lead to ADCC activity. Therefore, differences in afucosylation may result in differences in FcγRIIIa binding and ADCC activity. However, no differences were observed in ADCC activity. Additionally, comparative analytical acceptance criteria were met for binding to FcγIIIa 158V and, as explained in bullet 6, differences in differences in FcγIIIa 158F do not preclude a determination that PF-06410293 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established. Therefore, the observed differences in afucosylation do not preclude a determination that PF-06410293 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established.
2. N-linked terminal galactosylation: the galactosylation level in 3 out of 10 PF-06410293 batches (17.1-27.7%) was above the quality range of US-Humira (17.0-21.8%), and one of them was above the quality range of EU-Humira (14.8-24.2%). Increased galactosylation may increase C1q binding and CDC activity. However, this difference did not result in differences in CDC activity or C1q binding. Therefore, the observed differences in galactosylation do not preclude a determination of highly similar or a determination that the analytical part of the scientific bridge was established.
3. N-linked total high mannose: the high mannose content (percentage of high mannose containing antibody) in all PF-06410293 batches (0.9-1.9%) was below the quality ranges of US-Humira (5.1-9.6%) and EU-Humira (4.4-9.6%). The mean high mannose contents are 1.4%, 7.3% and 7.0% for PF-06410293, US-Humira and EU-Humira, respectively. The high mannose forms are one of the afucosylated glycans that may affect ADCC activity, therefore it is included in the sum of afucosylated glycans for evaluating the total impact on ADCC which is discussed under bullet 1. High mannose content may impact the PK of antibodies because antibodies containing high mannose glycans are cleared more rapidly than other glycan forms. There is a small difference in high mannose containing antibodies between PF-06410293 and US-Humira (~6%). Although there is currently no bioactivity assay (nor has there been one) that can assess the impact of differences in high mannose on PK, the applicant submitted a cell-based pharmacology study that evaluated the uptake of PF-06510293 and US-Humira to assess the potential functional effects of differences in high mannose content. We consulted with the non-clinical reviewers, who reviewed this study and found the results corroborate with the analytical finding, and the study suggested that the minor difference in high mannose would not differentially impact the PK/TK profiles. Additionally, the results from the Study B5381007, considered in the context of other information submitted by the applicant and the publicly available literature, have provided a framework for evaluating acceptable ranges in the comparative analytical assessment. On the basis of that acceptable range, differences in high mannose between PF-06410293 and U.S.-licensed Humira do not preclude a demonstration of highly similar. Based on the foregoing, the observed differences in high mannose content do not preclude a demonstration that PF-

06410293 is highly similar to US-Humira or a determination that the analytical part of the scientific bridge was established.

4. Antibody fragments: the levels of fragments in all PF-06410293 batches were slightly lower (0.3-0.4%) than the quality ranges of US-Humira (0.8-1.6%) and EU-Humira (0.6-1.5%). The fragment levels are very low in all PF-06410293, US-Humira, and EU-Humira batches. Because the levels are so low, we do not expect the slight differences to impact potency. The observed differences do not preclude a determination that PF-06410293 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established.
5. Charge variants: the acidic variants of 3 PF-06410293 batches (15.5-23%) were slightly above the quality ranges of US-Humira (10.4-21.3%) but were within the quality range for EU-Humira (9.2-24.8%). Pfizer provided characterization and biological activity data showing that acidic variants were enriched in sialylated N-glycans, glycation, deamidation and a clipped species. All of the acidic variants had similar biological activities to the main product, except for the clipped species which had reduced biological activity in the TNF- α neutralizing assay. Total clipped species (fragments) were analyzed by the reducing CGE method, and results show that product total clipped species are low in all PF-06410293, US-Humira, and EU-Humira batches (see bullet 4), which indicates that the relative abundance of this charge clipped species is negligible. Therefore, the differences seen in acidic variants do not preclude a determination that PF-06410293 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established.
6. Binding to Fc γ RIIIa receptor: Pfizer evaluated product binding to Fc γ RIIIa receptor using three assays, two of which are specific for Fc γ RIIIa 158V genotype and one for 158F genotype. Comparative analytical acceptance criteria were met for binding to Fc γ RIIIa 158V, however 7 out of 10 PF-06410293 batches (92-113%) had higher relative binding affinity to Fc γ RIIIa 158F and were outside of the quality range of US-Humira (62-101%), but within the quality range of EU-Humira (54-116%). Binding to Fc γ RIIIa is the primary mechanism that can lead to ADCC activity. Therefore, differences in binding to Fc γ RIIIa 158F may result in differences in ADCC for activity for patients with 158V/F or 158F/F genotypes. However, no differences were observed in ADCC activity using human PBMC of 158V/F or 158F/F genotypes. Therefore, the observed differences in binding to Fc γ RIIIa 158V do not preclude a determination that PF-06410293 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established.

Comparative analytical acceptance criteria were met for all attributes evaluated using visual display with the following exception:

7. N-linked total sialylation: All PF-06410293 batches have higher sialylation content (0.5-0.9%) than US-Humira (0.0-0.2%) and EU-Humira (0.1-0.3%). Higher terminal sialylated glycan levels may impact ADCC function [Li T., et al. PNAS Mar 2017, 114 (13) 3485-3490]. However, the difference is small, and the relative percentage of sialylation was low (< 1%) in all PF-06410293, US-Humira, and EU-Humira batches. No differences were observed in ADCC activity between PF-06410293, US-Humira and EU-Humira. Therefore, the observed differences in total sialylation do not preclude a determination that PF-06410293 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established.

V. Same Strength(s)

PF-06410293 has the same dosage form, and route of administration as US-Humira, but has a different formulation. Pfizer is seeking approval of 40 mg/0.8 mL PF-06410293 in a single-dose prefilled syringe, a single-dose prefilled pen, and a single-dose vial; 20mg/0.4mL PF-06410293 in a single-dose prefilled syringe; and 10mg/0.2mL PF-06410293 in a single-dose prefilled syringe. US-Humira is available at these strengths with these corresponding presentations. Comparative protein concentration (mg/mL) was assessed as part of the analytical similarity assessment. The deliverable volume (mL) and fill weight data were assessed as part of manufacturing process controls. Each proposed presentation of PF-06410293 has the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as the corresponding presentation of US-Humira. Each strength of PF-06410293 in PFS, PFP, and vial is the same as that of US-Humira.

III. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
Identity	Efficacy and safety	Intrinsic to the molecule	(b) (4)	
Potency (inhibition of TNF α induced apoptosis)	Direct link to Efficacy	Intrinsic to the molecule		Main MOA
Potency (ADCC)	Direct link to Efficacy	Intrinsic to the molecule		Level of afucosylation and ADCC activity are correlated. Pfizer agreed to implement additional control of ADCC activity in a PMC.
Potency (CDC)	Direct link to Efficacy	Intrinsic to the molecule		Level of galacosylation and CDC activity are correlated. Pfizer agreed to implement additional control of CDC activity in a PMC.
Potency (reverse signaling)	Direct link to Efficacy	Intrinsic to the molecule		
HMW species	Efficacy and safety.	Can be introduced during		Stability-indicating

		manufacturing process and storage	(b) (4)	
LMW species	Efficacy and safety.	Can be introduced during manufacturing process and storage		Stability-indicating
Charge variants (product related variants)	Efficacy and safety. Most of the acidic variants had similar biological activities to the main product, except for the clipped species which had reduced biological activity in the TNF- α neutralizing assay.	Intrinsic to the molecule, and the relevant abundance can change during manufacturing process and storage		Stability-indicating. The specific charge clipped species were controlled at DS and DP release and stability testing by CGE (total fragments)
High order structure	Direct link to efficacy	Intrinsic to the molecule		
N-linked Glycosylation	Efficacy and safety	Intrinsic to the molecule and introduced during manufacturing process		

DS - Drug Substance, DP - Drug Product, iCE – Imaged Capillary Isoelectric Focusing, SE-HPLC – Size Exclusion Chromatography, CGE - Capillary Gel Electrophoresis, HILIC: Hydrophilic Interaction Liquid Chromatography

B. Drug Substance [adalimumab-afzb] Quality Summary

COA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance COA Process Risk Identification and Lifecycle Knowledge Management.

COA (type)	Risk	Origin	Control Strategy	Other
Bioburden	Safety, purity, and efficacy (degradation or modification of the product by	Raw materials or contamination during manufacturing	(b) (4)	

	contaminating microorganisms)		(b) (4)
Endotoxin	Safety and purity	Raw materials or contamination during manufacturing	
HCP	Safety and immunogenicity	Cell culture process and during cell disruption	
hcDNA	Safety and immunogenicity	Process; during cell disruption	Pfizer demonstrated (b) (4)
Viruses (process related impurity)	Safety	Contamination of raw materials or during manufacture	
(b) (4) (Process related impurity)	Safety	(b) (4)	Pfizer demonstrated (b) (4)
(b) (4)	Safety	(b) (4)	
Leachables and extractables	Safety	Entire process	
(b) (4)	Safety	Formulation	See additional control at DP level. (b) (4)

DS - Drug Substance, DP - Drug Product, HCP: host cell protein, hc DNA: host cell DNA, (b) (4)

- Description:

PF-06410293 is a recombinant human IgG1 monoclonal antibody consisting of two light chains, each with a molecular weight of approximately 24 kDa (214 amino acids), and two heavy chains, each with a molecular weight of approximately 49 kDa (451 amino acids). It contains 16 intra-chain and inter-chain disulfide bonds. The total molecular weight of PF-06410293 is

approximately 148 kDa. One N-linked glycosylation site is located at Asn301 on each heavy chain. Glycans include, afucose, high mannose, galactose, and sialylated species.

- Mechanism of Action (MoA):

PF-06410293 specifically binds to soluble and transmembrane TNF- α and neutralizes its biological function by blocking its interaction with the cell surface TNF- α receptors. In addition, antibody dependent cell mediated cytotoxicity, complement dependent cytotoxicity, antibody mediated reverse signaling, and induction of regulatory macrophages have been identified in the scientific literature as potential mechanisms of action for anti-TNF monoclonal antibody products.

- Potency Assay:

The primary mechanism of action (MOA) of adalimumab products is binding to soluble TNF- α and neutralizes its biological function by blocking its interaction with the cell surface TNF- α receptors. Such biological activity is assessed by a cell-based assay measuring the inhibition of TNF α induced apoptosis in U937 cells, a human monocyte cell line that expresses TNF α receptors.

- Reference Materials (RM):

The clinical RM (128926-20) was used during product development for release and stability testing of PF-06410293 clinical and process validation materials, as well as characterization and similarity assessments. Pfizer has implemented a RM two-tiered system, involving primary reference materials (PRM) and working reference materials (WRM), to support the commercial product. The current reference materials (b) (4) were prepared (b) (4)

(b) (4)
The protocols for stability of the RM are acceptable. Protocols for qualification of future RM will be submitted (b) (4)

- Critical starting materials or intermediates:

(b) (4)

[Redacted] (b) (4)

- Manufacturing process summary:

PF-06410293 DS is manufactured in Wyeth BioPharma in Andover, MA USA. [Redacted] (b) (4)

[Redacted]

- Container closure:

[Redacted] (b) (4)

- Dating period and storage conditions: (b) (4) months at (b) (4) °C.

C. Drug Product, ABRILADA, Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product COAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy
Sterility	Infections in patients, product stability	Accidental during fill, container closure failure	[Redacted] (b) (4)
Endotoxin	Adverse reactions in patients, DP failure	Accidental throughout process	
Appearance (Clarity and color)	Product stability	(b) (4) on stability	
Appearance (PFP)	Pen device failure	(b) (4) on stability	
pH	DP failure	Formulation	

Osmolality	Product stability, patient discomfort	Formulation	(b) (4)
Deliverable volume	Inaccurate dosing	Manufacturing process	
Identity	Medication error	Manufacturing process	
Protein concentration	Inaccurate dosing	Manufacturing process	
Particulate matter (Sub-visible particles)	Safety and immunogenicity	accidental throughout manufacturing process, CCS and stability	
Polysorbate	Product stability	Formulation	
Visible particles	Safety and immunogenicity	accidental throughout manufacturing process, CCS and stability	
Break loose and extrusion force (PFS)	PFS devise failure	CCS, in process	

- Potency and Strength:
 - 40 mg/0.8 mL, 20mg/0.4mL and 10mg/0.2mL PF-06410293 in single-dose prefilled syringes,
 - 40 mg/0.8 mL PF-06410293 in a single-dose prefilled pen,
 - 40 mg/0.8 mL PF-06410293 in a single-dose vial.
- Summary of Product Design:
 - ABRILADA PFSs: DP is supplied in a 1 mL long (b) (4) glass prefilled syringe with a 29 gauge thin walled ½ inch staked needle. Each PFS contains 40 mg/0.8 mL, 20 mg/0.4 mL, or 10 mg/0.2 mL of PF-06410293 solution for injection. All PFS presentations comprise the same primary container closure system and device components (a backstop and a plunger rod). Color-coded labels are used to help the user differentiate between the dose strengths.
 - ABRILADA PFP: the autoinjector encloses a 40 mg/0.8 mL PF-06410293 PFS. The PFS is the primary CCS. The autoinjector assembly is 150 mm in length and 17 mm in diameter, with a white cap and activation button with a purple bezel.
 - ABRILADA vial: DP is supplied in a 2 mL (b) (4) clear glass vials with (b) (4) stoppers and crimp seals with flip-off caps. Each vial contains 40 mg/0.8 mL PF-06410293 solution for injection.
- List of Excipients:

Name of Excipient	Concentration (mg/mL)
L-Histidine	0.786
L-Histidine HCl monohydrate	3.132
Edetate Disodium Dihydrate	0.05

Sucrose	85
L-Methionine	0.2
Polysorbate 80	0.2

- Reference Materials: same as PF-06410293 DS reference material.
- Manufacturing process summary:

The manufacturing processes for all ABRILADA presentations (b) (4)

(b) (4)

The vial, fully assembled PFS and PFP were labeled and packaged into cartons as the final DPs.

All drug product-contact equipment and components are (b) (4)

(b) (4)

The maintenance of the integrity of the container closure system during product shelf-life is monitored on stability samples using a validated container closure integrity test.

- Container closure:
 - PFS: 1 mL (b) (4) glass syringe with a 29 gauge, ½ inch, thin-walled stainless steel staked needle, and (b) (4) elastomeric needle shield (rigid needle shield) within a non-product contact rigid (b) (4) cover.
 - PFP: the primary CCS for the PFP is the PFS described above. The pen assembly enclosing the syringe is made up of a transparent outer housing with a white cap on one end and a white activation button with a purple bezel at the other end.
 - Vial: clear and colorless 2mL (b) (4) glass vials with (b) (4) stoppers and crimp seals with flip-off caps.
- Dating period and storage conditions: 36 months at 2 - 8°C. ABRILADA may also be stored at a maximum of 30°C for a single period up to 30 days, but not exceeding the original expiration date.
- List of co-package components: None

D. Novel Approaches/Precedents: None

E. Special Product Quality Labeling Recommendations: None

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Cell bank manufacture and storage; DS manufacture; DS in-process control, release, and stability testing; DS storage; Management responsibilities for combination product (PFS and PFP); design controls; purchasing controls; CAPA	Wyeth BioPharma, Division of Wyeth Pharmaceuticals LLC, One Burtt Road Andover, MA 01810 USA	1222181	VAI	A three-item FDA Form 483 was issued on May 03, 2019. Deficiencies were adequately addressed in the firm's responses to the FDA-483, Inspectional Observations.	Approval
Cell bank storage	Pfizer Ireland Pharmaceuticals, Grange Castle Business Park and Clondalkin, Dublin 22 Ireland	3004145594	Approve – Based on previous history		Approval
WCB testing DS in-process testing (b) (4)	(b) (4)	(b) (4)			Approval
DS storage	(b) (4)	(b) (4)			Approval
DS storage	(b) (4)	(b) (4)			Approval
DRUG PRODUCT					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS storage (in readiness for DP manufacture),	(b) (4)	(b) (4)	Approve - Based on Previous History and waiver granted by		Approval

Manufacture Primary packaging, Release testing (sterility and endotoxin), Assembly of prefilled syringe, Secondary packaging and labeling.	(b) (4)		OBP/OPF. No Evaluation Necessary	
Release testing Stability testing	Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin, Dublin 22 Ireland	3004145594	Approve – Based on previous history	Approval
Assembly of PEP Labeling Release testing Stability testing Secondary packaging	(b) (4)	(b) (4)	Approve Based on Previous History and waiver granted by CDRH	Approval
Manufacture of PEP subassemblies		(b) (4)		Approval

G. Facilities:

Wyeth BioPharma, Division of Wyeth Pharmaceuticals LLC (FEI 1222181) is responsible for DS manufacturing. A PLI was conducted from 04/29/2019-05/03/2019. This inspection was system-based and covered Quality, Laboratory, Raw Materials, Facilities and Equipment, and Production Systems. A 3-item Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection. Refer to the EIR or the Form FDA 483 for a list of the 483 observations. Deficiencies were adequately addressed in the firm's responses to the Form FDA-483, Inspectional Observations. The inspection was classified as VAI. Approval of BLA761118 was recommended.

(b) (4) (FEI: (b) (4)) is responsible for DP manufacturing. The proposed manufacturing scheme for PF-06410293 vial is (b) (4)

The proposed manufacturing scheme for PF-06410293 syringe is (b) (4)

Additionally, (b) (4) was inspected during the (b) (4) inspection with a final recommendation of VAI. (b) (4) was inspected during the (b) (4) inspection with a final recommendation of VAI. OBP, DMA, and DIA concur to waive the pre-license inspection

(b) (4) in support of BLA761118 for PF-06410293 drug product manufacture.

(b) (4) (FEI: (b) (4)) is responsible for DP manufacturing (assembly of PEP, labelling and secondary packaging). CDRH reviewer concluded that a facility inspection is not required based on previous history. Approval of BLA761118 was recommended.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

1. PROT_24004 PF-06410293 (b) (4) Monitoring Protocol
2. PROT-19982 PF-06410293 (b) (4) Monitoring Protocol
3. PROT-24278, PF-06410293 (b) (4) Protocol
4. PROT-24279, PF-06410293 Drug Substance (b) (4) Protocol
5. 3.2.S.2.3 - Control of Materials - Protocol for the Preparation, Qualification and Storage of Renewal WCBs
6. 3.2.S.7.2 Post Approval Stability Protocol and Stability Commitment

ii. Outstanding review issues/residual risk: See Post Marketing Commitments in section I. D.

iii. Future inspection points to consider: despite that the iCE assay validation report in the BLA showed adequate assay precision, the submitted release and stability data suggest that the iCE assay has high variability on assay results obtained from different days. Future inspection should review the assay performance in real operation, such as adherence to SOP, peak integration and assay result trending.

b. Drug Product

i. Protocols approved:

1. 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment, (PFS 40 mg)
2. 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (PFS 20 mg)
3. 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (PFS 10 mg)
4. 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (Vial 40 mg)

5. 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (PFP 40 mg)
 - ii. Outstanding review issues/residual risk: See Post Marketing Commitments in section I. D.
 - iii. Future inspection points to consider: Same as in the DS section.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAOHENG N YAN
11/13/2019 08:50:23 AM

JOEL T WELCH
11/13/2019 08:59:10 AM



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

LABELS AND LABELING ASSESSMENT

Date of review:	November 1, 2019
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Assessor Office of Biotechnology Products (OBP)
Through:	Nailing Zhang, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761118
Applicant:	Pfizer Inc
Submission Date:	November 16, 2018
Product:	Abrilada (adalimumab-afzb)
Dosage form(s):	Injection
Strength and Container-Closure:	40 mg/0.8 mL in a single-dose prefilled pen 40 mg/0.8 mL in a single-dose prefilled glass syringe 20 mg/0.4 mL in a single-dose prefilled glass syringe 10 mg/0.2 mL in a single-dose prefilled glass syringe 40 mg/0.8 mL in a single-dose glass vial for institutional use only
Purpose of review:	The Applicant submitted a biologics license application for Agency review
Recommendations:	The prescribing information/medication guide and instructions for use (submitted on October 31, 2019), and container labels and carton labeling (submitted on September 20, 2019) are acceptable from an OBP labeling perspective.

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

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

CONCLUSION

The prescribing information/medication guide and instructions for use (submitted on October 31, 2019), and container labels and carton labeling (submitted on September 20, 2019) are acceptable from an OBP labeling perspective. (see Appendix C)

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information/Medication Guide/Instructions for Use (submitted on November 16, 2018 <\\cdsesub1\evsprod\bla761118\0001\m1\us\lab1350-lab1351-lab1352-lab1353-combined-annotated.pdf>)

Container Labels (submitted on November 16, 2018)

Prefilled pen



Appendix B: Evaluation Tables**Evaluation Tables: Label^{1,2} and Labeling³ Standards****Container⁴ Label Evaluation**

Proper Name	Acceptable
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form below the proper name)</i>	☒ Yes ☐ No ☐ N/A
Manufacturer name, address, and license number	Acceptable
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	☒ Yes

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

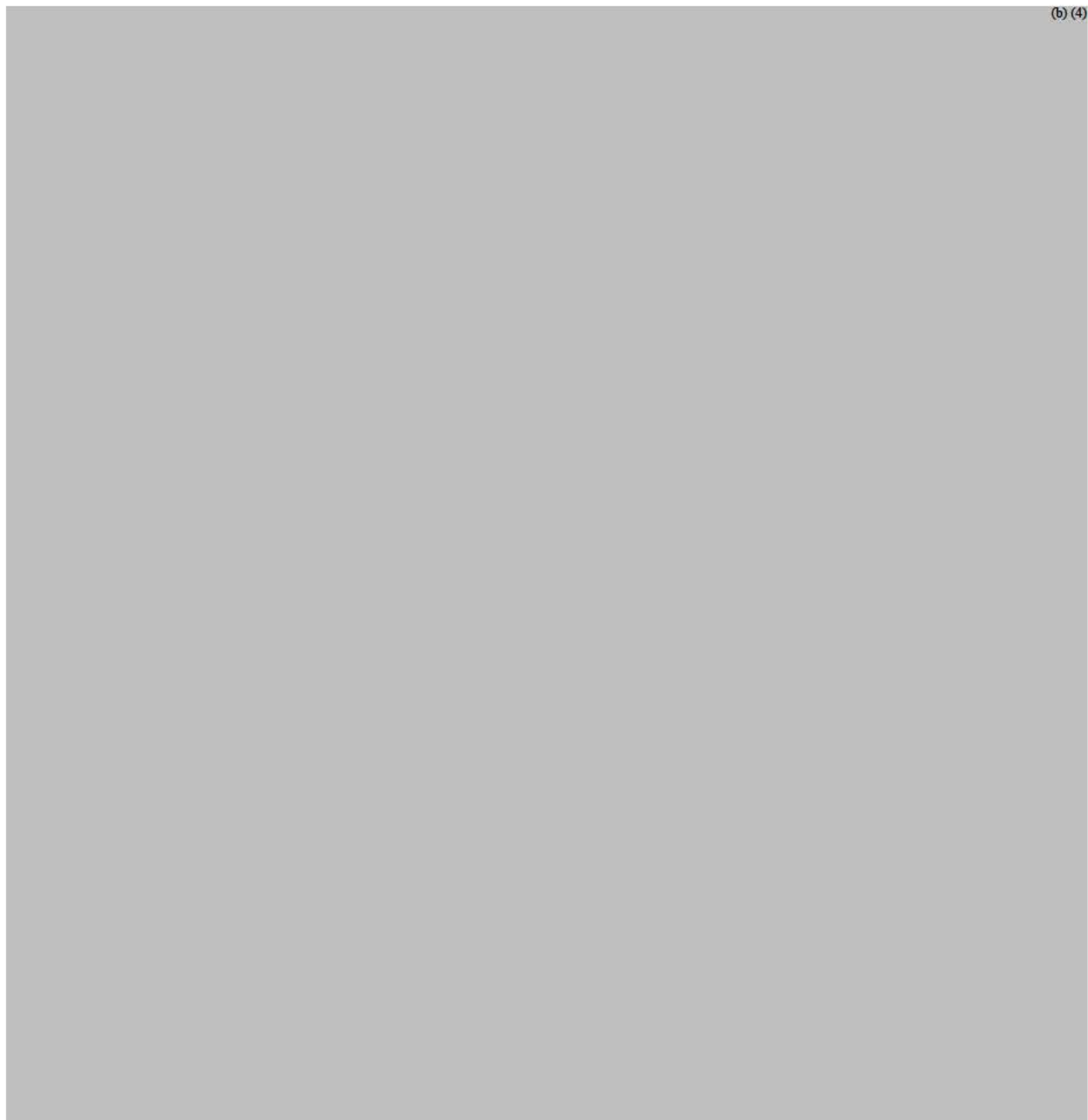
² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

	☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (U.S license number for container bearing a partial label)</i>	☒ Yes ☐ No ☐ N/A
Lot number or other lot identification	Acceptable
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	☒ Yes ☐ No ☐ N/A
Expiration date	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <7> Labeling Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A
Beyond Use Date (Multiple-dose containers)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A
Product Strength	Acceptable
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Multiple-dose containers (recommended individual dose)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55	☐ Yes ☐ No ☒ N/A
Statement: "Rx only"	Acceptable
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: For the prefilled pen container label, add the Rx Only statement <i>The Applicant revised as requested</i>	

<i>Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A
Medication Guide	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☒ Yes ☐ No ☐ N/A
No Package for container	Acceptable
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A
No container label	Acceptable
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A
Ferrule and cap overseal (for vials only)	Acceptable
<i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: FOR VIALS: Confirm there is no text on the ferrule and cap overseal of the vials. <i>Pfizer Response: Pfizer confirms that there is no text on the ferrule and cap overseal of the vials.</i> <i>The Applicant's response is acceptable</i>	
Visual inspection	Acceptable
Regulation: 21 CFR 610.60(e)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located <i>Pfizer Response: Pfizer confirms there is sufficient area on the containers to allow for visual inspection when the label is affixed to the containers. Images of the mock-up vial, prefilled syringes (PFS) and prefilled pen (PFP) are included in this submission. Please note, these pictures are representative to illustrate the visual inspection area. The text shown on the labels does not reflect the actual submission artwork.</i> <i>For the vial, there is a 5 mm gap that extends from the top of the container to the bottom of the container.</i> <i>For the syringe, there is a 10 mm gap at the needle end of the syringe that extends around the entire circumference of the syringe.</i> <i>For the pen, the pen label has transparent windows (front and back) that enable the user to view the drug product in the syringe through the label and pen</i>	



The Applicants response is acceptable

<i>NDC numbers</i>	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A
<i>Route of administration</i>	Acceptable
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No

	☐ N/A
Preparation instructions	Acceptable
Regulation: 21 CFR 201.5(g)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: space considerations	
<i>Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic</i>	☐ Yes ☐ No ☒ N/A
Package type term	Acceptable
<i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: For the prefilled pen, if space permits, add the package type term statement "single-dose prefilled pen" <i>The applicant revised as requested</i>	
Misleading statements	Acceptable
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A
Prominence of required label statements	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A
Spanish-language (Drugs)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Bar code label requirements	Acceptable
Regulations: 21 CFR 201.25, 21 CFR 610.67	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
Net quantity	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A
Statement of Dosage	Acceptable
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Consider revising the statement of dosage from (b) (4) (b) (4) to read "Dosage: See Prescribing Information" <i>The applicant revised as requested</i>	
Inactive ingredients	Acceptable
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A
Storage requirements	Acceptable
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
Dispensing container	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package⁵ Label Evaluation

Proper name	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	☒ Yes ☐ No ☐ N/A
Manufacturer name, address, and license number	Acceptable
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A
Lot number or other lot identification	Acceptable
Regulation: 21 CFR 610.61(c)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Ensure that the lot number appears on the PFS tray lidding labeling, vial carton labeling, and PFS carton labeling <i>Pfizer Response: Pfizer confirms that the lot numbers and expiration date appear on the PFS tray lidding labeling, vial carton labeling, and PFS carton labeling</i> <i>The Applicant's response is acceptable</i>	
Expiration date	Acceptable
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Ensure that the expiration date appears on the PFS tray lidding labeling, vial carton labeling, and PFS carton labeling <i>Pfizer Response: Pfizer confirms that the lot numbers and expiration date appear on the PFS tray lidding labeling, vial carton labeling, and PFS carton labeling</i> <i>The Applicant's response is acceptable</i>	
Beyond Use Date (Multiple-dose containers)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A
Preservative	Acceptable
Regulation: 21 CFR 610.61(e)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Add the words "No preservative" to the PFS tray lidding labeling <i>The Applicant revised as requested</i>	

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.

Number of containers	Acceptable
Regulation: 21 CFR 610.61(f)	☒ Yes ☐ No ☐ N/A
Product Strength	Acceptable
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Storage temperature/requirements	Acceptable
Regulation: 21 CFR 610.61(h)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: For the alternative storage instruction for the prefilled pen and PFS, date of injection can be different from the date the pen was removed from the refrigerator. Revise from (b) (4) to "Date Removed from Refrigerator". <i>Pfizer Response: Upon review of the carton labels of Pfizer's PFP and PFS, we realized that they already capture the language in the end panel for patients to note down the "date removed from refrigerator". See the example of Pfizer's PFP carton image below (right-hand part). We propose to remove the (b) (4) section from the bottom panel (the lefthand part). This approach (having "date removed from refrigerator" and not having (b) (4) (b) (4) section) is consistent with that of Humira's carton label for PFP and PFS. The Applicant's response is acceptable</i>	
Handling: "Do Not Shake", "Do not Freeze" or equivalent	Acceptable
Regulation: 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Add the instructions "Do not shake" to all carton labeling <i>The Applicant revised as requested</i>	
Multiple dose containers (recommended individual dose)	Acceptable
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A
Route of administration	Acceptable
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A

<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A
Known sensitizing substances	Acceptable
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A
Inactive ingredients	Acceptable
Regulations: 21 CFR 610.61, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Source of the product	Acceptable
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A
Minimum potency of product	Acceptable
Regulation: 21 CFR 610.61(r)	☒ Yes ☐ No ☐ N/A
Rx only	Acceptable
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A
Divided manufacturing	Acceptable
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A
Distributor	Acceptable
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☒ Yes ☐ No ☐ N/A
Bar code	Acceptable
Regulations: 21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i>	☒ Yes ☐ No

<i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)</i>	☐ N/A
<u>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</u>	<u>Acceptable</u>
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
<u>NDC numbers</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A
<u>Preparation instructions</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.5(g)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A
<u>Package type term</u>	<u>Acceptable</u>
<i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
<u>Misleading statements</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A
<u>Prominence of required label statements</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A
<u>Spanish-language (Drugs)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
<u>Phenylalanine as a component of aspartame</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.21(c)	☐ Yes

	☐ No ☒ N/A
Sulfites; required warning statements	Acceptable
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A
Net quantity	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A
Statement of Dosage	Acceptable
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Consider revising the statement of dosage from (b) (4) to read "Dosage: See Prescribing Information" <i>The Applicant revised as requested</i>	
Dispensing container	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A
Medication Guide	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☒ Yes ☐ No ☐ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A
DOSAGE AND ADMINISTRATION	Acceptable
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions</i>	☐ Yes ☐ No ☒ N/A
DOSAGE FORMS AND STRENGTHS	Acceptable
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) USP chapter <659> Packaging and Storage Requirements USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	Acceptable
Regulation: 21 CFR 201.57(c)(3)(iv)	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products</i>	☐ Yes ☐ No ☒ N/A
3 DOSAGE FORMS AND STRENGTHS	Acceptable
Regulation: 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: We added the identifying characteristics of the dosage form per 21 CFR 201.57(c)(4) <i>The Applicant revised as requested</i> We revised for readability and to remove information that is not required for this section. The syringe size and needle description are not required and are already provided in the more appropriate section 16 (How Supplied/Storage and Handling).	

<i>The Applicant revised as requested</i>	
<i>Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
11 DESCRIPTION	Acceptable
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i> Comment/Recommendation: We deleted (b) (4) <i>The Applicant revised as requested</i> We included the specific cell line as this may be considered important information for the healthcare professional (also see 21 CFR 610.61 (q)). <i>The Applicant revised as requested</i>	☒ Yes ☐ No ☐ N/A
16 HOW SUPPLIED/ STORAGE AND HANDLING	Acceptable
Regulation: 21 CFR 201.57(c)(17) Comment/Recommendation: We added the identifying characteristics per 21 CFR 201.57(c)(17). <i>The Applicant revised as requested</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	☒ Yes ☐ No ☐ N/A
MANUFACTURER INFORMATION	Acceptable
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A
MEDICATION GUIDE, PATIENT INFORMATION LABELING, INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	Acceptable
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	☒ Yes ☐ No ☐ N/A

<i>Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).</i>	☒ Yes ☐ No ☐ N/A
STORAGE AND HANDLING	Acceptable
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices for Patient Labeling or IFU: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: The language in the IFUs (b) (4) differs from the language in the PI and Medguide (protect from light). The storage information in the IFUs were revised for consistency (b) (4) <i>The Applicant revised as requested</i>	
INGREDIENTS	Acceptable
<i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: For the medication guide: We corrected the typo from (b) (4) to "dihydrate" <i>The Applicant revised as requested</i>	
MANUFACTURER INFORMATION	Acceptable
21 CFR 201.1, 19 CFR 134.11, 21 CFR 208.20(b)(8)(iii)	☒ Yes ☐ No ☐ N/A
<i>21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A

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Zhang

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BLA STN 761118

ABRILADA™ (PF-06410293) **A proposed biosimilar to adalimumab**

Pfizer, Inc.

Nailing Zhang, Ph.D., Primary Reviewer
Haoheng Yan, M.D., Ph.D., Application Technical Lead
Joel Welch, Ph.D., Review Chief

Division of Biotechnology Review & Research IV (DBRR IV)
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

OBP CMC Review Data Sheet

1. BLA#: STN 761118

2. Review Date: August 2, 2019

3. Primary Review Team:

a. Medical Officer:	Jin Chen (DPARP)
b. Pharm/Tox:	Xiaochun Chen (DPARP)
c. Product Quality Team:	
OBP:	Nailing Zhang (DS, DP, immunogenicity) Xuhong Li (analytical similarity) Haoheng Yan (ATL) Joel Welch (Review Chief) Vicky Borders-Hemphill (labeling)
DMA:	Aimee Cunningham / Maria (Reyes) Candau-Chacon
DIA:	Amy Devlin / Thuy Thanh Nguyen
CDRH:	Rumi Young / Sarah Mollo
d. Clinical Pharmacology:	Jianmeng Chen (DCPII)
e. Statistics:	William Koh (DBII)
f. RPM:	Colette Jackson (DPARP) Anh-Thy Ly (OPQ)

4. Major GRMP Deadlines:

a. Filing meeting:	01/04/2019
b. 74-Day Letter:	01/29/2019
c. Mid-cycle internal meeting:	04/15/2019
d. Mid-cycle communication:	04/29/2019
e. Labeling meeting:	06/11/2019
f. Late-cycle internal meeting:	07/15/2019
g. Primary review due:	07/16/2019
h. Secondary review due:	07/23/2019
i. Late-cycle sponsor meeting:	09/03/2019
j. Wrap-up meeting:	09/24/2019
k. BsUFA action date:	11/16/2019

5. Communications and submissions:

Communication/Document	Date	Submission	Review status
Original submission	11/16/2018	STN 761118/SN 0001, 11/16/2018	Complete
Filing review memo	01/10/2019	/	Complete
74-Day Letter	01/22/2019	STN 761118/SN 0008, 02/22/2019	Complete
/	/	STN 761118/SN 0012, 04/30/2019 (Minor CMC updates)	Complete
Information Request #1 (OPQ IR 005)	04/30/2019	STN 761118/SN 0013, 05/15/2019 STN 761118/SN 0014, 05/24/2019 STN 761118/SN 0017, 06/25/2019	Complete
Information Request #2 (OPQ IR 008)	06/20/2019	STN 761118/SN 0018, 07/08/2019	Complete
Information Request #3 (OPQ IR 009)	06/21/2019	STN 761118/SN 0018, 07/08/2019	Complete
Information Request #4 (OPQ IR 011)	07/03/2019	STN 761118/SN 0020, 07/12/2019	Complete
Information Request #5 (OPQ IR 012)	07/09/2019	STN 761118/SN 0020, 07/12/2019	Complete

Information Request #6 (OPQ IR 013)	07/17/2019	STN 761118/SN 0021, 07/31/2019	Complete
Information Request #7 (OPQ IR 014)	07/19/2019	STN 761118/SN 0021, 07/31/2019	Complete
Information Request #8 (PMC#1)	07/23/2019	STN 761118/SN 0021, 07/31/2019	Complete

6. Drug Product Name/Code/Type:

- a. Proprietary Name: ABRILADA
- b. Trade Name: ABRILADA™
- c. Non-Proprietary Name/USAN: Adalimumab-XXXX (pending)
- d. CAS Registry Number: 331731-18-1
- e. Common Name: Not applicable.
- f. INN Name: Adalimumab-XXXX (pending)
- g. Compendial Name: Not applicable.
- h. OBP Systematic Name: MAB HUMAN (IGG1) ANTI P01375
(TNFA_HUMAN) [PF06410293]
- i. Other Name(s): PF-06410293 (company code)

7. Pharmacological Category: Therapeutic recombinant human monoclonal antibody to human TNFα.

8. Dosage Form: Injection solution in prefilled pen (PFP), prefilled syringe (PFS), or glass vial.

9. Strength/Potency:

- (i): The concentration/strength of the drug product (DP): 40 mg/0.8 mL PFP/PFS/vial; 20 mg/0.4 mL PFS; 10 mg/0.2 mL PFS.
- (ii): Type of potency assay(s): A cell-based assay to determine the functional activity of PF-06410293 drug substance (DS) and DP by demonstrating the inhibition of TNFα induced apoptosis in U937 cells, a human monocyte cell line that expresses TNFα receptors.

10. Route of Administration: Subcutaneous injection.

11. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
			(b) (4) Yes	Letters of Authorization were provided.
			Yes	No review is required as all information related to safety and compatibility with the products has been provided in the BLA.
			Yes	
			Yes	
			Yes	
			Yes	Letters of Authorization were provided.
			Yes	Defer to DMA and DIA reviewers.
			Yes	
			Yes	
			Yes	

12. **Inspectional Activities:** The pre-license inspection on the DS manufacturing site and the analytical similarity testing site at Wyeth BioPharma, Division of Wyeth Pharmaceuticals LLC (One Burt Road, Andover, MA 01810, USA, FEI # 1222181) was conducted from April 29, 2019 to May 3, 2019 by Wayne Seifert (lead, CDER/OPQ/OPF/DIA), Amy Devlin (CDER/OPQ/OPF/DIA), Nailng Zhang (CDER/OPQ/OBP), and Gunther Boekhoudt (CDER/OPQ/OBP). The inspection was system-based and covered Quality, Facilities and Equipment, Production, Materials and Laboratory Control Systems. The inspection was limited to the manufacture of PF-06410293 drug substance and the analytical similarity data and components. A 3-item Form FDA 483 was issued for 1) Written procedures are not followed or are inadequate to ensure control over drug substance manufacture and laboratory operations, 2) Facilities, equipment and utilities are not adequately maintained, and 3) Corrective action (b) (4) (b) (4) has not been effective. It was recommended that the inspection be classified as voluntary action indicated (VAI) (Acceptable) for the subject supplement. Pfizer responded to Form 483 on May 20, 2019.

The pre-license inspections on the DP manufacturing site ((b) (4) FEI# (b) (4)) and the prefilled pen assembly site ((b) (4) FEI# (b) (4)) were waived.

13. **Consults Requested by OBP:** The device components of prefilled pen (PFP) and prefilled syringe (PFS) are reviewed by CDRH. Consult requests were processed by OPQ.

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

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

15. **Precedents:** None.

16. **Administrative:**
Signature Block

Name and Title	Signature and Date
Joel Welch, Ph.D. Review Chief, DBRRIV/OBP/OPQ/CDER	See electronic signature and date
Haoheng Yan, Ph.D. Application Technical Lead, DBRRIV/OBP/OPQ/CDER	See electronic signature and date
Nailing Zhang, Ph.D. Primary reviewer, DBRRIV/OBP/OPQ/CDER	See electronic signature and date

Summary of Quality Assessments

1. **Primary Reviewer Summary Recommendation:**

The data submitted in this Biologics License Application (STN 761118) support the conclusion that the manufacture of ABRILADA™ (PF-06410293), a proposed biosimilar to Humira, is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious

agents, and meets the standards recommended by FDA. The conditions used in the manufacturing process had been adequately validated, and the product had been consistently manufactured from multiple production runs. It is recommended that ABRILADA™ (PF-06410293) be approved for human use under conditions specified in the package insert.

We recommend an expiration dating period of (b) (4) months for PF-06410293 drug substance when stored at (b) (4) °C.

We recommend an expiration dating period of 36 months for PF-06410293 drug products when stored at 5 ± 3°C protected from light. If needed, the PF-06410293 drug product may be stored at room temperature up to a maximum of 30°C for a period of up to 30 days, with protection from light.

We recommend approval of the proposed release and shelf-life specifications for PF-06410293 drug substance and drug product.

A separate analytical similarity review was performed by Dr. Xuhong Li (OBP/DBRRIV), and the review memo will be uploaded as a separate file in Panorama.

2. List of Deficiencies to be Communicated:

There are no product quality deficiencies precluding approval of this BLA.

3. List of Post-Marketing Commitments/Requirements:

There is one product quality-related Post-Marketing Commitment (PMC) being negotiated with the applicant: to implement a control strategy for effector function. In IR Response SN0021, 07/31/19, the applicant committed to submit the proposed control strategy as a Prior Approval Supplement (PAS) by September 30, 2020.

Product quality-related protocols to be approved within BLA 761118 are listed in the table below:

Protocol Title	eCTD Location
PROT_24004 PF-06410293 (b) (4) Monitoring Protocol	3.2.S.2.5 Process Validation and/or Evaluation
PROT-19982 PF-06410293 (b) (4) Monitoring Protocol	3.2.S.2.5 Process Validation and/or Evaluation
PROT-24278, PF-06410293 (b) (4) Protocol	3.2.S.2.5 Process Validation and/or Evaluation
PROT-24279, PF-06410293 Drug Substance (b) (4) Protocol	3.2.S.2.5 Process Validation and/or Evaluation
3.2.S.2.3 - Control of Materials - Protocol for the Preparation, Qualification and Storage of Renewal WCBs	3.2.S.2.3 Control of Materials
3.2.S.7.2 Post Approval Stability Protocol and Stability Commitment	3.2.S.7 Stability
3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment, (PFS 40 mg)	3.2.P.8 Stability (PFS 40 mg)
3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (PFS 20 mg)	3.2.P.8 Stability (PFS 20 mg)
3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (PFS 10 mg)	3.2.P.8 Stability (PFS 10 mg)
3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (Vial 40 mg)	3.2.P.8 Stability (Vial 40 mg)
3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (PFP 40 mg)	3.2.P.8 Stability (PFP)

4. Review of Common Technical Document - Quality Module 1:

A. Environmental Assessment of Claim of Categorical Exclusion

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

5. Primary Container Labeling Review:

A separate primary container labeling review was performed by Vicky Borders-Hemphill (OBP), and the review memo will be uploaded as a separate file in Panorama.

6. Review of Common Technical Document - Module 2.3 Quality Overall Summary and Quality Module 3.2: The review of Modules 2.3 and 3.2 is included in this review memorandum.

7. Review of Immunogenicity Assays - Module 5.3.1.4:

The ECL-based anti-drug antibody (ADA) screening assay has a sufficient sensitivity of 10.3 ng/mL and can detect 250 ng/mL ADA in the presence of 6.4 µg/mL of on-board PF-06410293. The cell-based neutralizing antibody (NAb) assay has sufficient sensitivity of 133 ng/mL and can detect 2500 ng/mL NAb in the presence of 0.1 µg/mL of on-board PF-06410293. The drug tolerance levels are sufficient which is supported by the high ADA and NAb detection rates in clinical studies. Equivalent sensitivities of both ADA and NAb assays have been demonstrated for PF-06410293, US-licensed adalimumab, and EU-approved adalimumab. The immunogenicity assays have been adequately validated. The review of the assays is included in the end of this review memorandum.

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Yan

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Zhang

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Submission:	BLA 761118
Subject:	Analytical Similarity Assessment
Date Received:	16 Nov 2019
Assessment/Revision Date:	05 Mar 2019/10 Jul 2019.
Primary Assessor:	Xuhong Li, Chemist, OBP Div. IV
Secondary Assessor:	Haoheng Yan, Team Lead, OBP Div. IV
Tertiary Assessor:	Joel Welch, Review Chief, OBP Div. IV
RBPM:	Anh-Thy Ly
Applicant:	Pfizer
Product:	PF-06410293, Biosimilar to US-Humira

ANALYTICAL SIMILARITY ASSESSMENT

Summary:

To support a demonstration that PF-06410293 is analytically similar to US-licensed Humira, and to establish a 3-way scientific bridge, Pfizer performed an analytical similarity assessment using a sufficient number of PF-06410293, U.S.-licensed Humira, and E.U.-approved adalimumab drug substance (PF-06410293 only) and drug product lots. Adalimumab molecular/quality attributes are collectively assigned to the correct statistical “Tiers” of statistical analysis as described in the withdrawn Guidance for Industry: “Statistical Approaches to Evaluate Analytical Similarity”. For simplicity, the sponsor terminology is maintained throughout the review. Similarity was evaluated using appropriate statistical methods. The similarity data package was generated using methods that are considered appropriately validated or qualified for their intended purpose. PF-06410293 meets the statutory “same strength” requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act. All molecular/quality attributes are analytically similar except for high mannose content. The mean high mannose contents are 1.4%, 7.3% and 7.0% for PF-06410293, US-licensed Humira and EU-Humira, respectively. It is known that high mannose glycans of therapeutic monoclonal antibodies increases serum clearance in human. Scientific literature also indicates that up to 5% difference in high mannose glycans differences does not significantly impact clearance of monoclonal antibodies [Goetze A.M. et al. Glycobiology, Volume 21, Issue 7, July 2011, Pages 949–959]. Albeit the difference in high mannose between PF-06410293, U.S.- Humira, and E.U.-Humira was slightly higher than 5%, the analytical difference alone does not preclude a demonstration that PF-06410293 is highly similar to US-Humira. This conclusion is further corroborated by the results of the comparative PK study, in which PK similarity is demonstrated between PF-06410293, US-Humira and EU-Humira (provided by clinical pharmacology reviewer Dr. Jianmeng Chen).

Overall, the analytical data provided support the conclusion that PF-06410293 is highly similar to U.S.-licensed Humira. In addition, the data support the adequacy of the analytical component of the scientific 3-way bridge to justify the use of clinical data generated using E.U.-approved Humira.

Note: Reviewer comments are italicized. Unless otherwise stated, all tables and figures in this review have been copied from the BLA submission.

3.2.R Analytical Similarity Assessment

3.2.R.3.1 Overall Strategy

3.2.R.3.1.1 Overall Strategy

The 40 mg/0.8 mL PFS presentation was used in the clinical studies, including one study arm in which the 40 mg/0.8 mL PFS was incorporated into the prefilled pen. Four drug product (DP) presentations of the PF-06410293 were included in the analytical similarity assessment. As to the reference product, primarily the 40 mg/0.8 mL PFS and Pen presentations of US-licensed and EU-approved Humira were included in the analytical similarity assessment, because only these configurations were regularly available on the open market. Since the primary container closure in the PFS and PFP are the same (PFP was made by the insertion of PFS into an auto injector), the applicant considered these licensed product configurations the same for the analytical similarity assessment. Three comparisons were conducted to demonstrate analytical similarity:

1. PF-06410293 to US-licensed Humira (US-Humira)
2. PF-06410293 to EU-approved Humira (EU-Humira)
3. EU-Humira to US-Humira

There are three additional DP configurations for pediatric indication (20 mg/0.4 mL PFS, 10 mg/0.2 mL PFS and 40 mg/0.8 mL vial), but limited supplies of the US-licensed and EU-approved Humira product are available. To obtain maximum information from the limited number of lots available and assess for impact of drug product configuration including container closure on product quality and stability, these configurations are included in the side-by-side forced degradation studies assessing similarity of PF-06410293 to US-Humira and EU-Humira. (Section 3.2.R.3.3 Comparative Forced Degradation Studies).

The applicant has ranked product quality attributes (QAs) based on their potential impact on activity, PK/PD, safety, and immunogenicity, using risk assessment principles set forth in the ICH guidelines Q8, Q9, Q10 and Q11, and guided by published scientific literature on the licensed product. The adalimumab QA rankings (“Tier 1 to 3”) are provided in Table 3.2.R.3.1.1-1 and Table 3.2.R.3.1.1-2 of this submission. Equivalence testing was applied to results for quality attributes with the highest ranking (“Tier 1”). For “Tier 2” quality attributes, the analytical similarity is established if 90% or greater of test lot fall within the statistical quality range established based on the reference lots. For “Tier 3” quality attributes, the similarity assessment was done using side-by-side graphical comparisons of the raw data.

Reviewer’s Comment: *The proposed ranking for the quality attribute and statistical methods used in the similarity assessment has been discussed and agreed upon at the IND 114729 BPD Type 3 meeting with the FDA held on March 8, 2018.*

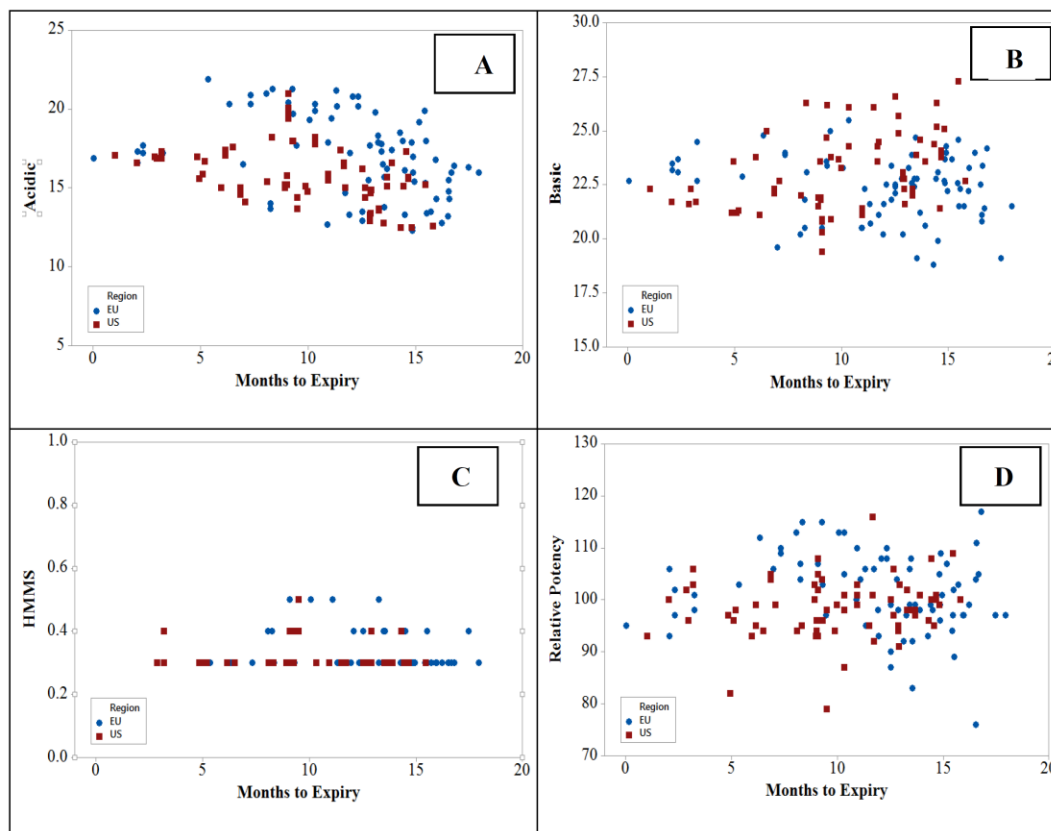
3.2.R.3.1.2 Lots Enrolled in Similarity Assessment

Licensed Product Lots

A total of 145 product lots (68 US-Humira drug product lots and 77 EU-Humira drug product lots, 40 mg/0.8 mL PFS or PFP) were included in the similarity assessment. Licensed product lots at various age were used in the similarity assessment (received, recorded and prepared for analysis at < 1 month to 18 months before expiry). The inclusion of lots of various ages has allowed the impact of drug product age to be a component of the similarity assessment. The applicant also showed data to provide that no significant difference in stability-indicating quality attributes over the product shelf-life for the licensed

products (see figure below). These quality attributes were chosen because they are significant to similarity and were shown to be stability-indicating for the licensed product in forced degradation studies).

Figure 3.2.R.3.1.2-1. Assessment of Stability Indicating Attributes Against Adalimumab-US and Adalimumab-EU Lot Age at Time of Testing



PF-06410293 Lots (independent lot selection)

Total 9 DS batches and 26 DP lots produced at the commercial scale are included in the similarity assessment. In addition, a development scale DS batch (14P137K605 at (b) (4) scale) which has demonstrated to be representative and comparable to the commercial scale was also included in the similarity assessment.

Lot genealogy leading to independent lot selection		
Drug Substance Batch	Drug Product Presentation	Drug Product Lot
12L137L002	40 mg/0.8 mL	MJP1-01-004
12L137L003	40 mg/0.8 mL	008A13 ^a
	40 mg/0.8 mL	021B14 ^{a, b}
12L137L005	10 mg/0.2 mL	ENG16017
	10 mg/0.2 mL	082B16
	20 mg/0.4 mL	079B16
	40 mg/0.8 mL	ENG16046
	40 mg/0.8 mL	003C13
	40 mg/vial	ENG16013
	40 mg/vial	068B16

Lot genealogy leading to independent lot selection		
Drug Substance Batch	Drug Product Presentation	Drug Product Lot
13L137L006	10 mg/0.2 mL	083B16
	10 mg/0.2 mL	ENG16048
	20 mg/0.4 mL	080B16
	40 mg/0.8 mL	004C13
	40 mg/vial	ENG16047
	40 mg/vial	069B16
14P137K605 (development lot)	N/A	N/A
15L137L001	10 mg/0.2 mL	081B16
	20 mg/0.4 mL	078B16
	40 mg/0.8 mL	007F15^b
	40 mg/vial	067B16
16L137L001	10 mg/0.2 mL	029M16
	20 mg/0.4 mL	026M16
	40 mg/0.8 mL	023M16
	40 mg/vial	020M16
16L137L002	10 mg/0.2 mL	030M16
	20 mg/0.4 mL	027M16
	40 mg/0.8 mL	024M16
	40 mg/vial	021M16
16L137L003	10 mg/0.2 mL	031M16
	20 mg/0.4 mL	028M16
	40 mg/0.8 mL	025M16
	40 mg/vial	022M16
16L137L004	N/A	N/A
a. Lot used in comparative PK study b. Lot used in comparative safety and efficacy study Bold, DS batches and DP lots were selected as independent lots for statistical analyses. N/A = No drug product made from the drug substance		

“Tier”	Methodology/Quality Attribute	Number of independent Pfizer Lots	PF-06410293 DS Lots	PF-06410293 DP Lots	Independent Lot Selection Rationale
1	Inhibition of apoptosis assay	10	14P137K605 , 12L137L002 , 16L137L004	007F15 (40mg PFS)	“Tier 1” and “Tier 2” analyses were conducted using 10 independent lots (3 DS and 7 DP) for these biological activity methods.
1	Binding to target (sTNF)			020M16 (40mg vial),	
2	Reverse Signaling			021B14 (40mg PFS)	
2	Primary NK cell ADCC assay			025M16 (40mg PFS),	
2	PBMC ADCC assay			027M16 (20mg PFS)	
2	FcγRIIIa (158F and 158V) binding (SPR)			069B16 (40mg vial),	
2	CDC assay			082B16 (10mg PFS)	

“Tier”	Methodology/Quality Attribute	Number of independent Pfizer Lots	PF-06410293 DS Lots	PF-06410293 DP Lots	Independent Lot Selection Rationale
2	Binding to target (mTNF)	10	14P137K605 , 12L137L002 , 12L137L005 , 13L137L006 16L137L004	007F15, 025M16, 027M16, 020M16, 008A13	Data for these quality attributes were generated prior to receiving the FDA requirement for independent lots. Therefore, the lot selection is different for these attributes. All existing data for all lots was used but the set of independent lots is still 10.
2	FcγRIIIa reporter gene assay				
2	C1q binding				
2	FcRn binding (SPR)				
2	Protein Concentration	13	N/A	007F15, 020M16, 021M16, 022M16, 023M16, 024M16, 025M16, 026M16, 027M16, 028M16, 029M16, 030M16, 031M16	DP lots made using the same DS are considered independent, as protein concentration is a quality attribute specific to DP manufacture. For demonstration of similarity, only lots manufactured and tested with the updated specific absorption coefficient are included which allows statistical analysis of protein concentration using 13 DP lots.
2	Total Afucosylation	10	14P137K605 , 12L137L002 , 12L137L003 , 12L137L005 , 13L137L006 , 15L137L001	N/A	N-linked glycan testing is only performed on DS. Reviewer’s Comment: <i>this is acceptable because it is scientifically valid that fill-finish DP manufacturing process does not impact product glycosylation.</i>
2	Terminal Galactosylation				
2	Acidic Species	10	14P137K605 , 12L137L002 , 16L137L004	007F15, 020M16, 021B14, 025M16, 027M16, 069B16, 082B16	“Tier 2” analysis was conducted using 10 independent lots (3 DS and 7 DP) for these quality attributes.
2	Monomer	10			
2	HMMS	10			
2	Intact IgG	10			

Reviewer’s Comment: *The number of independent lots selected for the analytical similarity is acceptable. DP lots used in the comparative clinical studies were included in the analytical similarity assessment. Although different group of DS/DP lots were used among the tested attributes, all 10 DS lots (either using DS or using one of the DP presentation from the DS lot) were included in the assessment for each attribute. DP lots used for the analytical similarity assessment (listed in the table above) were made from different DS lots except for the assessment for protein concentration. The 13 DP lots used to assess protein concentration are: one 40 mg/0.8mL PFS from DS lot 15L137L001 (used for*

clinical comparative study), and four DP presentation lots (40 mg/0.8 mL PFS and vial, 20 mg/0.4 mL PFS, 10 mg/0.2 mL PFS) each from DS lot 16L137L001, lot 16L137L002 and lot 16L137L003. Although the pen presentation was not included in the similarity assessment, this is acceptable because the assembly into the secondary packaging component of the autoinjector does not have impact on product quality attributes except for minor difference seen in subvisible particles (DP product quality review by Dr. Nailong Zhang). It is also acceptable to use DP lots made with the same DS lot for the similarity assessment for protein concentration, because protein concentration in DP is solely dependent on the manufacturing product of the DP.

Sample Handling

Lots used in the similarity assessment were aliquoted within manufacturer's labeled expiry, then frozen and stored at -60 to -90°C until testing was initiated. Frozen aliquots of licensed adalimumab product were intended for single use only. The supporting data to demonstrate that licensed product quality attributes are not impacted by the freezing process is provided in Section 3.2.R.3.6 Appendix Sample Handling

Reviewer's Comment: Information provided indicates that up to 3 freeze/thaw and up to 55 months storage has no impact on product quality. Reference product sample handling in the similarity assessment is acceptable.

3.2.R.3.1.3 Characterization Methods

The methods used during the analytical similarity assessment were summarized, together with the similarity assessment results, in the table below.

Reviewer's Comment: One lot of reference material (lot# 128926-20) was used throughout the similarity assessments.

3.2.R.3.7 Analytical Similarity Testing Sites

The applicant provided detailed site information for where each lot testing was conducted.

3.2.R.3.2 Similarity Assessment Results Summary Table

Analytical Similarity Assessment Results of PF-06410293 (generated by this reviewer)

Characteristics	Quality Attribute	Test Method	Analysis "Tier"	No. of lots (PF: US: EU)	PF-06410293 Range	US-Humira Range	EU-Humira Range	Conclusion Met statistical or descriptive criteria for similarity (Y or N) PF vs. US / PF vs. EU/ EU vs. US
Primary Structure and Post-translational Modifications	Amino Acid Sequence	LC/MS/MS – Peptide Mapping with specialized bioinformatics	3	10:5:18	The determined sequences, including all respective Leu and Ile residues, were identical for PF-06410293, US-Humira, and EU-Humira			Primary amino acid sequence verified.
		SEC/ESI/MS	3	1:1:1	Same major and minor glycoforms were identified in PF-06410293, US-Humira, and EU-Humira at similar abundances, with no new species in any of the three products			Y/Y/Y
		Peptide Mapping/Edman degradation	3	1:1:1	Identical sequences among PF-06410293, US-Humira, and EU-Humira			Y/Y/Y
		LC/MS-subunit analysis	3	10:5:18	Agreement in the relative abundances of each individual isotopic species between each of the three products, and with the respective theoretical isotopic distributions			Y/Y/Y
		LC/MS/MS-peptide mapping	3	1:1:1	Identical sequences among PF-06410293, US-Humira, and EU-Humira			Y/Y/Y
	Disulfide bonds	LC/UV-Non-Reduced Peptide Mapping (Lys-C)	3	1:1:1	Superimposable chromatographic profiles.			Y/Y/Y
		LC/MS Non-Reduced Peptide Mapping (Lys-C)	3	1:1:1	All predicted disulfide bonds were detected.			Y/Y/Y
		Reviewer's Comment: One lot each were used for the characterization of amino acid sequence and disulfide bonds. The primary sequence is unlikely to change during manufacturing process therefore one lot each is sufficient for comparison. Disulfide scrambling has not been reported for IgG1, one lot each for LC/MS non-reduced peptide mapping is sufficient to characterize the disulfide bonds in each product.						

Characteristics	Quality Attribute	Test Method	Analysis "Tier"	No. of lots (PF: US: EU)	PF-06410293 Range	US-Humira Range	EU-Humira Range	Conclusion Met statistical or descriptive criteria for similarity (Y or N) PF vs. US / PF vs. EU/ EU vs. US		
		Sulfhydryl Analyses (UV/Vis Spectroscopy using Ellman's Reagent)	3	3:5:15	0.2 ± 0.02 (mean ± SD) mol SH/ mol	0.3 ± 0.02 mol SH/ mol	0.3 ± 0.03 mol SH/ mol	Y/Y/Y		
Purity	Monomer	SEC	2	36 (10 ^a): 68:77	99.4-99.7%	99.3-99.7%	99.3-99.7%	Y/Y/Y		
		SEC-MALS	3	Not provided	Weight-average molar mass for the main peak was consistent with the monomeric four-chain adalimumab IgG1 molecule			Y/Y/Y		
	HMMS	SEC	2	36 (10 ^a): 68:77	0.3-0.5%	0.2-0.5%	0.2-0.5%	Y/Y/Y		
		SEC-MALS	3	Not provided	the weight-average molar mass of the HMMS peak was consistent with that of an IgG1 dimer			Y/Y/Y		
		AUC	3	Not provided	Absence of quantifiable HMMS larger than dimer. Similar dimer content (all below quantitation limit of 1%)			Y/Y/Y		
	<i>Reviewer's Comment: For SEC-MALS and AUC, representative chromatographs/profiles were provided for one lot each of the three comparators. Given the low level of aggregates observed in all three comparators, one lot each is sufficient to provide aggregates characterization and orthogonal assessment to support the similarity conclusion. Thus, no further clarification regarding the number of lot used was requested.</i>									
	Fragments	rCGE	2	36 (10 ^a): 68:77	0.3-0.4%	1.0-1.6%	0.7-1.3%	N/N/Y		
		<i>Reviewer's Comment: Although, statistical difference was observed on fragment by rCGE, the levels of the fragments is lower in the PF lots, thus the observed difference is not likely to have meaningful clinical impact.</i>								
		SDS-PAGE (Coomasie Blue)	3	1:1:1	No detectable fragment band on the gel			Y/Y/Y		
	Intact IgG	nrCE-SDS	2	36 (10 ^a): 68:77	96.5-98.0%	91.7-98.3%	91.1-98.1%	Y/Y/Y		
Glycans	N-linked Glycan Profile	HILIC/MS	3	10 ^a : 68:77	Differences were observed in the levels of total afucosylated, galactosylated, and high mannose species (see below)			N/N/Y		
	Total Afucosylation	HILIC/MS	2	10 ^a : 68:77	5.5-7.5%	6.9-10.0%	6.6-11.1%	N/N/Y		

Characteristics	Quality Attribute	Test Method	Analysis "Tier"	No. of lots (PF: US: EU)	PF-06410293 Range	US-Humira Range	EU-Humira Range	Conclusion Met statistical or descriptive criteria for similarity (Y or N) PF vs. US / PF vs. EU/ EU vs. US		
		Reviewer's Comment: Three out of 10 PF-06410293 lots were outside of the "Tier 2" statistical analysis acceptance criteria. However, the observed difference is small (mean difference is 1.8%) and did not result in difference in ADCC activity (see review for Section 3.2.R.3.2.2 Characterization of Antibody-Dependent Cellular Cytotoxicity (ADCC) Function). Therefore, the differences in afucosylation do not preclude a demonstration that PF-06410293 is highly similar to US-Humira.								
	Terminal galactosylation	HILIC/MS	2	10 ^a : 68:77	17.1-27.7%	17.5-21.4%	17.4-23.4%	N/N/Y		
		Reviewer's Comment: Three out of 10 PF-06410293 lots exhibits higher levels of terminal galactosylation that were outside of the "Tier 2" statistical analysis acceptance criteria. The atypical galactosylation level observed from the three lots (b) (4) (b) (4) has been resolved). Similar CDC and ADCC biological function were demonstrated among the three products.								
	High mannose	HILIC/MS	2	10 ^a : 68:77	0.9-1.9%	5.9-8.9%	5.5-9.7%	N/N/Y		
		Reviewer's Comment: None of the PF-06410293 lots are within the quality range of US-Humira. The difference is ~6%. The high mannose form may potentially impact PK. The PK impact of the observed high mannose difference are addressed in the comparative PK study.								
	Total sialylation	HILIC/MS	3	10 ^a : 68:77	0.5-0.9%	0-0.2%	0.1-0.3%	N/N/ Y		
		Reviewer's Comment: PF-06410293 contains <1% of sialylated N-linked glycans, where Neu5Ac is the predominate sialic acid form. The difference is unlikely to have any clinical impact.								
Charge	Acidic variants	iCE	2	36 (10 ^a): 68:77	13.4-23.6%	12.5-21.0%	12.3-21.9%	N/N/Y		
				Reviewer's Comment: 3 out of 10 PF 06410293 lots showed higher level of acidic peaks than the upper limit of the quality range defined by US-Humira. The highest acidic peak detected in PF 06410293 lots is <3% more than the highest observed from US-Humira lots. The charge variance characterization studies indicate that all peaks but one acidic peak separated by CEX retained full potency. One of the 3 acidic peaks has reduced potency due to a clipped form. This acidic peak with reduce potency are 2.2%, 2.4% and 2.6% in PF 06410293, US-Humira and EU-Humira lots, respectively. Taken together, the difference seen in charge variants is unlikely to affect product activity and similarity.						
	Basic variants			36 (10 ^a): 68:77	12.7-28.5%	19.4-27.3%	18.8-25.5%	Not statistically compared. Main and basic species retains potency		
Main	36 (10 ^a): 68:77	53.1-71.2%	55.4-64.7%	54.2-66.8%						

Characteristics	Quality Attribute	Test Method	Analysis "Tier"	No. of lots (PF: US: EU)	PF-06410293 Range	US-Humira Range	EU-Humira Range	Conclusion Met statistical or descriptive criteria for similarity (Y or N) PF vs. US / PF vs. EU/ EU vs. US
Characterization of charged species		LC/MS	3	2:1:1	PF-06410293 is different from the adalimumab US and EU with dialylated N- linked glycans on Asn301 on 1 H chain, mono-sialylated N-linked glycans on Asn301 on 1 H chain and signal peptide sequence extension (⁻³ VHS ⁻¹) on 1 L and 1H chains			<i>The signal sequence extension seen only in PF-06410293 is unlikely to have clinical impact.</i>
		Carboxypeptidase B Treatment	3	2:3:2	After carboxypeptidase B treatment, the iCE profile of PF-06410293 was similar to that of US-Humira and EU-Humira and all products exhibit similar low levels of basic species (mean relative area % of basic species are 5.4%, 6.0 % and 5.8% for US-Humira, Pfizer lot and EU-Humira, respectively).			<i>The result supports that the difference seen in the percentage of basic species between PF-06410293, US-Humira and EU-Humira is mainly due to the different levels of C-terminal lysine.</i>
		Potency test on CEX peaks	3	2:1:1	Reduced biological activity was observed in peak 1 of the acidic species. All other peaks, the main peak, basic peaks, as well as peak 2 and peak 3 of acidic species, showed similar potency (inhibition of apoptosis assay).			N/A
Higher Order Structure	Secondary Structure	Far-UV CD	3	5:5:24	superimposable spectra and crystal structures			Y/Y/Y
		FTIR		5:3:3				
	Tertiary Structure	Near-UV CD	3	5:5:24	superimposable spectra and crystal structures			Y/Y/Y
		X-ray crystallography	3	1:1:1				
		Fluorescence	3	5:3:3				
Melting temperature	DSC	3	5:5:24	Superimposable thermal gram			Y/Y/Y	
Drug product related	Protein Concentration	UV absorbance	2	13:68:77	46.2-50.4 (mg/mL)	48.9-54.1 (mg/mL)	48.1-54.4 (mg/mL)	Y/Y/Y
Biological Activity - Fab	Blockade of sTNF	Inhibition of Apoptosis Assay	1	36 (10 ^a): 68:77	74-125%	79-116%	76-117%	Y/Y/Y
		Inhibition of ELAM-1 Expression	3	5:7:7	87-122%	88-102%	87-99%	Y/Y/Y
		Binding by ELISA	1	11(10 ^a): 10: 10	88-103%	83-105%	80-110%	Y/Y/Y

Characteristics	Quality Attribute	Test Method	Analysis "Tier"	No. of lots (PF: US: EU)	PF-06410293 Range	US-Humira Range	EU-Humira Range	Conclusion Met statistical or descriptive criteria for similarity (Y or N) PF vs. US / PF vs. EU/ EU vs. US	
	Binding to mTNF	cell apoptosis mTNF-NS0 cell	2	11 (10 ^a): 11:17	82-114%	84-111%	90-121%	Y/Y/Y	
	Reverse Signaling	cell apoptosis mTNF-Jurkat cells	2	10 ^a : 10:10	97-113%	90-106%	95-115%	Y/Y/Y	
	Off-target binding	LT- α binding ELISA	3	1:1:1	Confirmed no binding to LT- α			Y/Y/Y	
Biological Activity-Fc	ADCC Activity	NK Cell ADCC Assay (158V/V)	2	10 ^a : 12:10	82-168%	111-275%	115-239%	Y/Y/Y	
		PBMC ADCC Assay (158 V/F)	2	10 ^a : 12:10	84-146%	78-160%	97-147%	Y/Y/Y	
		PBMC ADCC Assay (158 F/F)	2	10 ^a : 10:10	82-147%	70-148%	73-121%	Y/Y/Y	
		Binding to Fc γ RIIIa (RGA)	2	11 (10 ^a):10:10	88-112%	92-128%	98-116%	Y/Y/Y	
		Binding to Fc γ RIIIa/158V Relative K _D % (SPR)	2	10 ^a : 15:10	98-116%	90-115%	87-128%	Y/Y/Y	
		Binding to Fc γ RIIIa/158F Relative K _D % (SPR)	2	10 ^a : 15:10	92-113%	72-94%	74-110%	N/N/Y	
	<i>Reviewer's Comment: The observed binding difference did not cause significant impact on functional assays. Similar ADCC activity was observed from the primary PBMC ADCC assays for FcγRIIIa 158V/F and FcγRIIIa 158F/F genotypes.</i>								
	CDC Effector Function	CDC Assay	2	10 ^a : 10:10	91-110%	83-116%	78-107%	Y/Y/Y	
		C1q Binding ELISA	2	12 (10 ^a): 10:10	89-133%	75-110%	76-110%	Y/Y/Y	
Induction of Regulatory Macrophages	Mixed Lymphocyte Reaction (MLR) Assay	3	5:5:5	Comparable inhibition of the proliferation of T cells in a dose-dependent manner in the MLR, for of Fc γ RIIIa 158 V/V, V/F and F/F donor types.			Y/Y/Y		

Characteristics	Quality Attribute	Test Method	Analysis "Tier"	No. of lots (PF: US: EU)	PF-06410293 Range	US-Humira Range	EU-Humira Range	Conclusion Met statistical or descriptive criteria for similarity (Y or N) PF vs. US / PF vs. EU/ EU vs. US
	Additional Fcγ Receptor Binding: FcγRIIIa (131H & R), FcγRIIb, and FcγRIIIb	SPR	3	5:5:5	visually comparable SPR sensorgrams. All lots tested have binding affinity $K_D > 2500\text{nM}$			Y/Y/Y
	Binding to FcγRI	SPR Relative K_D %	3	5:6:6	107±8.4	101±5.7	95±8.0	Y/Y/Y
	Binding to FcRn	SPR Relative K_D %	2	13 (10 ^a): 11:10	96-123%	100-127%	93-127%	Y/Y/Y
Comparative Forced Degradation studies	Thermal Stress	"Tier 3": Tested attributes include appearance, pH, protein concentration, HMMS, Monomer and LMMS by SEC, charge variants by iCE, fragments by rCGE, intact IgG by nrCGE, potency by cell-based assay, methionine oxidation by Limited Lysyl Endopeptidase Peptide and primary structure by LC/MS/MS-Peptide Mapping (Lys- C/Trypsin), binding to FcRn by SPR		9:8:6	Reviewer's Comment: Forced degradation comparison results indicate that the Pfizer product and US-Humira and EU-Humira follows the same degradation pathway. No new degraded species were observed in PF-06410293 as compared to US-Humira and EU-Humira. Although some apparent differences in degradation rates were observed, they may be explained by the different formulation used for Pfizer product and Humira products. Overall, the Pfizer formulation appears to provide a slightly better protection of the product under the forced degradation conditions, specifically, the thermal, light and deamidation stresses. The minor differences observed in the forced degradation studies do not preclude a determination that PF06410293 is highly similar to US-Humira and support the analytical bridge with EU Humira.			
	Light Exposure			3:2:2				
	Forced Deamidation			1:1:1				
	Forced Oxidation			1:1:1				

3.2.R.3.2.1 Primary Structure and Posttranslational Modifications

Amino acid sequences for adalimumab were established from literature search and experimentally verified using licensed adalimumab products.

3.2.R.3.2.1.1 Verification of Adalimumab Amino Acid Sequence

The primary structure verification was performed using one lot each of PF-06410293, US-Humira, and EU-Humira, because the primary structure is an inherent attribute of the cell lines used, thus does not vary from lot-to-lot.

LC/MS-subunit analysis was conducted to compositionally compare the primary structure of the three products. Two orthogonal *de novo* sequencing methods (automated Edman degradation and LC/MS/MS-peptide mapping with specialized bioinformatics) were applied to assess possible alternative or transposed residues, as well as differentiate the isomeric Leu and Ile residues. Following results were obtained.

3.2.R.3.2.1.1.2.1. Verification of Adalimumab Amino Acid Sequence via LC/MS –Subunit Analysis

PF-06410293, US-Humira, and EU-Humira were analyzed by LC/MS – subunit analysis to compare the primary structure of the three products. Following enzymatic reactions, three antibody fragments (scFc, Fd', and L chain) were subject to LC/MS (RP-UHPLC/UHR ESI-QTOF MS) test.

The LC/MS subunit analysis results shown that the observed monoisotopic masses for the predominant isoforms of the L chain and H chain scFc (residues 240-449) and Fd' (residues 1-239) domains demonstrated excellent agreement with each other and the respective theoretical mass values.

The LC/MS – subunit analysis mass spectra were also plotted with a narrow mass range to reveal the isotopic profiles for the major isoforms of the scFc, Fd' and L chain. There was excellent agreement in the relative abundances of each individual isotopic species between each of the three products, and with the respective theoretical isotopic distributions.

The comparable mass and abundance measurements results indicates that the amino acid composition for each subunit or domain of the three products is identical.

3.2.R.3.2.1.1.2.2. Verification of Adalimumab Amino Acid Sequence via De Novo Sequencing

To complement the LC/MS – subunit analysis, amino acid-by-amino acid verification of the primary sequence for PF-06410293, US-Humira, and EU-Humira was performed using Peptide Mapping/ Edman Degradation and LC/MS/MS – Peptide Mapping with Specialized Bioinformatics.

Peptide Mapping/ Edman Degradation: A commercial pulsed liquid-phase sequencing instrument was used with the standard recommended vendor procedures. The first fifty N-terminal residues of the intact L and H chains were sequenced by Edman degradation. Then, internal L and H chain amino acid sequences were derived by Edman N-terminal sequencing using separate trypsin, Asp-N, and chymotrypsin digestions of the isolated chains and subsequent fractionation by LC/MS – peptide mapping.

LC/MS/MS – Peptide Mapping with Specialized Bioinformatics: the instrument used is an ESI-equipped, standard-resolution quadrupole ion trap mass spectrometer that was auto-tuned, auto-calibrated, and maintained with vendor recommended procedures. Samples were denatured, reduced,

alkylated, and desalted, and then digested with separate endoproteinases (trypsin ($\pm$ PNGaseF), chymotrypsin, Lys-C, Asp-N and V8) for analyze. To differentiate between Lys and Gln (both $\sim$ 128 Da), Lys-containing tryptic peptides were selectively guanidinated to create a homoarginine side chain and a unique +42 Da mass addition. Leu and Ile were distinguished with a proprietary software algorithm that considers the statistical occurrence of each residue at a particular variable or constant region site, along with the local sequence environment, all in conjunction with an extensive antibody database.

First, automated Edman degradation was used to sequence the respective variable regions of L and H chains following LC/MS – peptide mapping with multiple endoproteinases and targeted fraction collection. The amino acids 1 to 107 for L chain, and 1 to 125 for H chain were found to correctly match the target “adalimumab” sequences amino acid-by- amino acid, and identical among PF-06410293, adalimumab-US, and adalimumab-EU.

Second, de novo sequencing by LC/MS/MS – peptide mapping with specialized bioinformatics was applied. 100% sequence coverage, including Leu and Ile differentiation in all three samples were obtained. Again, the determined sequences, including all respective Leu and Ile residues, were identical for PF-06410293, adalimumab-US, and adalimumab-EU, and matched the target “adalimumab” sequences.

3.2.R.3.2.1.2 Characterization of Molecular Mass, Primary Structure and Posttranslational Modifications

One lot each of PF-06410293, US-Humira, and EU-Humira were analyzed at the intact, subunit, and peptide levels, and compared side-by-side to assess the similarity of molecular mass, primary structure, and posttranslational modifications.

3.2.R.3.2.1.1.2.2. Molecular Mass

Molecular masses were determined for the intact glycoforms using organic size-exclusion chromatography (acetonitrile mobile phase) coupled to electrospray ionization mass spectrometry (SEC/ESI MS) with a high-resolution, hybrid quadrupole time-of-flight mass spectrometer.

As shown in tables below (table modified from the submission), the same major and minor glycoforms were identified in PF-06410293, US-Humira, and EU-Humira at similar abundances, with no new species in any of the three products.

Glycoforms	Theoretical Mass (Da)	Observed Molecular Masses (Da)		
		PF-06410293	US-Humira	EU-Humira
G0F/G0F	148081.4	148084.3	148084.0	148084.3
G0F/G1F	148243.5	148246.2	148245.4	148245.5
G1F/G1F ^c	148405.7	148408.9	148406.8	148408.4

3.2.R.3.2.1.2.2. LC/MS – Subunit Analysis

Mass spectral data obtained from LC/MS – subunit analysis was also used for product isoform identification and profiling comparison.

The results for the H chain scFc domain (²⁴¹GPS...SPG⁴⁵⁰) indicate that the G0F and G1F were the predominant N-glycoforms in all three products. *The observed masses compared well with the theoretical masses of the scFc (25188.491 and 25350.544 Da) with all four cysteines in the reduced form and no C-terminal lysine.* Additional minor- to trace-level of N-linked glycoforms were observed

in all three products and the trends are consistent with the N-linked glycoform distributions observed in SEC/ESI MS analysis and HILIC/MS N-linked glycan profiling.

For the H Chain Fd' domain (1EVQ LLG240), the masses for all three products agreed with the theoretical mass (25442.523 Da) with all seven cysteines in the reduced form. PF-06410293 contained a trace isoform on the H chain Fd' domain with a signal peptide sequence extension, ⁻³VHS⁻¹.

For the L chain subunit (1DIQ...GEC214), the observed masses for all three products agree with the theoretical masses (23397.609 Da), with all five cysteines in the reduced form. PF-06410293 contained a trace isoform on the L chain with a signal peptide sequence extension ⁻³VHS⁻¹.

3.2.R.3.2.1.2.3. LC/MS – Peptide Mapping (Lys-C)

In these studies, the three products were reduced, alkylated, and digested with endoproteinase Lys-C. The resulting peptides were analyzed by reversed-phase high performance liquid chromatography with UV detection at 214 nm, and all peaks in the peptide map were then identified by on-line electrospray ionization mass spectrometry (LC/MS).

The chromatographic peptide map UV profiles the three products were superimposable. The observed masses for the respective UV peaks in the three products were consistent with the expected Lys-C peptides.

The detected peptides represent 209 of 214 residues of the L chain sequence (97.7% coverage) and 441 of 451 residues of the H chain sequence (97.8% coverage). Note: Short L3, L12, H12, H20, H21 were not recovered.

The LC/MS – Peptide Mapping (Lys-C) Results are summarized in the table below (see next page).

Chain	Property	Experimental Observation			Results/Conclusion
		PF-06410293	US-Humira	EU-Humira	
L Chain	Sequence Coverage	97.7%	97.7%	97.7%	Identical sequence coverage observed and the same peptides observed for all three products
	N-terminal peptide	¹ DIQMTQSPSSLSAS VGDRVITTCRASQG IRNYLAWYQQK ³⁹			N-terminal peptide has expected amino acid composition for all three products
	C-terminal peptide	²⁰⁸ SFNRGEC ²¹⁴			C-terminal peptide has expected amino acid composition for all three products
	Additional observations	<u>N-terminal peptide</u> Trace signal peptide sequence extension (⁻³ VHS ⁻¹)	N/A	N/A	Trace levels of N-terminal signal peptide sequence extension detected in PF-06410293.
H Chain	Sequence Coverage	97.8%	97.8%	97.8%	Identical sequence coverage was observed and the same peptides were observed for all three products
	N-terminal peptide	¹ EVQLVESGGGLVQ PGRSLRLSCAASGF TFDDYAMHWVRQ APGK ⁴³			N-terminal peptide has expected amino acid composition for all three products
	C-terminal peptide	⁴⁴⁴ SLSLSPG ⁴⁵⁰			C-terminal peptide has expected amino acid compositions and <i>des</i> -Lys form is predominant for all three products
	N-linked glycosylation	N-linked glycosylation confirmed on H17H18 peptide			N-linked glycosylation observed on the H17H18 peptide containing N ³⁰¹ ST consensus sequence site for all three products
	Predominant N-linked glycoforms	G0F and G1F			Predominant N-linked glycoforms are the same and have highly similar relative abundances for all three products
	Additional observations	<u>Asn deamidation</u> Minor: H27 (N388, N393), H30 (N425, N428) <u>Met Oxidation</u> Trace: H15 (Met256), H30 (Met432) <u>N- and C-terminal peptides</u> Trace: pyroglutamic acid form (Glu1) on the H1 peptide Minor: lysine form (Lys451) on the H31 peptide Trace: amidated proline (Pro449) on the H31 peptide Trace: signal peptide sequence extension (⁻³ VHS ⁻¹)	<u>Asn deamidation</u> Minor: H27 (N388, N393), H30 (N425, N428) <u>Met Oxidation</u> Trace: H15 (Met256), H30 (Met432) <u>N- and C-terminal peptides</u> Trace: pyroglutamic acid form (Glu1) on the H1 peptide Minor: lysine form (Lys451) on the H31 peptide Trace: amidated proline (Pro449) on the H31 peptide	Similar modifications observed on same peptides in all 3 products by LC/MS-peptide mapping (Lys-C). Trace levels of N-terminal pyroglutamic acid form in all 3 products. Minor levels of C-terminal lysine in all 3 products. Trace levels of C-terminal amidated proline in all 3 products. Trace levels of N-terminal signal peptide sequence extension detected in PF-06410293	

Reviewer’s Comment: *the peptide mapping information provided in the initial submission was high level description and it wasn’t clear whether the entire primary sequences for PF-06410293, US-Humira, and EU-Humira were experimentally verified (collectively by the multiple methods used). The verification of the primary sequence was addressed through an information request.*

Information Request: *You conducted primary sequence analysis using LC/MS and LC/MS/MS based peptide mapping. We require additional information to verify the primary sequence of PF-06410293 is identical to US-licensed Humira:*

- a. *Five small peptides (L3, L12, H12, H20 and H21) were not recovered in the LC/MS LysC peptide map (Table 3.2.R.3.2.1-6). Submit peptide mapping data from additional protease digestions to cover these regions which were not recovered in the LysC peptide map or additional information describing how the amino acid residues associated with these peptides are verified to be identical for PF-06410293 and US-licensed Humira.*
- b. *In section 3.2.R.3.2.1.1.2.2, you claim that the primary sequence of PF-06410293 was elucidated amino acid-by-amino acid with 100% sequence coverage by LC/MS/MS peptide mapping with bioinformatic analysis. However, amino acid sequence assignments from MS/MS spectra are not provided. Provide a summary table or figure to show the amino acid sequence assignments from the MS/MS spectra obtained from peptide mapping experiments to confirm that the primary sequence of PF-06410293 is identical to US-licensed Humira. You may use different underlines and/or shades to distinguish results obtained from different protease digestions.*

The Applicant’s Response (received 04/30/2019):

The applicant reports that four different endopeptidases were used to create overlapping peptides (trypsin, chymotrypsin , Asp-N and V-8) for the de novo sequencing. Overlapping peptides of light chain and heavy chain for PF-06410293 and US-licensed Humira from the are provided. For both PF-06410293 and US-licensed Humira, the full-length light chain heavy chain sequences, including the N- and C-termini, were derived via LC/MS/MS from the trypsin and chymotrypsin proteolytic peptides exclusively. The identity and order of all amino acids in the respective light and heavy chain proteolytic peptide sequences for PF-06410293 and US-licensed Humira were confirmed via LC/MS/MS with collision-induced dissociation. The final adalimumab light chain and heavy chain sequence alignments for PF-06410293 and US-licensed Humira are also provided and the respective primary sequences for PF-06410293 and US-licensed Humira were confirmed to be identical.

Reviewer’s Comment: *The response is adequate. The amino acid sequence of PF-06410293 is experimentally determined and it is identical to US-Humira, and EU-Humira.*

3.2.R.3.2.2 Potency/Biological Activity

Similarity Assessment of Biological Activity

The assays used for the analytical similarity assessment of biological activity/potency are summarized in the table below:

Mechanism of Action	Assay	Assay Purpose
Binding sTNF	Inhibition of Apoptosis Assay	Assess primary MoA of adalimumab: binding to sTNF and inhibition of TNF-induced apoptosis. This assay was used for drug substance and drug product release testing and stability testing.
	Inhibition of ELAM-1 Expression Assay	Orthogonal functional assay to assess binding to sTNF and inhibition of TNF-induced ELAM-1 expression.

Mechanism of Action	Assay	Assay Purpose
	Binding to sTNF Target Antigen by ELISA	Assess relative binding to sTNF
Binding mTNF	Binding to mTNF Target Antigen by Flow Cytometry	Assess binding to mTNF on engineered NS0 cells
Reverse Signaling	Reverse Signaling by Flow Cytometry	Assess reverse signaling activity through the cell apoptosis induced by the adalimumab binding to mTNF on engineered Jurkat cells
Absence of Binding to LT-a	LT-a Binding ELISA	Demonstrate expected lack of binding activity
ADCC	Primary NK Cell ADCC Assay	Assess ADCC activity using human donor NK cells (158 V/V donor genotype)
	PBMC ADCC Assay, 158V/F	Assess ADCC activity using human donor PBMC cells (158 V/F donor genotype)
	PBMC ADCC Assay, 158 F/F	Assess ADCC activity mechanism using human donor PBMC cells (158 F/F donor genotype)
	FcγRIIIa Reporter Gene Assay (RGA)	Assess partial ADCC mechanism, binding to FcγRIIIa and activation of downstream signaling pathway, using Jurkat effector cells transfected with FcγRIIIa 158V and a luciferase reporter gene under the control of nuclear factor of activated T-cell (NFAT) response elements, with mTNF-expressing NS0 cells as the target cell.
	Binding to FcγRIIIa by SPR	Assess binding affinities and kinetics to FcγRIIIa 158F and 158V
CDC Activity	CDC Assay	Assess the adalimumab induced death of NS0 cells that overexpress mTNF
	C1q Binding Assay (ELISA)	Assess binding to C1q protein
Regulatory Macrophage	Inhibition of T Cell Proliferation in MLR Assay	Assess Fc functionality of adalimumab and demonstrate immunosuppressive activity in a physiologically relevant system
Fcγ Receptor Binding	Binding to FcγRI, FcγRIIa, FcγRIIb and FcγRIIIb by SPR	Assess binding affinities and kinetics to FcγRI, FcγRIIa 131H and 131R, FcγRIIb and FcγRIIIb
FcRn Receptor	Binding to FcRn by SPR	Assess binding affinities and kinetics to FcRn

3.2.R.3.2.2. Functional Characterization of the Fab Domain

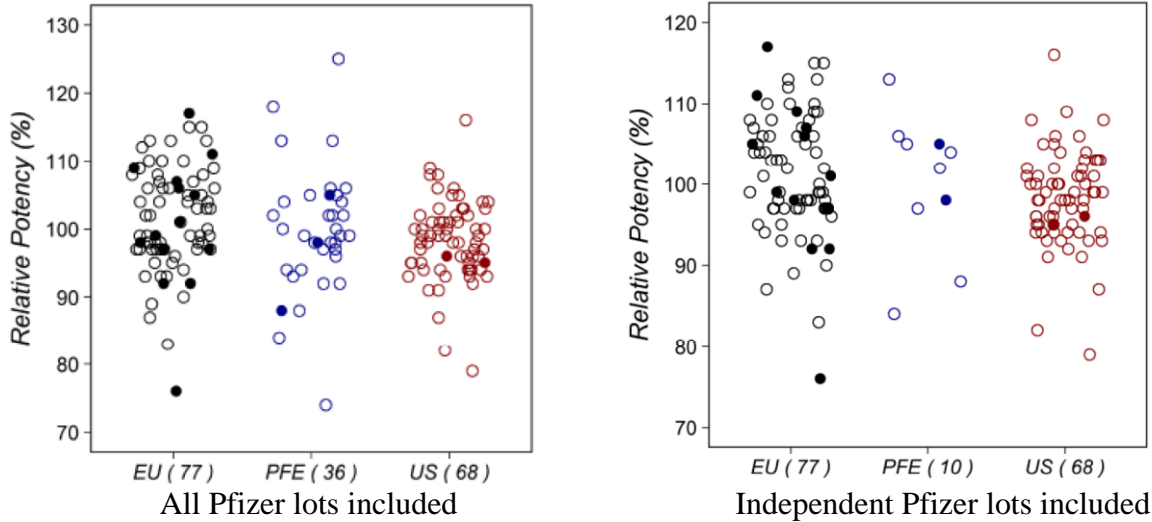
3.2.R.3.2.2.1. Functional Assays Demonstrating Blockade of sTNF

3.2.R.3.2.2.1.1. Inhibition of Apoptosis Assay

U937 cell-based inhibition of apoptosis assay was used to assess the blockade of sTNF by adalimumab. Total 36 PF-06410293 DS and DP lots (*including 10 independent lots*), 68 US-Humira and 77 EU-Humira drug product lots were evaluated by inhibition of apoptosis assay. The results are summarized in the Table (*table modified by the reviewer*) and individual data points are presented in the Figures below for comparison (The solid circles represent the lots that have been used in the clinical studies).

Region	N	Relative Potency (%)				Min	Max
		Mean	SD	CV (%)			
EU	77	101	7.6	7.5	76	117	
Pfizer	36 (total)	100	9.2	9.3	74	125	
	10 (independent)	100	8.7	8.7	84	113	
US	68	98	5.9	6.0	79	116	

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



Apoptosis results were statistically evaluated by equivalence tests, and the applicant reports that the results indicate that PF-06410293 is equivalent to US-Humira and EU-Humira, and EU-Humira is equivalent to US-Humira with respect to potency.

Reviewer’s Comment: *The U937 cell-based inhibition of apoptosis assay used in the similarity assessment is the same as the proposed release assay for the DS and DP. The proposed method as well as the method validation are reviewed as part of the DS review and found to be acceptable. The statistical analysis (equivalence test) of the assay results were reviewed by OB reviewer Dr. Tianjiao Dai (review in DARRTS 05/06/2019), and it is concluded that that the apoptotic inhibition activity of PF-06410293 is statistically equivalent to US-Humira and EU-Humira.*

3.2.R.3.2.2.1.2. Inhibition of ELAM-1 Expression

Adalimumab inhibits TNF-induced ELAM-1 (endothelial-leukocyte adhesion molecule 1 or E-Selectin) expression on human umbilical vein endothelial cells (HUVEC). Pfizer has developed a HUVEC based method to evaluate the adalimumab potency, which is orthogonal to the inhibition of apoptosis assay. Briefly, serial dilutions of adalimumab samples (600 to 3 ng/mL) were pre-incubated with TNF before added to plated HUVEC, and then incubated for 4 hours. Expression of ELAM-1 on the HUVEC surface was detected by Enzyme-Linked Immunosorbent Assay (ELISA). EC50 of each sample was expressed relative to that of PF-06410293 reference material on each assay plate. A mean relative % EC50 was then calculated from three assay plates (n=3) for each test sample. Representative dose response curves are provided (*Figure 3.2.R.3.2.2-5 in the submission*) to show that PF-06410293 DS and DP, US-Humira, and EU-Humira all block sTNF binding to receptors and expression of ELAM-1 in a dose-dependent manner. The method was qualified using PF-06410293 and confirmed to be suitable for use in the range of 50 to 150% relative to the reference material (*the % RSD was 8-21% and the % accuracy was 100 -104 %*. Refer to INX100289113).

Five PF-06410293 lots, 7 US-Humira and 7 EU-Humira drug product lots were randomly selected and tested for the ELAM-1 expression inhibition. The results are presented in the Table and Figure below.

Relative EC 50(%)						
Region	N	Mean	SD	CV (%)	Min	Max
EU	7	95	4.6	4.8	87	99
Pfizer	5	100	13.5	13.5	87	122
US	7	96	4.5	4.7	88	102

Relative EC 50(%)						
Region	N	Mean	SD	CV (%)	Min	Max
N = sample size, SD = standard deviation, CV = coefficient of variation, Min = minimum, Max = maximum						

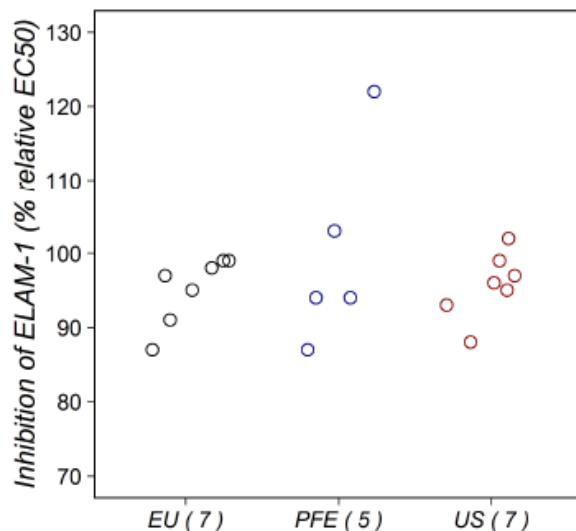
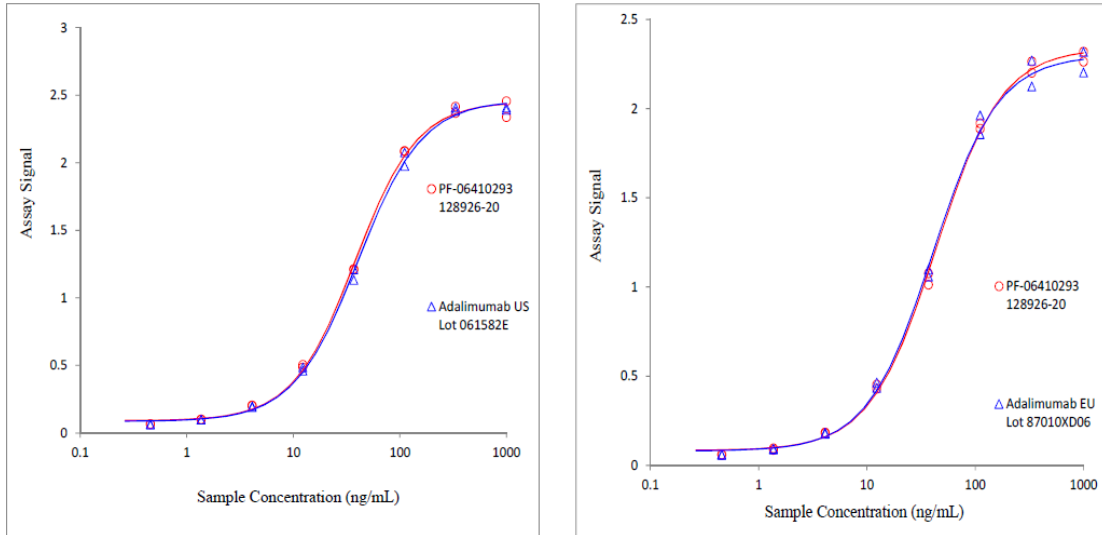


Figure 3.2.R.3.2.2-6. Inhibition of ELAM-1 Expression of EU-Humira, PF-06410293, and US-Humira

Reviewer’s Comment: Inhibition of ELAM-1 Expression is a “Tier 3” attribute which was assessed using side by side graphical comparison. Majority (4/5) of the testing results are visually comparable to the results from US-Humira and EU-Humira, which indicates that PF-06410293, US-Humira and EU-Humira exhibit similar activities in blocking sTNF as measured by the inhibition of ELAM-1 expression in HUVEC cells.

3.2.R.3.2.2.1.3. Binding to sTNF Target Antigen by ELISA

The binding of adalimumab to sTNF target antigen were evaluated using an ELISA method. Briefly, 96-well plates are coated with 0.5 µg/mL TNFα. Serial dilutions of PF-06410293 (1000 - 0.457 ng/mL) in assay buffer are added to assay plates (blocked with 1% BSA/PBST), shaking at ambient temperature for 60 - 100 minutes, then incubated with goat anti-Human IgG conjugated to horseradish peroxidase (HRP) for 45 - 80 minutes (each step was followed by a washing step). After addition of the TMB, the absorbance of the plates is monitored for optical density by at 650 nm. After reaction is quenched with sulfuric acid, absorbance was read at a wavelength of 450 nm. The resulting plate data is analyzed using a standard 4-parameter logistic curve fit. Relative potency values for the test samples are calculated by comparison of the PF-06410293 reference material dose response curve to the test sample curve. The representative dose-response curves for all three materials are shown below:



The method is qualified in terms of precision and accuracy with the range of 50-150% relative potency and found acceptable (*method description and qualification info are submitted in INX100273408*):

Parameter	Result
Precision (Intermediate)	5.8 % RSD at target (100% RP)
Linearity	Visually the plot is linear from 50% to 150% RP; $R^2 = 0.9991$; Slope = 1.044
% Accuracy	103 % at Target (100% RP)
Range	50% to 150% RP

Eleven PF-06410293 lots (including 10 independent lots), 10 US-Humira and 10 EU-Humira drug product lots were tested. The results are shown in the figure below:

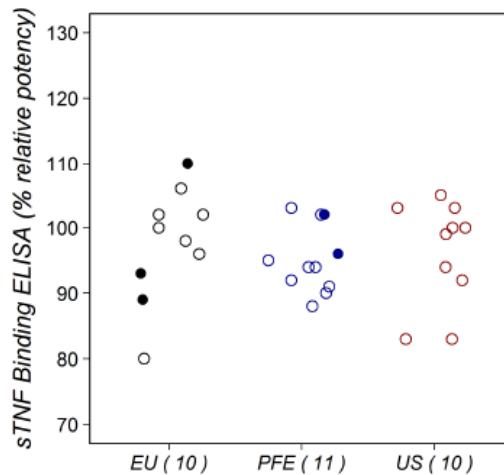


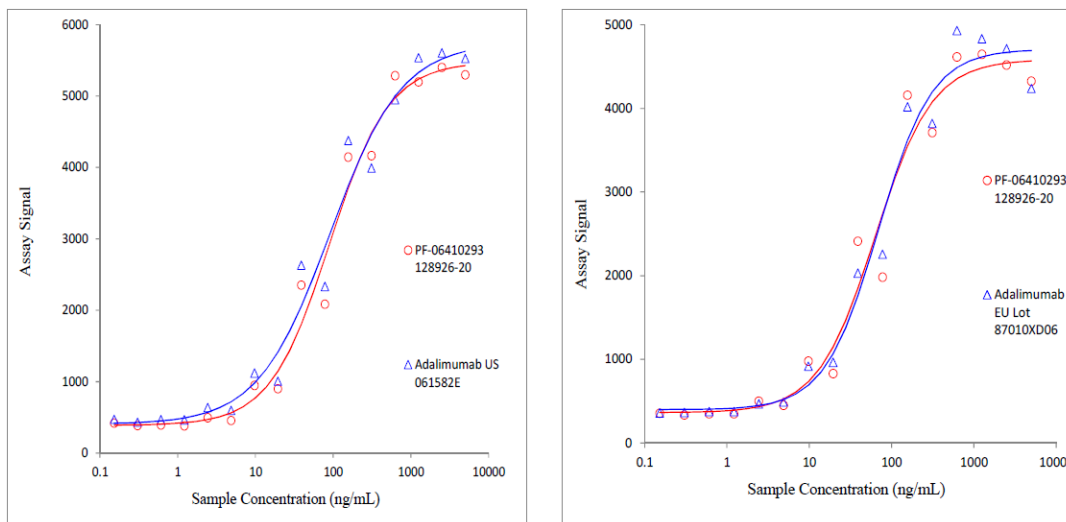
Figure 3.2.R.3.2.2-8. The solid circles represent the lots that have been used in the clinical studies.

Reviewer’s Comment: Binding to sTNF is a clinically relevant MoA for adalimumab. The proposed ELISA method is acceptable for the measurement of target binding to sTNF. The statistical analysis (equivalence test) of the assay results were reviewed by OB reviewer Dr.Tianjiao Dai (review in DARRTS 05/06/2019) and it is concluded that the binding activity of PF-06410293, US-Humira and EU-Humira to sTNF measured by ELISA are statistically equivalent.

3.2.R.3.2.2.2. Functional Assays Demonstrating mTNF Binding Activity

3.2.R.3.2.2.2.1. Binding to mTNF Target Antigen on NS0 Cells

Binding to mTNF is a clinically relevant MoA of adalimumab in preventing the inflammatory response for inflammatory bowel disease. The applicant uses a flow cytometry method to monitor the dose-dependent binding to mTNF expressed on NS0 cell line. Briefly: mTNF expressing NS0 cells are counted, plated, and centrifugated to collect the cell pellets. Series dilution of samples and reference materials are added to the plate and incubated. Stain is added after unbound adalimumab is removed and incubated to allow stain binding to adalimumab. The stained cells are read on a flow cytometer. Representative dose-response curves are shown below (from Figure 3.2.R.3.2.2-10 of the submission):



Each panel represents one assay plate

Each sample was tested on three assay plates, and a mean relative %EC50 was calculated. Relative EC50 is reported by compared to EC50 of PF-06410293 reference material. The performance of the method was evaluated in the range of 50 to 150% relative to the reference material and is considered qualified for the use within that range (see table below for the performance assessment results):

Parameter	Result
Specificity	Non-Specific Binding Measured with Isotype Control
Precision (Intermediate)	RSD: 7 %, 1 % and 5 % at 50%,100% and 150%, respectively
Linearity	Visually the plot is linear from 50% to 150% $R^2 = 0.9991$, Slope = 0.8838
% Accuracy	88 %, 90 % and 88% at 50%, 100%, and 150 %, respectively
Range	50% to 150%

Statistical analysis (quality range) was conducted on 11 PF-06410293 lots (including 10 independent lots), 11 US-Humira and 17 EU-Humira lots. The statistical quality range was derived from the 11 US-Humira lots (mean± 3 SD). As illustrated in the plot below, 100% of PF-06410293 and 94% of EU-Humira lots met the quality range acceptance criteria.

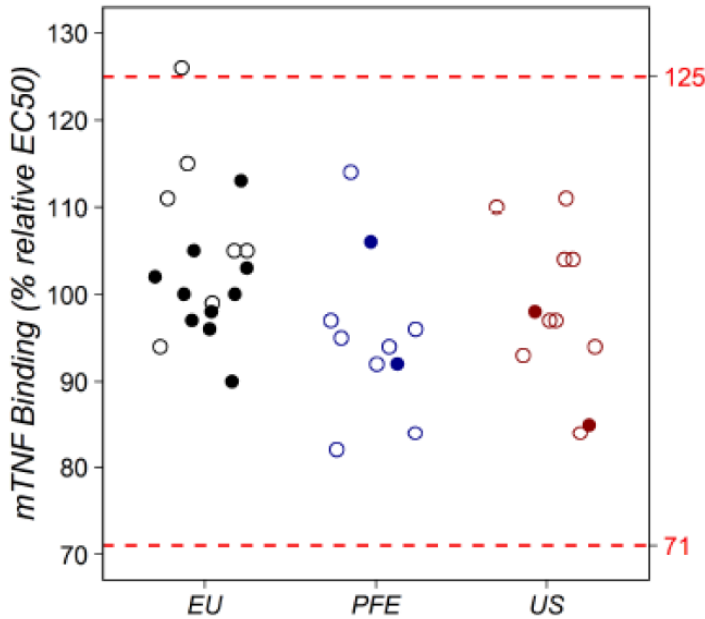
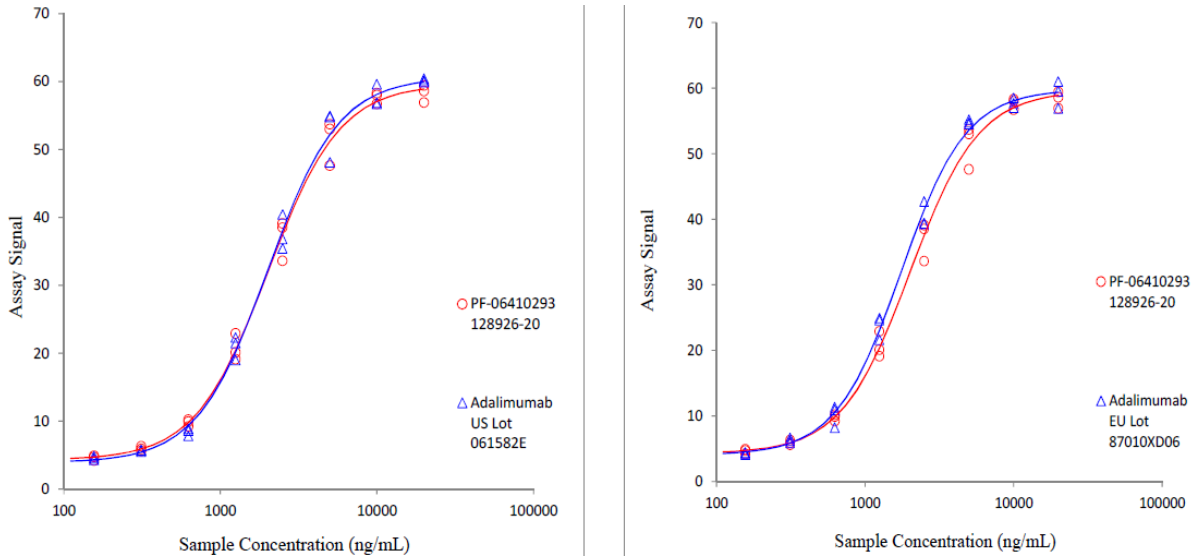


Figure 3.2.R.3.2.2-11. illustrates the distribution of results for mTNF binding (Relative % EC50) as well as the upper and lower limits of the statistical quality range (the red dashed lines) from testing individual lots of adalimumab-EU (17 lots), and adalimumab-US (11 lots) with PF-06410293 (10 lots from DS + DP). The solid circles represent the lots used in the clinic. Tabulated data can be found in 3.2.R.3.5 Appendix Table 3.2.R.3.5-14.

Reviewer’s Comment: The mTNF binding activity data show that 100% of PF-06410293 lots and 94% of EU-Humira lots are within the quality range ($mean \pm 3SD$) of the US-Humira lots; and 100% of the PF-06410293 lots are within the quality range ($mean \pm 3SD$) of EU-Humira lots. Overall, PF--06410293, US-Humira and EU-Humira showed similar activities in binding to mTNF Target Antigen.

3.2.R.3.2.2.2. Reverse Signaling

Reverse signaling activity was measured through the cell apoptosis induced by the adalimumab binding to mTNF on engineered Jurkat cells. Briefly, serial dilutions of adalimumab samples are added to assay plate containing engineered Jurkat cells; after 24 hours incubation at 37°C, the cells are washed, stained with Annexin V and 7-AAD (apoptotic/necrotic cells were stained) and analyzed by flow cytometer; plate data collected from the flow cytometer is batch analyzed using a 4-quadrant analysis with x-axis as Annexin V and y-axis as 7-AAD; the sum of cells in quadrant 2 and quadrant 4 of each sample were used to prepare dose response curves; each sample was tested in 3 independent runs, and a mean relative %EC50 is calculated; %EC50 is reported by comparing to EC50 of PF-06410293 reference material. The representative dose response curves are shown below (Figure 3.2.R.3.2.2-12. of the submission):



The performance of the method was evaluated in the range of 50 to 150% relative to the reference material and qualified for the use within that range (*see table below for the performance assessment results*).

Parameter	Result
Specificity	Non Specific Binding Measured with Isotype Control
Precision (Intermediate)	4% RSD at target
Linearity	$R^2 = 0.9999$; Slope = 1.0518
% Accuracy	101 % at Target
Range	50% to 150%

A statistical analysis was conducted based on the results from 10 independent PF-06410293 lots, 10 US-Humira and 10 EU-Humira lots, using quality range derived from the 10 US-Humira lots (mean $\pm$ 3 SD). As illustrated in the Figure below, 90% of PF-06410293 and 90% of EU-Humira lots are within the quality range of US-Humira lots.

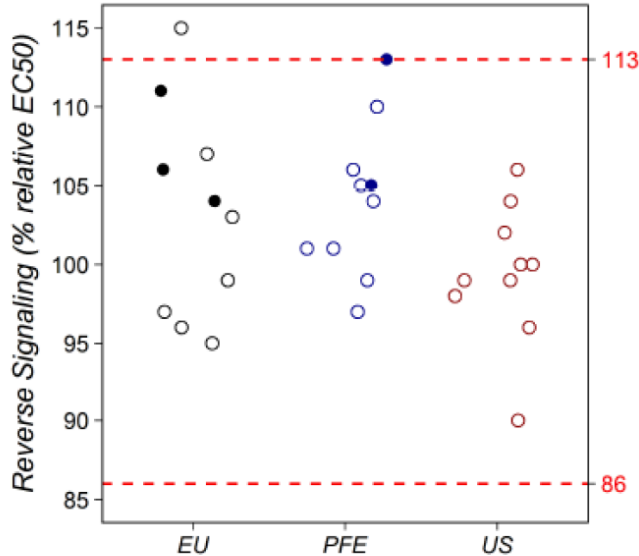


Figure 3.2.R.3.2.2-13. The solid circles represent the lots that have been used in the clinical trials. Tabulated data can be found in 3.2.R.3.5 Appendix Table 3.2.R.3.5-14.

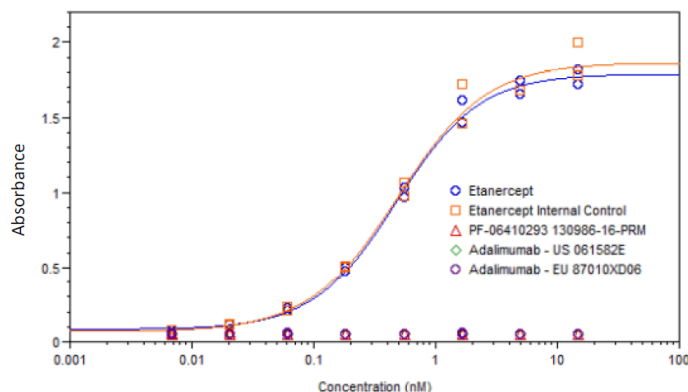
Reviewer’s Comment: Reverse signaling data show that 90% of PF-06410293 and 90% of EU-Humira lots are within the quality range (mean ± 3SD) of the US-Humira lots; 100% of the PF-06410293 results are also within the ±3SD of EU-Humira. Overall, PF--06410293, US-Humira and EU-Humira exhibit similar reverse signaling activity.

3.2.R.3.2.2.3. Lymphotoxin alpha (LT-a) Binding Activity

To demonstrate the specific binding to TNF α , not LT- α (previously known as TNF β), an LT- α binding ELISA method was developed. Briefly, serial dilutions of samples are added to LT- α coated assay plates, incubated to allow binding, then incubated with Goat anti-Human IgG conjugated to horseradish peroxidase (HRP), developed with TMB, quenched with sulfuric acid before reading absorbance at 450 nm. The resulted plate data is analyzed using a standard 4 parameter logistic curve fit. Relative potency is reported. This method is qualified to demonstrate the accuracy, precision and linearity within the range of 50-150% relative potency (*technical report INX100320771*):

Parameter	Result
Precision (Intermediate)	4.2% RSD at target (100% RP)
Linearity	linear from 50% to 150%, RP R ² = 0.9951, Slope = 0.9280
% Accuracy	104% at Target (100% RP)
Range	50% to 150% RP

As shown in the dose response curves below (*from Figure 3.2.R.3.2.2-14 of the submission*), while etanercept, which is known to bind to LT-a, showed dose dependent binding, no binding is observed from PF-06410293, US-Humira or EU-Humira lots.



Reviewer’s Comment: The results confirm that none of PF-06410293, US-Humira and EU-Humira binds to LT- α .

3.2.R.3.2.2. Functional Characterization of the Fc Domain

3.2.R.3.2.2.1. Antibody-Dependent Cellular Cytotoxicity (ADCC) Function

The similarity assessment for the ADCC function of PF-06410293, US-Humira and EU-Humira were done using 3 ADCC assays evaluating 3 Fc γ RIIIa polymorphism population genotypes (158 V/V, 158 V/F and 158 F/F), a cell-based reporter gene assay (RGA) evaluating the Fc γ RIIIa1-158V genotype, and a Fc γ RIIIa SPR binding assay evaluating the binding to human Fc γ RIIIa 158V and 158F. Assay features are shown in the table below.

Effector Cell Type	Donor genotype	Single/Multi Donor	Fresh/Frozen	Target cells
NK	Fc γ RIIIa 158V/V	Single	Frozen	Engineered NS0
PBMC	Fc γ RIIIa 158V/F	Multi	Fresh	Engineered CHO
PBMC	Fc γ RIIIa 158F/F	Multi	Fresh	Engineered CHO

Reviewer’s Comment: The effector cell and target cell selection for the ADCC evaluation are acceptable. Details about the assays are reviewed in this memo below.

3.2.R.3.2.2.1.1. Lot Selection

The lots used for the ADCC function assessment are summarized by the applicant (*modified by this reviewer*) in the table below. Slight differences in total afucosylated species for licensed product were due to material availability at the date of assay.

Lot	Total Afucosylation (%)	Primary NK Cell ADCC Assay	Total PBMC ADCC Assay (158 V/F)	Total PBMC ADCC Assay (158 F/F)	Fc γ RIIIa RGA	Fc γ RIIIa Binding by SPR (158 V and 158 F)
PF-06410293	5.5 – 7.5 (n=10)	5.5 – 7.5 (n=10)	5.5 – 7.5 (n=10)	5.5 – 7.5 (n=10)	5.5 – 7.5 (n=10)	5.5 – 7.5 (n=10)
US-Humira	6.9 – 10.0 (n=68)	7.8 – 10.0 ^a (n=12)	7.8 – 10.0 ^a (n=12)	7.8 – 10.0 ^a (n=10)	6.9 – 9.6 (n=10)	7.8 – 10.0 ^a (n=15)
EU-Humira	6.6 – 11.1 (n=77)	6.9 – 11.1 (n=10)	6.9 – 11.1 (n=10)	6.9 – 11.1 (n=10)	6.6 – 9.2 (n=10)	6.9 – 11.1 (n=10)

a. There was a lack of available Humira-US lots having levels of afucosylated species in the lower range (6.9 – 7.7%) at the time of this assay. The entire range is represented in the Humira-EU lots.

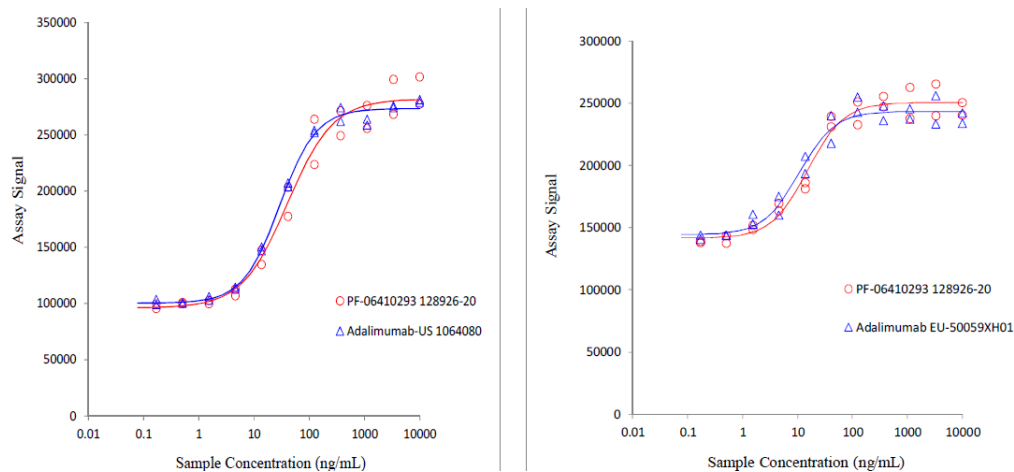
Reviewer’s Comment: Higher level of afucosylation has shown to enhance FcγRIIIa binding and subsequently increases ADCC in monoclonal antibodies (Umana P et al, Nature Biotechnology volume 17, pages176–180 (1999)). The 10 EU-Humira lots selected represent the range seen in the entire 77 EU Humira lots in the similarity assessment program. The levels of afucosylation in the US-Humira lots used were slightly higher than the observed range (7.8-10.0 % used vs 6.9-10.10% from all 68 US-Humira lots tested). The US-Humira lots selected for ADCC evaluation had higher afucosylation level than the PF-06410293 lots; a larger difference of afucosylation between the PF-06410293 and US-Humira would enhance differences in ADCC, if any, between PF-06410293 and US-Humira. Therefore, lot selection for the US-Humira (for comparing ADCC function) is also acceptable.

3.2.R.3.2.2.1.2. Primary NK Cell ADCC Assay (158 V/V donor genotype)

NK cells isolated from a healthy human donor having the FcγRIIIa 158 V/V genotype were used for the primary NK cell ADCC assay. The target cell is an NS0 target cell line engineered to overexpress mTNF. To conduct the test, target cells and serial dilution of samples are incubated at 37°C/5%CO₂ for 1 hour prior to adding NK cells; after an additional 6 hours of incubation, cell death is then measured with CytoTox Glow Reagent using luminiscence. Each sample is tested on 3 assay plates. Assessment of ADCC activity is based on the comparison between the dose response of PF-06410293 reference material and the dose response of a test sample. The method was qualified in the range of 50 to 150% relative to the reference material (*Technical report LF-520-R-103-17*):

Summary of Qualification Results	
Parameter	Results
Accuracy	102.0%-114.8%
Intermediate Precision	% CV: 1.8 -22.3% (12% at target)
Linearity	R ² ≥0.99
Specificity	No response for non-related molecule
Range	50-150% EC50

Representative dose response curves are shown below (*Figure 3.2.R.3.2.2-2 in the submission*):



A statistical analysis (quality range) was done based on the results from 10 independent PF-06410293 lots, 12 US-Humira and 10 EU-Humira lots, using quality range derived from the 12 US-Humira lots (mean± 3 SD). As illustrated in the plot below (*Figure 3.2.R.3.2.2-3 from the submission*), all PF-06410293 and EU-Humira lots met the quality range acceptance criteria.

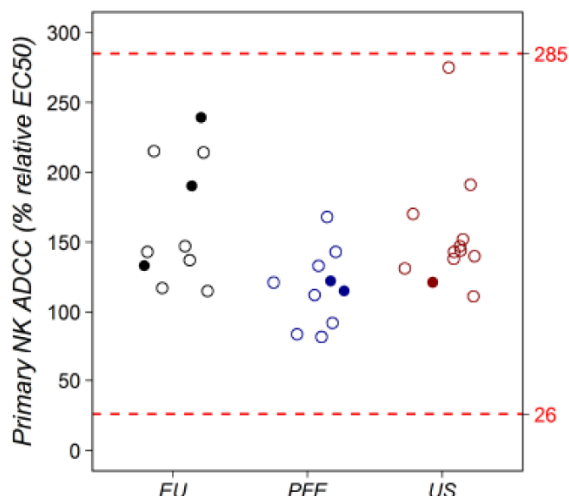


Figure 3.2.R.3.2.2-3. illustrates the distribution of results for NK cell ADCC activity (Relative % EC50) as well as the upper and lower limits of the statistical quality range (the red dashed lines) from testing individual lots of adalimumab-EU (10 lots), and adalimumab-US (12 lots) with PF-06410293 (10 lots from DS + DP). Tabulated data can be found in 3.2.R.3.5 Appendix Table 3.2.R.3.5-15.

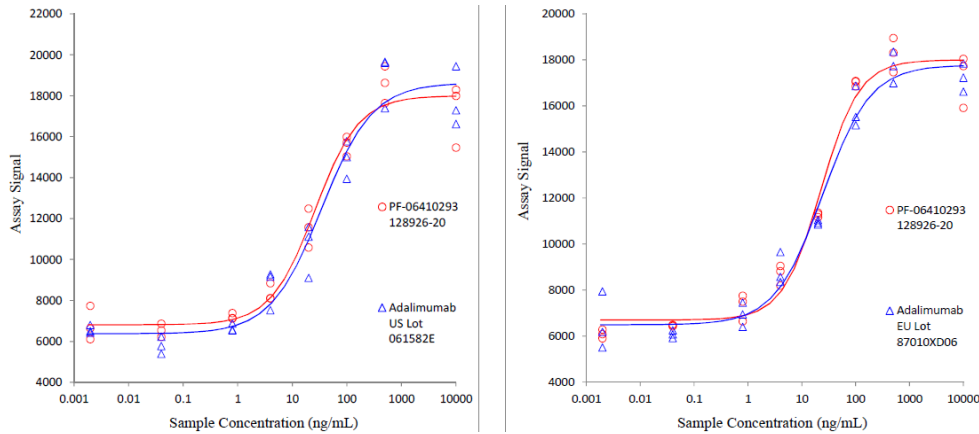
Reviewer’s Comment: The primary NK cell assay results show that 100% of PF-06410293 and 100% of EU-Humira lots are within the quality range (mean± 3SD) of the US-Humira lots; 100% of the PF-06410293 results are also within the ±3SD of EU-Humira. Overall, PF--06410293, US-Humira and EU-Humira exhibit similar ADCC function based on the primary NK cell assay.

3.2.R.3.2.2.1.3. PBMC ADCC Assay (158 V/F donor genotype)

Effector cells from multiple donors having the FcγRIIIa 158 V/F genotype were freshly prepared on the day of the ADCC assay. The target cell is a CHO cell line that overexpresses mTNF. To conduct the test, target cells in the assay plate are incubated at 37°C for 18-24 hour prior to adding serial dilution of samples and PBMCs with effector cells. The plate is then incubated at 37°C for 18 to 22 hours before the cell death is measured with CytoTox Glow Reagent using luminescence. Each sample is tested on 3 assay plates. The mean from 3 valid plates is the final reportable result. Assessment of ADCC activity in the total PBMC assay is based on a comparison between the dose response of PF-06410293 reference material and the dose response of a test sample. The method was qualified for use in the range of 50 to 150% of the target reference material concentration (*Technical report INX 100299173*):

Parameter	Results
Precision (Intermediate)	RSD15.3%, 14.2% and 19.6% at 50%, 100% and 150% of target, respectively.
Linearity	The plot is linear from 50 - 150%, R ² = 0.9999; Slope = 1.1
% Accuracy	95, 97% and 99% at 50%, 100% and 150% of target, respectively
Range	50 - 150%

Representative dose response curves are shown below (*Figure 3.2.R.3.2.2-2 in the submission*):



A statistical analysis was done based on the results from 10 independent PF-06410293 lots, 12 US-Humira and 10 EU-Humira lots, using quality range derived from the 12 US-Humira lots (mean $\pm$ 3 SD). As illustrated in the plot below (*Figure 3.2.R.3.2.2-5 from the submission*), all PF-06410293 and EU-Humira lots met the quality range acceptance criteria.

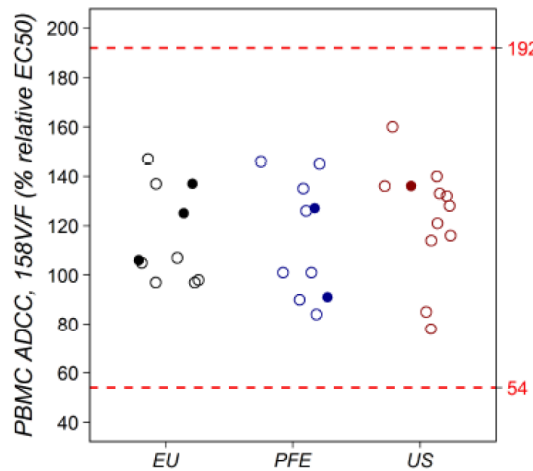


Figure 3.2.R.3.2.2-5 The results of PBMC ADCC (158 V/F) activity. The red dashed lines represent the upper and lower limits of the quality range. Solid circles represent the lots used in the clinic

Reviewer’s Comment: PBMC ADCC Assay (158 V/F donor genotype) results show that 100% of PF-06410293 and 100% of EU-Humira lots are within the quality range (mean $\pm$ 3SD) of the US-Humira lots; 100% of the PF-06410293 results are also within the $\pm$ 3SD of EU-Humira. Overall, PF-06410293, US-Humira and EU-Humira exhibit similar ADCC function when the assay is conducted using donor cells with the 158 V/F genotype.

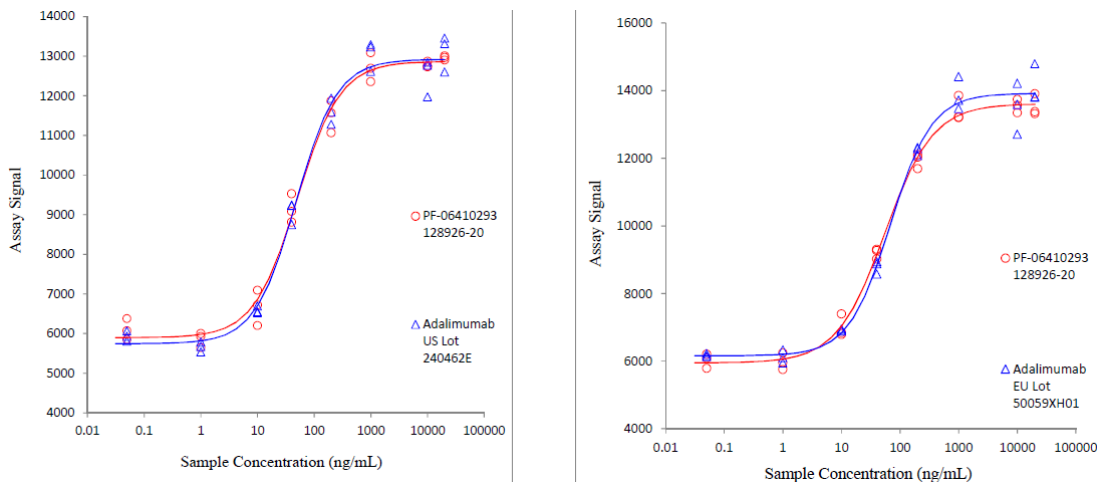
3.2.R.3.2.2.1.4. PBMC ADCC Assay (158 F/F donor genotype)

Effector cells from multiple donors having the Fc γ RIIIa 158 F/F genotype were freshly prepared on the day of the ADCC assay. The target cell is a CHO cell line that overexpresses mTNF. To conduct the test, target cells in the assay plate are incubated at 37°C for 18-24 hour prior to adding serial dilution of samples and PBMCs with effector cells. The plate is then incubated at 37°C for 18 to 22 hours before the cell death is measured with CytoTox Glow Reagent using luminescence. Each sample is tested on 3 assay plates. The mean from 3 valid plates is the final reportable result. Assessment of ADCC activity in the total PBMC assay is based on a comparison between the dose response of PF-06410293 reference

material and the dose response of a test sample on each plate. The method was qualified in the range of 50 to 150% of the target reference material concentration (*Technical report INX 100332531*):

Parameter	Results
Precision (Intermediate)	RSD18.3%, 15.5% and 19.8% at 50%, 100% and 150% of target, respectively.
Linearity	The plot is linear from 50 - 150%, $R^2 = 0.9998$; Slope = 1.01
% Accuracy	89%, 94% and 97% at 50%, 100% and 150% of target, respectively
Range	50 - 150% of target

Representative dose response curves are shown below (*Figure 3.2.R.3.2.2-6 in the submission*):



A statistical analysis was done based on the results from 10 independent PF-06410293 lots, 12 US-Humira and 10 EU-Humira lots, using quality range derived from the 12 US-Humira lots (mean ± 3 SD). As illustrated in the plot below (*Figure 3.2.R.3.2.2-7 from the submission*), all PF-06410293 and EU-Humira lots met the quality range acceptance criteria.

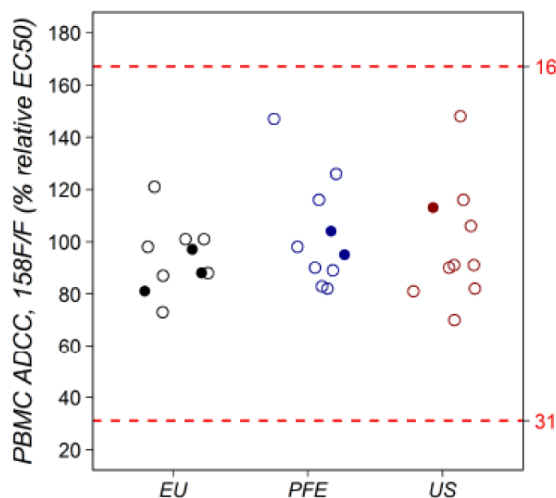


Figure 3.2.R.3.2.2-7. The results of PBMC ADCC (158 F/F) activity. The red dashed lines represent the upper and lower limits of the quality range. Solid circles represent the lots used in the clinical studies.

Reviewer’s Comment: PBMC ADCC Assay (158 F/F donor genotype) results show that 100% of PF-06410293 and 100% of EU-Humira lots are within the quality range (mean ± 3SD) of the US-Humira lots; 100% of the PF-06410293 results are also within the ±3SD of EU-Humira. Overall,

PF--06410293, US-Humira and EU-Humira exhibit similar ADCC function when the assay is conducted using donor cells with the 158 F/F genotype.

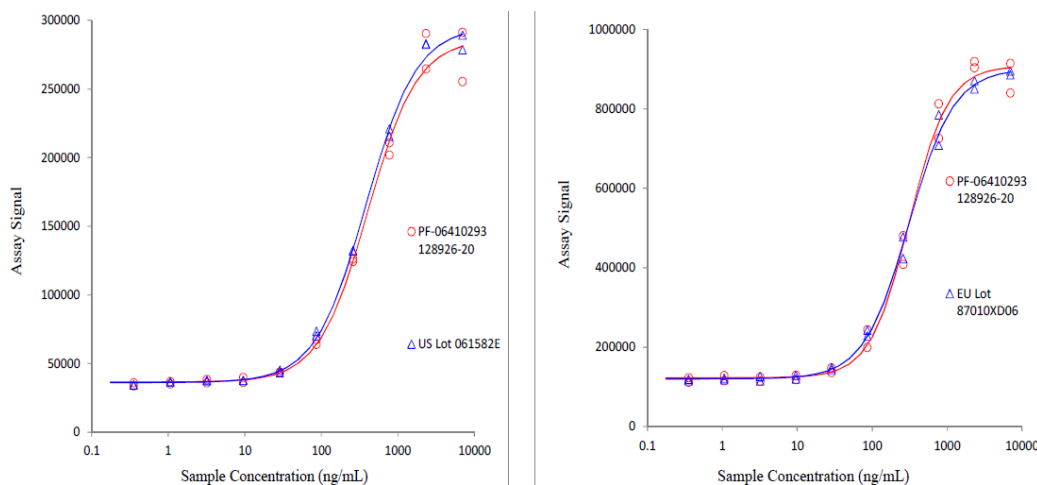
3.2.R.3.2.2.1.5. FcγRIIIa Reporter Gene Assay (RGA)

The FcγRIIIa RGA assay uses Jurkat effector cells transfected with FcγRIIIa 158V and a luciferase reporter gene under the control of nuclear factor of activated T-cell (NFAT) response elements. The mTNF-expressing NS0 cells were used as the target cell. Adalimumab bound to mTNF on target cells via the Fab domain can bind simultaneously to FcγRIIIa receptors on Jurkat effector cells via the Fc domain, thereby activating the downstream signaling pathways leading to NFAT-driven reporter gene expression and luciferase production. The FcγRIIIa RGA assay does not measure target cell lysis but provides a cell-based analysis of adalimumab binding to FcγRIIIa and downstream signaling events.

To conduct the test, plated NS0 target cells are first incubated at 37°C/5%CO₂ for 25-30 minute prior to adding serial dilution of samples and incubated at 37°C/5%CO₂ for 1-2 hour. Then, the Jurkat effector cells are added to assay plate and incubated overnight. OneGlo reagent is added to the plate and read under luminometer. Each sample is tested on 3 assay plates and a mean relative % EC₅₀ is calculated. Assessment of reporter gene activity is based on a comparison between the dose response of PF-06410293 reference material and the dose response of a test sample on each plate. The method was qualified in the range of 50 to 150% of the target reference material concentration (*Technical report INX 100292127*):

Parameter	Results
Specificity	No Response with alternate target cells
Precision (Intermediate)	RSD: 16%, 12% and 11% at 50%, 100% and 150% of target, respectively
Linearity	The plot is linear from 50 - 150%, R ² = 0.9913; Slope = 1.0713
% Accuracy	92%, 108% and 102% at 50%, 100% and 150% of target, respectively
Range	50 - 150%

Representative dose response curves are shown below (*Figure 3.2.R.3.2.2-9 in the submission. Each panel represents one assay plate*):



A statistical analysis was done based on the results from 10 independent PF-06410293 lots, 10 US-Humira and 10 EU-Humira lots, using quality range derived from the 10 US-Humira lots (mean ± 3 SD).

As illustrated in the plot below (*Figure 3.2.R.3.2.2-10 from the submission*), all PF-06410293 and 90% of EU-Humira lots met the “Tier 2” acceptance criteria when compared with US-Humira.

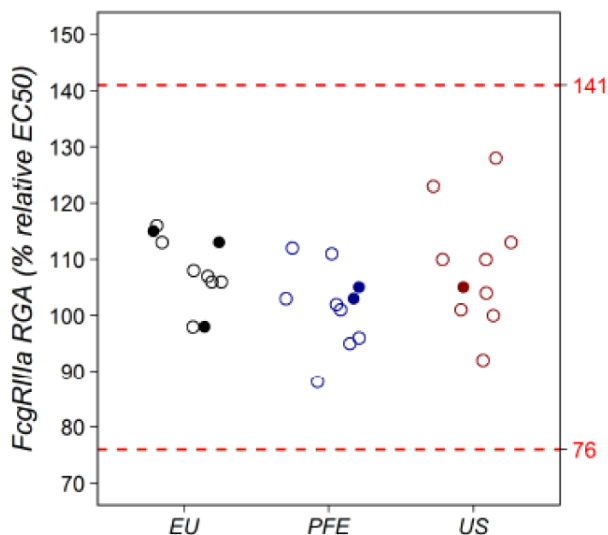


Figure 3.2.R.3.2.2-10. The results of FcγRIIIa RGA. The red dashed lines represent the upper and lower limits of the quality range. Solid circles represent the lots used in the clinic.

Reviewer’s Comment: *FcγRIIIa Reporter Gene testing results show that 100% of PF-06410293 and 100% of EU-Humira lots are within the quality range (mean± 3SD) of the US-Humira lots; 100% of the PF-06410293 results are also within the ±3SD of EU-Humira. Overall, PF--06410293, US-Humira and EU-Humira exhibit similar FcγRIIIa binding and downstream pathways activation.*

3.2.R.3.2.2.1.6. Binding to FcγRIIIa by Surface Plasmon Resonance (SPR) Analysis

FcγRIIIa SPR binding assay was also used to assess the binding affinity and kinetics of adalimumab to recombinant human FcγRIIIa 158V and 158F.

The kinetics of Adalimumab binding to FcγIIIa (158F and 158V) receptor were determined by surface plasmon resonance (SPR)-based measurements with a Biacore 200 instrument. To perform the test, Series S CM5 biosensor was first immobilized with anti-PENTA Histidine Mab, then a freshly prepared FcγRIIIa (158F or 158V) was captured across the biosensor through the His-tag on a FcγRIIIa receptor. Rate constants for the Adalimumab- FcγIIIa receptor interaction were derived by making kinetic binding measurements at six different analyte concentrations. The equilibrium dissociation constant (M) of the reaction between FcγIIIa receptor and Adalimumab was then calculated from the kinetic rate constants by the following formula: $KD = kd / ka$. The method has been qualified in terms of assay precision for both FcγRIIIa 158F and FcγRIIIa 158V based on acceptance criteria of 80%- 125% for the relative % K_D results (*Technical report LF-520-R-271-17/INX100299901*).

Statistical analysis, using quality range derived from the 15 US-Humira lots (mean± 3 SD), were done based on the results from 10 independent PF-06410293 lots, 15 US-Humira and 10 EU-Humira lots. As illustrated in the plot below (*Figure 3.2.R.3.2.2-12 from the submission*), all PF-06410293 and 90% EU-Humira lots met the quality range acceptance criteria for FcγRIIIa 158V assay. However, for the FcγRIIIa158F assay, only 30% of PF-06410293 had results within the established quality range and 90% EU-Humira lots were within the range. The remaining 70% of PF-06410293 lots are slightly above the upper limit of the quality range of 101% with values from 107 – 113% relative K_D .

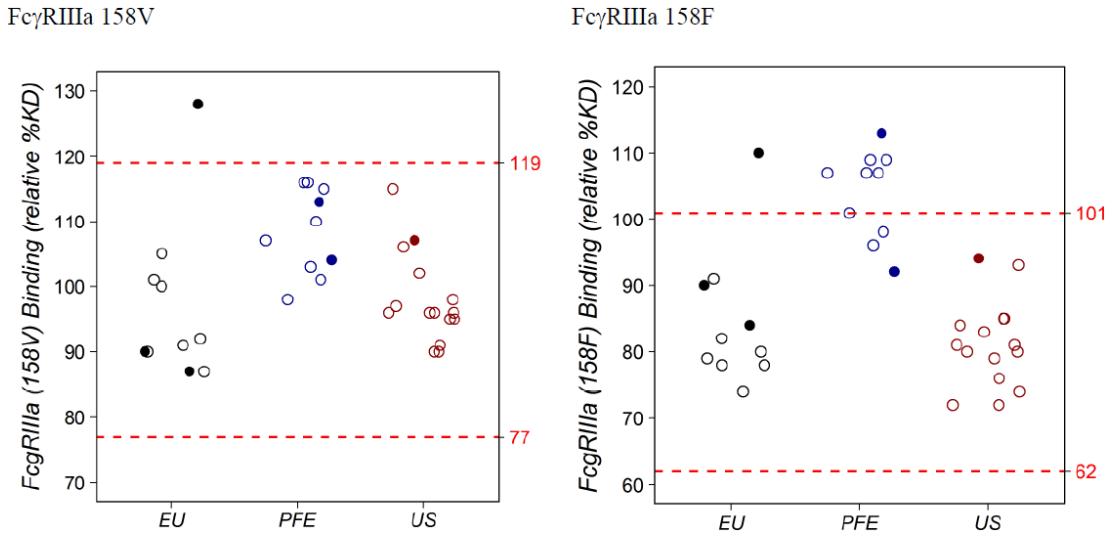


Figure 3.2.R.3.2.2-12. % KD of binding to FcγRIIIa. The red dashed lines represent the upper and lower limits of the quality range. Solid circles represent the lots used in the clinical studies.

The applicant evaluated K_a , K_d , KD values from PF-06410293, US-Humira, and EU-Humira lots (see table below, modified from Table 3.2.R.3.2.2-9 and Table 3.2.R.3.2.2-10 of the submission), and confirms that binding to FcγRIIIa 158V and 158F were medium to low affinity which are consistent with published literature. FcγRIIIa 158F is a weaker binder than FcγRIIIa 158V and has more variability. The applicant claims that overall differences in k_a , k_d , and KD values were minor, and ADCC functional assays with FcγRIIIa 158F present in donor effector cells (PBMC ADCC FcγRIIIa 158V/F and PBMC ADCC FcγRIIIa 158F/F) providing supportive evidence that effector function activity is not affected by differences in binding observed.

FcγRIIIa 158V		PF-06410293 (N=10)		US-Humira (N=15)		EU-Humira (N=10)	
		158V	158F	158V	158F	158V	158F
ka (1/Ms), x10 ⁴	Mean	4.31	5.42	5.99	7.64	5.73	7.53
	SD	0.30	0.34	0.92	0.29	0.98	1.01
	% RSD	6.97	6.24	15.31	3.78	17.12	13.42
kd (1/s), x10 ⁻³	Mean	9.55	4.91	15.33	8.49	14.79	7.94
	SD	0.20	0.20	0.60	0.31	0.34	0.33
	% RSD	2.08	3.98	3.93	3.63	2.31	4.21
KD (M), x10 ⁻⁷	Mean	2.26	9.11	2.64	11.23	2.66	10.74
	SD	0.16	0.58	0.39	0.34	0.37	1.14
	% RSD	7.11	6.37	14.79	3.06	13.77	10.66

Reviewer’s Comment: The FcγRIIIa 158V binding testing results show that 100% of PF-06410293 and 90% of EU-Humira lots are within the quality range (mean ± 3SD) of the US-Humira lots; 100% of the PF-06410293 results are also within the ±3SD of EU-Humira. Overall, PF--06410293, US-Humira and EU-Humira are similar in terms of binding to FcγRIIIa 158V.

The FcγRIIIa 158F binding testing results show that 30% of PF-06410293 and 90% of EU-Humira lots are within the quality range (mean ± 3SD) of the US-Humira lots; 100% of the PF-06410293 results are within the ±3SD of EU-Humira. Although the statistical analysis on FcγRIIIa 158F binding failed the quality range acceptance criteria, the difference seen in the FcγRIIIa 158F binding SPR results does not coincide with the results of the cell based ADCC assays conducted using FcγRIIIa 158V/F and FcγRIIIa

158F/F genotypes (no difference observed). Thus, the difference observed in the FcγRIIIa 158F binding does not preclude the similarity claim among PF--06410293, US-Humira and EU-Humira.

Overall, the combination of binding and cell- based assay data provided to assess ADCC function supports a demonstration that PF-06410293 is highly similar to US-Humira, as well as the analytical component of the scientific 3-way bridge to justify the use of clinical data generated using EU- Humira.

3.2.R.3.2.2.2. Complement Dependent Cytotoxicity (CDC) Function

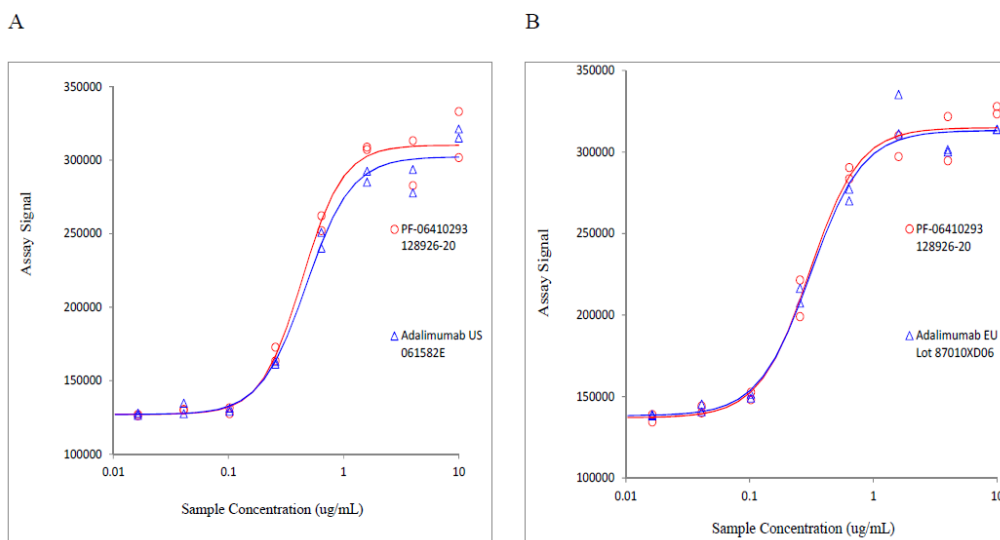
3.2.R.3.2.2.2.1. CDC Assay

The CDC activity of adalimumab were evaluated using an in vitro test that measures the adalimumab induced death of NS0 cells that overexpress mTNF. Briefly, serial dilutions of samples (20 -0.033 µg/mL) are incubated for 45 minutes in a 96-well assay plate containing 5x10⁴ NS0 cells/well, then a dilution of human serum complement (1/80 total dilution in well) was added to the assay plate, incubated for 2 hours, and Cytotox-Glo reagent was added prior to reading the plate on a luminometer. EC50 ratio of test sample relative to PF-06410293 lot 128926-20 is calculated from a single plate assay format. The method was qualified in the range of 50 to 150% of the target reference material concentration in terms of method precision and accuracy (*Technical report INX 100267169*):

Parameter	Results
Precision	RSD: 8.6%, 6.9% and 4.6% at 50%, 100% and 150% of target, respectively
Linearity	The plot is linear from 50 - 150%, R ² = 0.9997; Slope = 0.95
% Accuracy	102%, 100% and 97% at 50%, 100% and 150% of target, respectively
Range	50 - 150%

The dose response curves are shown below:

Figure 3.2.R.3.2.2-13. Representative Dose Response Curves of PF-06410293, Adalimumab-US, and Adalimumab-EU in CDC Assay



Statistical analysis was performed on the results from 10 independent PF-06410293 lots, 10 US-Humira and 10 EU-Humira lots, using quality range derived from the 10 US-Humira lots (mean± 3 SD). As illustrated in the plot below (*Figure 3.2.R.3.2.2-14 from the submission*), all PF-06410293 and EU-Humira lots met the quality range acceptance criteria.

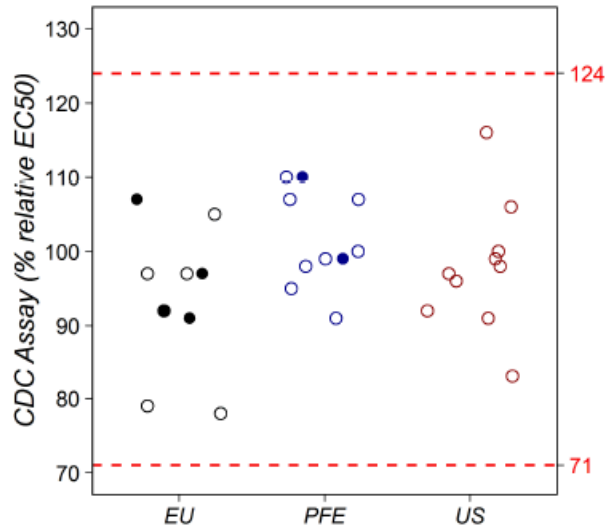


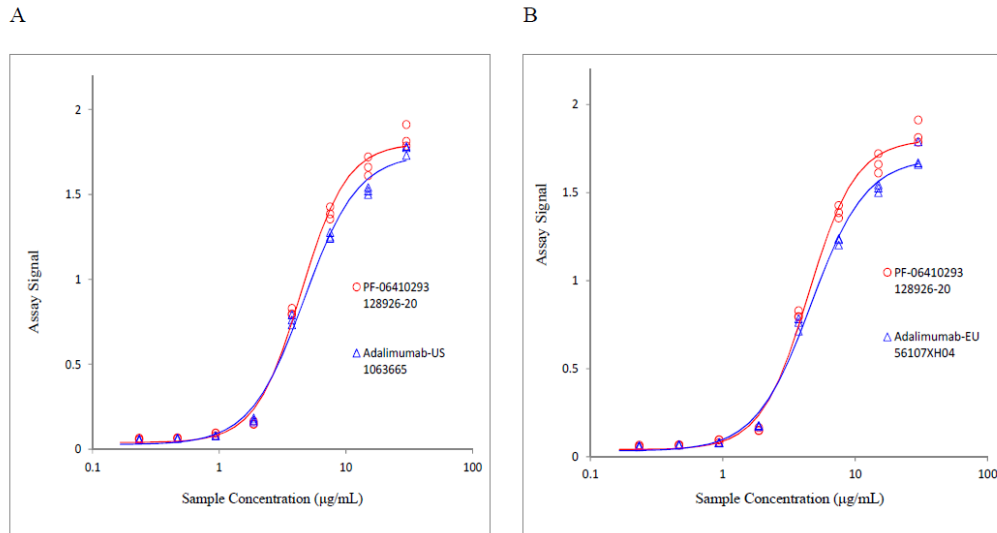
Figure 3.2.R.3.2.2-14. The results of CDC (Relative % EC50). The red dashed lines represent the upper and lower limits of the quality range. Solid circles represent the lots used in the clinic.

Reviewer’s Comment: CDC assay results show that 100% of PF-06410293 and 100% of EU-Humira lots are within the quality range (mean $\pm$ 3SD) of the US-Humira lots; 100% of the PF-06410293 results are also within the $\pm$ 3SD of EU-Humira. Overall, PF-06410293, US-Humira and EU-Humira exhibit similar CDC function.

3.2.R.3.2.2.2.2. C1q Binding ELISA

Adalimumab binding to C1q was measured by an ELISA. To perform the test, 96 well plates are coated with 8-point serial dilutions of adalimumab overnight, then blocked with 100% casein buffer and incubated with human C1q at 2.5 μ g /mL for 90 mins, followed by incubation with human anti-C1q goat antibody for 1 hour, followed by incubation with donkey anti-goat HRP tagged antibody for 1 hour. Each step was followed by a washing step. The plate is developed by adding TMB and absorbance was checked on a spectrophotometer at 650 nm. After addition of a sulfuric acid stop solution, absorbance was read at 450 nm. The plate data was analyzed using a standard 4-parameter logistic curve fit. Relative potency to PF- 06410293 reference material values are reported. Representative dose-response curves are shown below:

Figure 3.2.R.3.2.2-15. Representative Dose Response Curves of PF-06410293, Adalimumab-US, and Adalimumab-EU in C1q Binding Assay



The method was qualified in the range of 50 to 150% of the target reference material concentration (*Technical report INX 100272413*):

Parameter	Result
Precision (Intermediate)	1.7 % RSD at target (100% RP)
Linearity	The plot is linear from 50% to 150% RP $R^2 = 0.9995$; Slope = 1.0358
% Accuracy	97% at Target (100% RP)
Range	50% to 150% RP

Statistical analysis was performed on the results from 10 independent PF-06410293 lots, 10 US-Humira and 10 EU-Humira lots, using quality range derived from the 10 US-Humira lots (mean $\pm$ 3 SD). As illustrated in the plot below (Figure 3.2.R.3.2.2-16 from the submission), all PF-06410293 and EU-Humira lots met the quality range acceptance criteria.

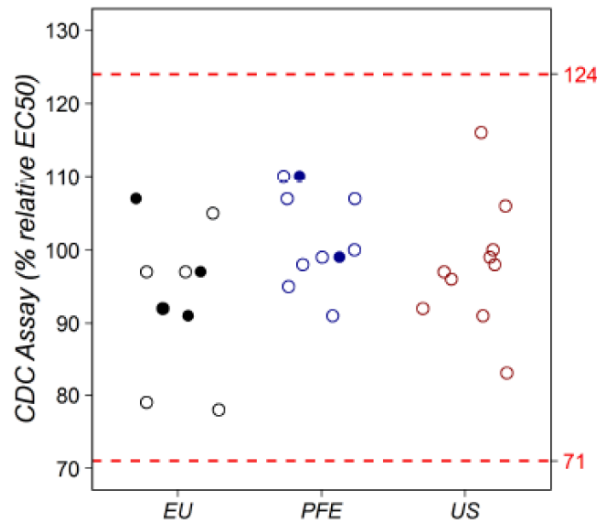


Figure 3.2.R.3.2.2-14. The results of C1q binding (Relative % EC50). The red dashed lines represent the upper and lower limits of the quality range. Solid circles represent the lots used in the clinic.

Reviewer's Comment: C1Q binding results show that 100% of PF-06410293 and 100% of EU-Humira lots are within the quality range (mean ± 3SD) of the US-Humira lots; 100% of the PF-06410293 results are also within the mean ± 3SD of EU-Humira. Overall, PF-06410293, US-Humira and EU-Humira exhibit similar C1Q binding. Both the cell-based CDC function assay results and the C1Q binding assay results support a determination that PF-06410293 is highly similar to US-Humira in terms of CDC activity. The data also support the analytical portion of the scientific bridge.

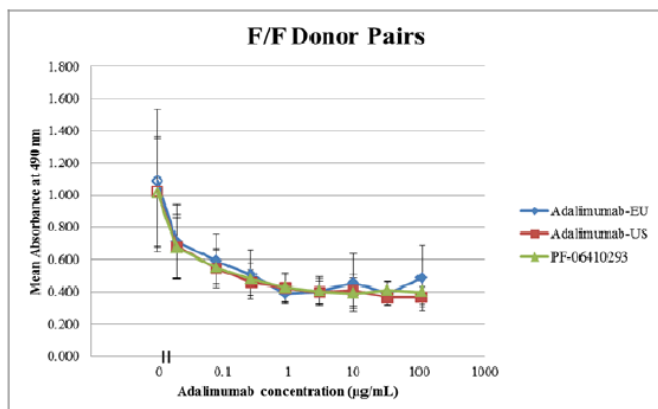
3.2.R.3.2.2.3. Mixed Lymphocyte Reaction (MLR) Assay

Suppressed proliferation of activated T cell may also contribute to the mechanism of action of adalimumab in treatment of CD. The adalimumab induced inhibition of T cell proliferation is thought to occur via Fc-dependent, anti-TNF-induced generation of a regulatory macrophages. Thus, an inhibition of T-cell proliferation mixed lymphocyte reaction (MLR) assay was also used to support the assessment of Fc function of adalimumab.

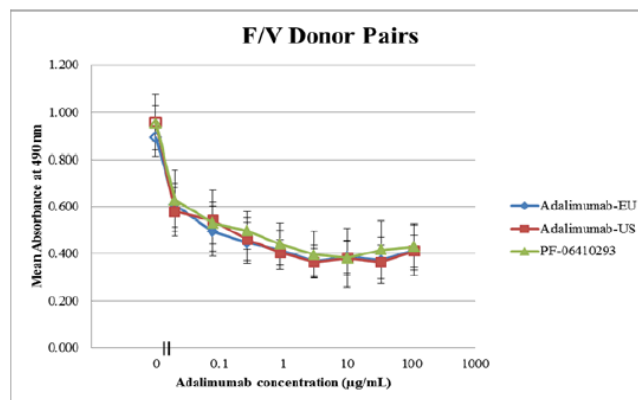
In a 2-way MLR assay, PBMCs from 2 individuals (1 donor pair) are co-cultured, and T cells become activated and proliferate in response to differences in major histocompatibility complex (MHC) antigens between the 2 individuals. Three independent MLRs were conducted with PBMCs from donors with each of the 158 F/F, 158 V/F and 158V/V FcγRIIIa genotypes. Cells from the donor pair were mixed in 96-well plates in triplicate. Following 2 days of incubation at 37°C, serial dilutions of samples were added to cells. After an additional 5 days of incubation at 37°C, cell proliferation was assessed using a CellTiter 96® Aqueous Non-Radioactive Cell Proliferation Assay kit. Absorbance (at 490 nm) was measured. *(note that the applicant reports that a previous study has shown that ≥98% of the proliferating cells in an MLR after 7 days of culture were T cells, thus the absorbance values obtained from the Cell Titer Assay represent T cell proliferation).* Results are reported as mean absorbance (at 490 nm) of the triplicate samples. IgG1 kappa was used as a non-specific negative control antibody. Certolizumab pegol and etanercept were used to demonstrate specificity of the response.

Samples from 5 lots each of PF-06410293, US-Humira and EU-Humira were tested by the MLR assay. As shown in Figures below, PF-06410293, US-Humira and EU-Humira demonstrated comparable inhibition of the proliferation of T cells in a dose-dependent manner in the MLR, regardless of FcγRIIIa genotype.

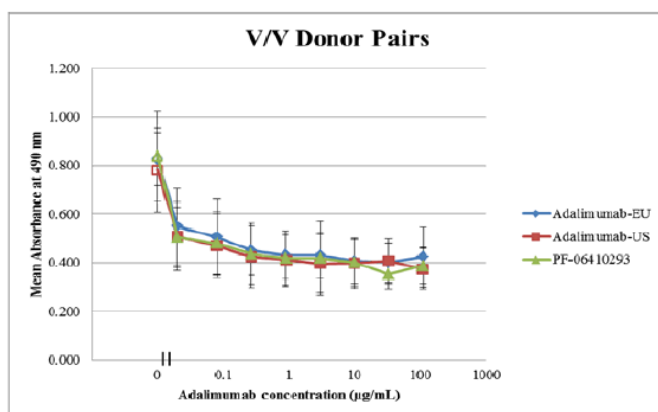
A. FcγRIIIa 158 F/F



B. FcγRIIIa 158 V/F



C. FcγRIIIa 158 V/V



Reviewer’s Comment: *Suppressed proliferation of T cell via Fc-dependent, anti-TNF-induced generation of a regulatory macrophages is a potentially clinically relevant, biological function of the Fc domain. Comparable dose-dependent inhibition of T cells proliferation curves supports a determination that PF-06410293 is highly similar to US-Humira for suppressing proliferation of activated T cells. The data also support the analytical portion of the scientific bridge.*

3.2.R.3.2.2.4. Additional Fcγ Receptor Binding SPR Assays

Binding to FcγRI, FcγRIIa (131H and 131R), FcγRIIb, and FcγRIIIb are also known to be involved in Fc-mediated functions, but to a lesser extent than FcγRIIIa. SPR assay is used to evaluate the adalimumab binding to these receptors.

The kinetics of Adalimumab binding to Fcγ receptors were determined by SPR-based measurements with a Biacore T200 instrument. Briefly, a Series S CM5 biosensor was first immobilized with anti-PENTA Histidine Mab, and then a freshly prepared Fcγ receptor was captured across the biosensor through the His-tag on the Fcγ receptor. Rate constants for the Adalimumab- Fcγ receptor interaction were derived by making kinetic binding measurements at six different analyte concentrations. The equilibrium dissociation constant (M) of the reaction between Fcγ receptor and Adalimumab was then calculated from the kinetic rate constants by the following formula: $KD = kd / ka$.

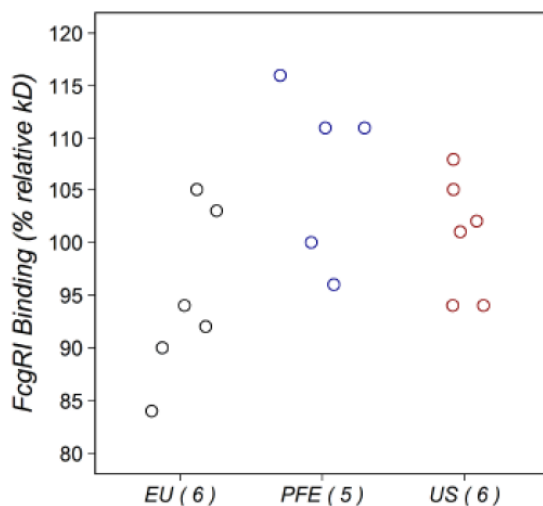
Method performance was evaluated by testing PF-06410293 reference material against itself as a sample (internal control) in multiple runs over multiple days. For FcγRI, the method accuracy was 104% and

the precision was 7.1% RSD from 9 independent runs. However, the applicant claims that FcγRIIIa (131H and 131R), FcγRIIb, and FcγRIIIb are low affinity receptors which have binding affinity outside the Biacore instrument optimal operation range. The applicant reports that the method accuracy and precision for these receptors could not be properly quantified, thus demonstration of similarity in term of these Fcγ receptors were based on raw data comparison from representative lots. (*Technical Report INX100329232*)

Reviewer’s Comment: *The SPR experimental design and optimization were submitted in Technical Report INX100329232. The method and conditions used are acceptable for the intended purpose.*

The applicant performed visual comparison of SPR sensorgrams and conclude that the binding of PF-06410293, US-Humira, and EU-Humira to FcγRI, RIIa131H, RIIa 131R, RIIb and RIIIb are similar.

The KD values of FcγRI binding from 6 lot each of PF-06410293, EU-Humira, and US-Humira were measured. The relative KD (% KD) results, as illustrated in Figure below (*Figure 3.2.R.3.2.2-19 from the submission*), indicate that the FcγRI binding activity of PF-06410293, EU-Humira, and US-Humira are similar.



Reviewer’s Comment: *The relative KD of PF-06410293, US-Humira, and EU-Humira are overlapping within a narrow range of 84 to 116 % for FcγRI, which indicate similar binding activity.*

3.2.R.3.2.2.5. Function FcRn Binding SPR Assay

IgG1 binding to the FcRn may impact the in vivo half-life of an antibody, thus, the adalimumab binding to FcRn were evaluated using SPR method. To perform the test, Biotin FcRn was captured on a Series S Sensor SA (streptavidin) biosensor chip and adalimumab in solution phase was flowed through to bind to the FcRn and binding signal is collected. Due to rapid kinetic rate, the kinetic constants (ka, kd) were not determined for the FcRn binding, instead, the KD was calculated by measuring the concentration-dependence of the steady-state signal reached near the end of the injection. To qualify the method, control and test samples were run in duplicate in each assay run and the assays were repeated three times across different days (n=3). SPR experiments from multiple days were tested at the same temperature, comparable buffer conditions and with comparable biotin FcRn immobilization levels. Method precision and accuracy were found acceptable (RSD =7% and %; accuracy = 98%. From Technical Report INX100299881).

Statistical analysis was done based on the results from 10 independent PF-06410293 lots, 10 US-Humira and 10 EU-Humira lots, using quality range derived from the 10 US-Humira lots (mean $\pm$ 3 SD). As illustrated in the plot below, all PF-06410293 and EU-Humira lots met the "Tier 2" acceptance criteria when compared with US-Humira.

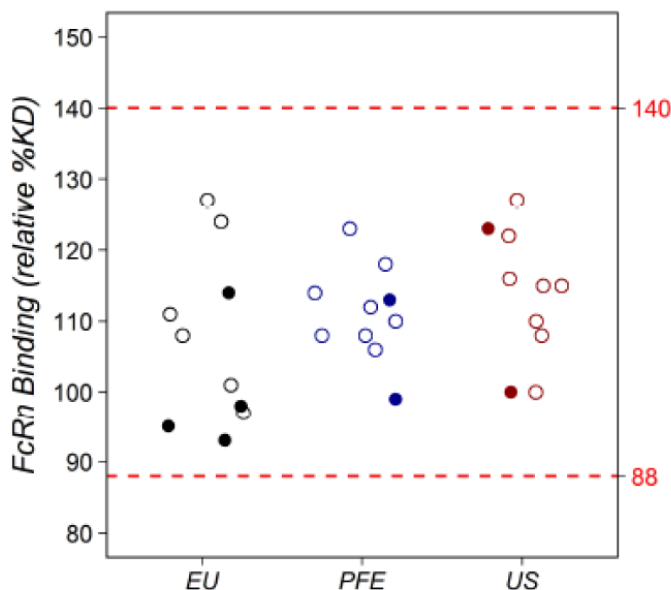


Figure 3.2.R.3.2.2-21. illustrates the distribution of results for FcRn binding (% Relative K_D) as well as the upper and lower limits of the statistical quality range (the red dashed lines) from testing individual lots of adalimumab-EU (10 lots), and adalimumab-US (10 lots) with PF-06410293 (5 DS + 5DP). The solid circles represent the lots that have been used in the clinical trials. Tabulated data can be found in [3.2.R.3.5 Appendix Table 3.2.R.3.5-17](#).

Reviewer’s Comment: FcRn binding SPR results show that 100% of PF-06410293 and 100% of EU-Humira lots are within the quality range (mean $\pm$ 3SD) of the US-Humira lots; 100% of the PF-06410293 results are also within the $\pm$ 3SD of EU-Humira. Overall, PF--06410293, US-Humira and EU-Humira exhibit similar FcRn binding capability.

3.2.R.3.2.3. N-Glycan

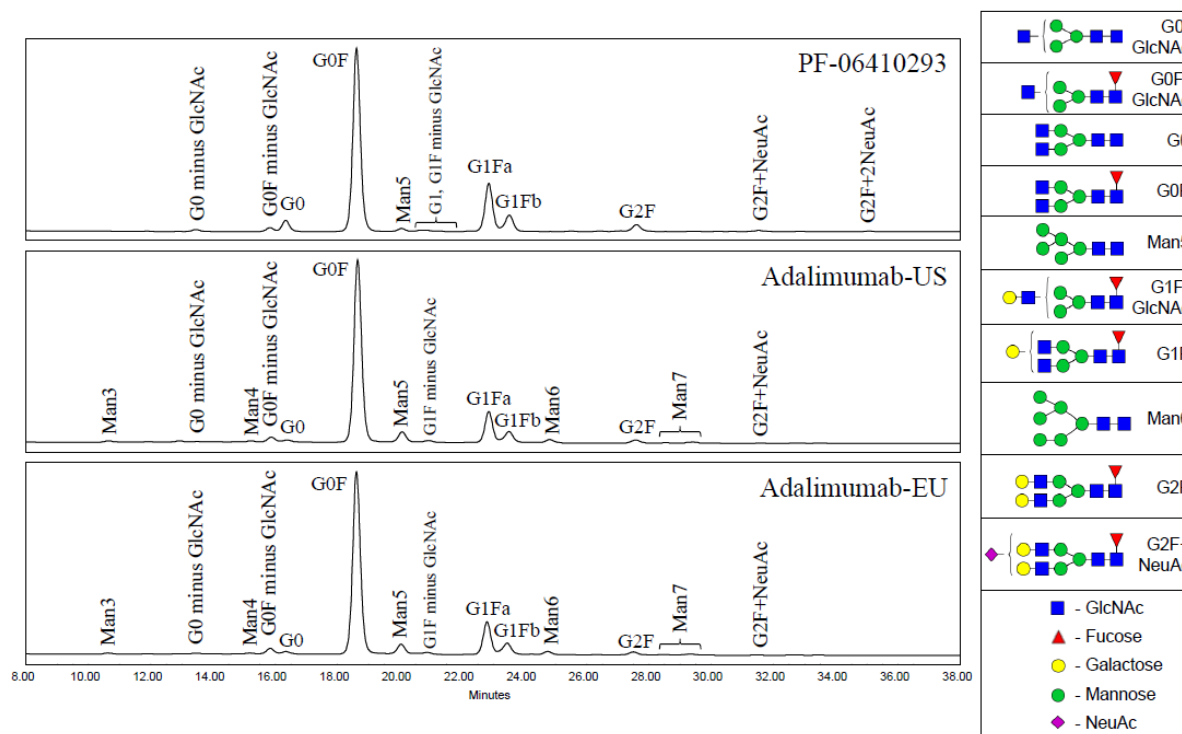
The N-linked glycan assessment is important because the effector function activity (ADCC, CDC) is a one of the mechanisms of action for adalimumab. The N-glycan similarity assessment was primarily done using hydrophilic interaction liquid chromatography (HILIC) glycan mapping method. Briefly, N-linked glycans were enzymatic released by peptide-N-glycosidase F (PNGaseF) followed by labeling with 2-aminobenzamide (2-AB) and analysis by hydrophilic interaction liquid chromatography (HILIC) with fluorescence detection. (note: the HILIC method is used for drug substance release test and has been validated for the intended purpose, see review memo by Dr. Nailong Zhang).

Characterization

The individual glycan species eluting by HILIC mapping method were identified using HILIC/MS. The structures, monosaccharide identity, and glycosidic linkages of the N-linked glycans from adalimumab were confirmed by sequential digestion of the total released pool of adalimumab 2-AB-labeled N-linked glycans with different exoglycosidases.

The representative HILIC profiles and peak designations are shown in the figure below.

Figure 3.2.R.3.2.3-1. Representative HILIC Profiles of 2-AB N-Linked Glycans of PF-06410293, Adalimumab-US, and Adalimumab-EU



G0F and G1F (the predominant N-linked glycans), as well as small levels of G0 minus GlcNAc, G0F minus GlcNAc, G0, Man5, G2F, and G2F+NeuAc were observed in all three products. Trace levels of Man3, Man4, Man6, and Man7 were observed in US-Humira and EU-Humira, but not in PF-06410293. Similarity assessment of the N-glycans among PF-06410293, US-Humira and EU-Humira is reviewed below.

Analytical similarity Assessment

The quantity of the glycan species for 10 PF-06410293 DS batches, 68 US-Humira and 77 EU-Humira drug product lots are summarized in the table below (Table 3.2.R.3.2.3-1. in “product quality” section of the submission):

Glycan Species	PF-06410293 (n=10)	US-Humira (n=68)	EU-Humira (n=77)
Man3	-	0.3-0.5	0.2-0.5
G0 minus GlcNAc	0.6-1.1	0.1-0.5	0.2-0.4
Man4	-	0.2-0.5	0.2-0.6
G0F minus GlcNAc	1.3-2.7	2.0-2.8	1.8-3.6
G0	3.1-3.9	0.6-1.0	0.7-1.1
G0F	64.7-74.0	66.4-71.3	64.9-71.0
Man5	0.9-1.9	3.1-4.9	2.8-4.9
G1	0.5-0.9	-	-
G1F minus GlcNAc	-	0.8-1.5	0.9-1.7
G0 - TriF	0.1-0.3	0.0-0.3	0.1-0.3
G1Fa	10.5-17.5	10.5-12.9	10.3-14.5
G1Fb	4.5-6.5	4.4-5.3	4.1-5.8
G1 - TriF	0.1-0.1	0.0-0.3	0.0-0.3

Glycan Species	PF-06410293 (n=10)	US-Humira (n=68)	EU-Humira (n=77)
Man6	-	1.2-2.3	1.2-3.3
G2	-	0.0-0.1	0.0-0.3
G1F + NeuAc	0.2-0.3	-	-
G2F	1.3-2.7	1.1-1.6	1.1-1.8
Man7	-	0.2-1.1	0.5-1.4
G2F + NeuAc	0.2-0.4	0.0-0.2	0.1-0.3
G2F + 2NeuAc	0.1-0.2	-	-

The individual glycoforms are sorted by the quality attribute for similarity assessment (*Table 3.2.R.3.2.3-2. in “product quality” section of the submission*):

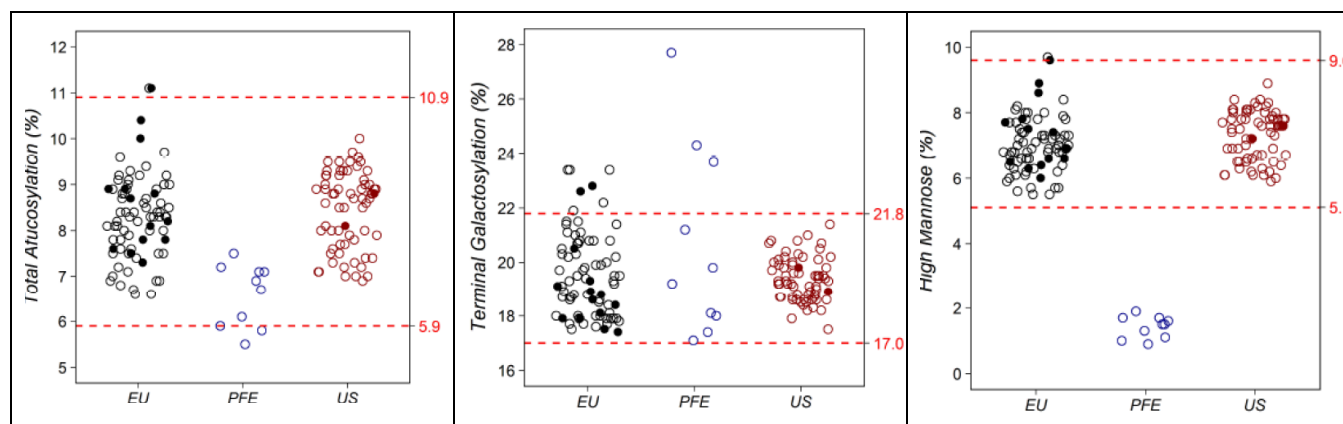
Quality Attribute	Level	PF-06410293	US-Humira	EU-Humira
Total Afucosylation	Main Glycan	G0	Man5	Man5
	Others:	Others: G0 minus GlcNAc, G1, Man5	Others: Man3, G0, G0 minus GlcNAc, Man4, Man6, G2, Man7	Others: Man3, G0, G0 minus GlcNAc, Man4, Man6, G2, Man7
Terminal Galactosylation	Main Glycan	Main Glycan: G1F(a+b)	Main Glycan: G1F(a+b)	Main Glycan: G1F(a+b)
	Others:	Others: G1, G1- TriF, G2F	Others: G1F minus GlcNAc, G1-TriF, G2, G2F,	Others: G1F minus GlcNAc, G1-TriF, G2, G2F
Total High Mannose	Main Glycan	Main Glycan: Man5	Main Glycan: Man5	Main Glycan: Man5
	Others:	Others: ND	Others: Man3, Man4, Man6, Man7	Others: Man3, Man4, Man6, Man7
Total Sialylation	Main Glycan	Main Glycan: G2F+NeuAc	Main Glycan: G2F+NeuAc	Main Glycan: G2F+NeuAc
	Others:	Others: G1F+NeuAc, G2F+2NeuAc	Others: ND	Others: ND

Testing results for total afucosylation, terminal galactosylation and high mannose of 10 PF-06410293 DS batches, 68 US-Humira and 77 EU-Humira drug product lots are summarized in the table below (*Table 3.2.R.3.2.3-3 through Table 3.2.R.3.2.3-6 in “product quality” section of the submission*).

	Region	N	Mean	SD	CV (%)	Min	Max
Total Afucosylation (%)	EU	77	8.3	0.93	11.2	6.6	11.1
	PFE	10	6.6	0.70	10.6	5.5	7.5
	US	68	8.4	0.83	9.9	6.9	10.0
Terminal galactosylation (%)	EU	77	19.5	1.57	8.0	17.4	23.4
	Pfizer	10	20.7	3.53	17.1	17.1	27.7
	US	68	19.4	0.80	4.1	17.5	21.4
High Mannose (%)	EU	77	7.0	0.86	12.3	5.5	9.7
	PFE	10	1.4	0.33	23.4	0.9	1.9
	US	68	7.3	0.75	10.3	5.9	8.9
Total Sialylation (%)	EU	77	0.1	0.02	22.2	0.1	0.3
	PFE	10	0.6	0.15	24.8	0.5	0.9
	US	68	0.1	0.02	21.4	0.0	0.2

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

Statistical analysis was performed for the total afucosylation and terminal galactosylation results, using a quality range of mean $\pm$ 3SD from 68 US-Humira lots. The statistical analysis results are illustrated in the figures below (Figure 3.2.R.3.2.3-2. To Figure 3.2.R.3.2.3-4. from the submission).



Each circle represents testing results from individual lots of adalimumab sourced in the EU (77 lots) and US (68 lots) with PF-06410293 (10 DS batches). The solid circles represent the lots that have been used in the clinical studies. The red dashed lines are the statistical quality range.

Afucosylation: 7 of 10 (70%) lots of PF-06410293 and 97% of EU-Humira lots fall within the quality range for total afucosylation. The 3 lots of PF-06410293 DS falling outside the range were $<$ 0.5% below the lower quality range limit. *The three PF-06410293 lots with the lowest level of afucosylation have experienced (b) (4) (described in S.2.6 Manufacturing Process Development History).*

Reviewer’s Comment: *Afucosylation of PF-06410293 did not meet the pre-determined criteria to US-Humira based on the statistical analysis (quality range of mean $\pm$ 3SD). However, the observed difference is small (mean difference is 1.8%) and did not result in difference in ADCC activity (see review for Section 3.2.R.3.2.2 Characterization of Antibody-Dependent Cellular Cytotoxicity (ADCC) Function). Therefore, the differences in afucosylation do not preclude a demonstration that PF-06410293 is highly similar to US-Humira.*

The impact (b) (4) on product quality includes change in N-glycans and charge heterogeneity (3.2.S.2.6). The data and the subsequent mitigation strategy were reviewed by Dr. Nailng Zhang (see DS review).

Terminal galactosylation: 7 of 10 (70%) lots of PF-06410293 and 91% of EU-Humira lots fall within the quality range for terminal galactosylation. The applicant explains that the higher levels of terminal galactosylation observed in the three lots that contain higher level of terminal galactosylation were (b) (4) *These are the same three lots showed the lowest level of afucosylation.*

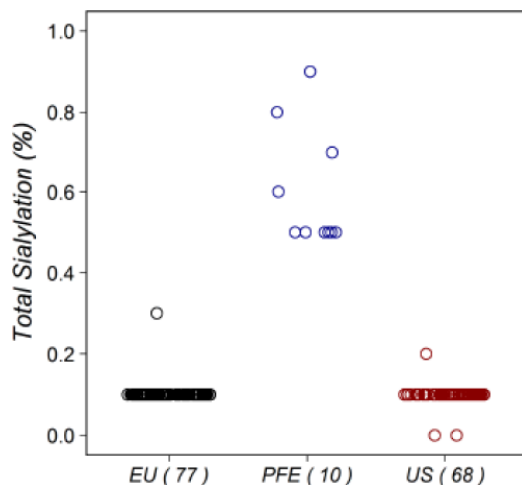
Reviewer’s Comment: *Although apparent differences in the galactosylation levels are observed based on the 10 PF-06410293 lots used for the analytical similarity assessment, these differences do not preclude a demonstration that PF-06410293 is highly similar to US-Humira because:*

- *The level of difference in galactosylation did not result in differences in ADCC activity.*
- *The level of difference in galactosylation did not result in differences in CDC activity.*
- *The lots manufactured post corrections (b) (4) are within the quality range determined by the US-Humira lots.*

High Mannose: All PF-06410293 lots have high mannose level lower than US-Humira or Humira EU lots; 97% of EU-Humira lots fall within the established range.

Reviewer’s Comment: *The level of high mannose forms of PF-06410293 are not analytically similar to US-Humira, with a mean difference of 5.9% (PF vs US: 1.4% vs 7.3%). It is known that high mannose glycans of therapeutic monoclonal antibodies increases serum clearance in human. Scientific literature also indicates that up to 5% difference in high mannose glycans differences does not significantly impact clearance of monoclonal antibodies [Goetze A.M. et al. Glycobiology, Volume 21, Issue 7, July 2011, Pages 949–959]. Albeit the difference in high mannose between PF-06410293, U.S.- Humira, and E.U.-Humira was slightly higher than 5%, the analytical difference alone does not preclude a demonstration that PF-06410293 is highly similar to US-Humira. This conclusion is further corroborated by the results of the comparative PK study, in which PK similarity is demonstrated between PF-06410293, US-Humira and EU-Humira (provided by clinical pharmacology reviewer Dr. Jianmeng Chen).*

Total sialylation: <1% of total sialylated N-linked glycan were found in PF-06410293 lots, and even smaller amounts were observed in US-Humira and EU-Humira lots (*Figure 3.2.R.3.2.3-5. from the submission*):



The applicant reports that, qualitatively, N-acetylneuraminic acid (Neu5Ac) was observed as the predominant sialic acid form with low levels of N-glycolylneuraminic acid (Neu5Gc) in PF-06410293, US-Humira and EU-Humira materials.

Reviewer’s Comment: *PF-06410293, US-Humira and EU-Humira all contain <1% of sialylated N-linked glycans, where Neu5Ac is the predominate sialic acid form. Although, Neu5Gc is generally not found in human proteins thus has the potential to be immunogenic, the small amount identified is not likely to impact the safety or immunogenicity of PF-06410293.*

3.2.R.3.2.4. CHARGE HETEROGENEITY

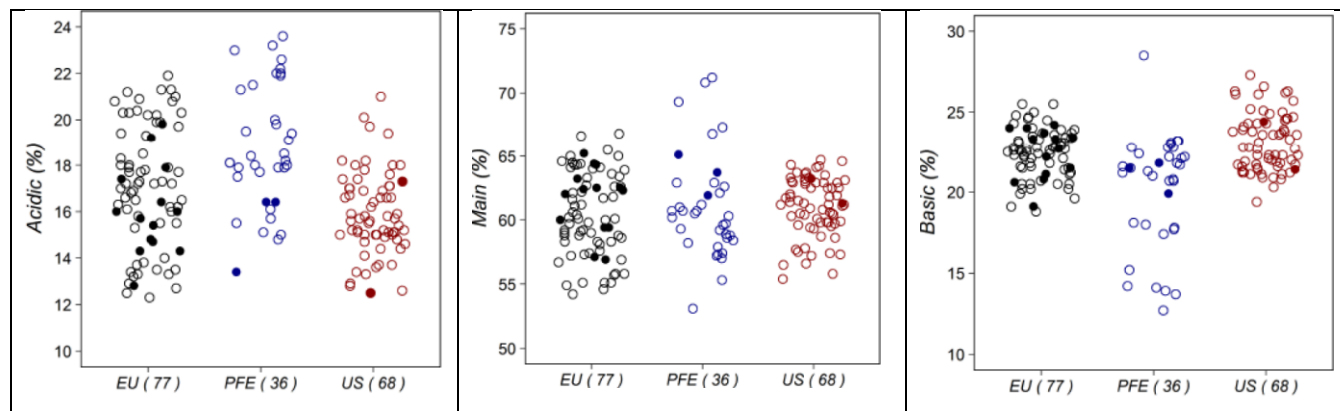
Analytical similarity in terms of charge heterogeneity was primarily evaluated using an imaged capillary electrophoresis (iCE) method. The peaks of the charge variances were fractionated using preparative CEX-HPLC and further characterized to understand the composition of each charge fractions as well as the biological activities of the peaks.

Similarity Assessment by iCE

The similarity assessment for acidic, basic, and main species included the comparison of 36 PF-06410293 DS and DP lots, to 68 US-Humira and 77 EU-Humira drug product lots. Results are summarized in the table (*modified from Table 3.2.R.3.2.4-1 through Table 3.2.R.3.2.4-4 in the submission*) and the figures (*Figure 3.2.R.3.2.4-2 to Figure 3.2.R.3.2.4-4 in the submission*) below:

	Region	N	Mean	SD	CV (%)	Min	Max
Acidic Species %	EU	77	17.0	2.59	15.2	12.3	21.9
	Pfizer	36 (Total)	18.8	2.69	14.3	13.4	23.6
		10 (Independent)	18.9	2.70	14.3	15.5	23.0
	US	68	15.9	1.82	11.5	12.5	21.0
Basic Species %	EU	77	22.4	1.53	6.8	18.8	25.5
	Pfizer	36 (Total)	20.2	3.47	17.2	12.7	28.5
	US	68	23.1	1.78	7.7	19.4	27.3
Main %	EU	77	60.6	3.23	5.3	54.2	66.8
	Pfizer	36 (Total)	61.1	4.07	6.7	53.1	71.2
	US	68	61.0	2.29	3.8	55.4	64.7

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



The solid circles represent the lots that have been used in the clinical trials

Statistical analysis was performed on acidic species to compare 10 independent PF-06410293 lots to all US-Humira and EU-Humira lots. Based on the quality range derived from US licensed product lots (10.4-21.3 % based on mean $\pm$ 3SD), 99% of EU-Humira lots fall within the established range, but only 70% of independent PF-06410293 lots fall within the range. The highest of acidic species in Pfizer lots is <3% greater than the maximum value observed for the US-Humira lots. These differences of acidic species have been justified as not impacting the safety, immunogenicity, or efficacy of PF-06410293 (*see review below for the characterization results*).

Reviewer’s Comment: 70% of independent PF-06410293 lots fall within the quality range (mean $\pm$ 3SD) determined by the US-Humira lots. In the characterization section (*see below*), the applicant provided data to demonstrate that the main and basic fractions of PF-06410293, US-Humira and EU-Humira showed comparable level of potency to the reference standard (measured by inhibition of apoptosis assay). The applicant also quotes literature to demonstrate that the minor differences in basic peak compositions observed are not expected to have impact on the safety or efficacy of the product. Thus, it is acceptable that statistical analysis for similarity (quality range) was performed on acidic species only. The characterization study did identify reduced biological activity for the first acidic fraction (peak 1), the difference is due to a clipped species in the CDR3 region which can be measured

and controlled by reducing CGE. The abundance of peak 1 was $\leq 3.0\%$ of the total peaks area in all lots tested (range 2.2-2.6%). Considering that the highest of acidic species in Pfizer lots is <3% more than the maximum value observed for the US-Humira lots, the observed difference, although statistically significant (i.e., failed quality range acceptance criteria), is not likely to be clinically significant.

Characterization

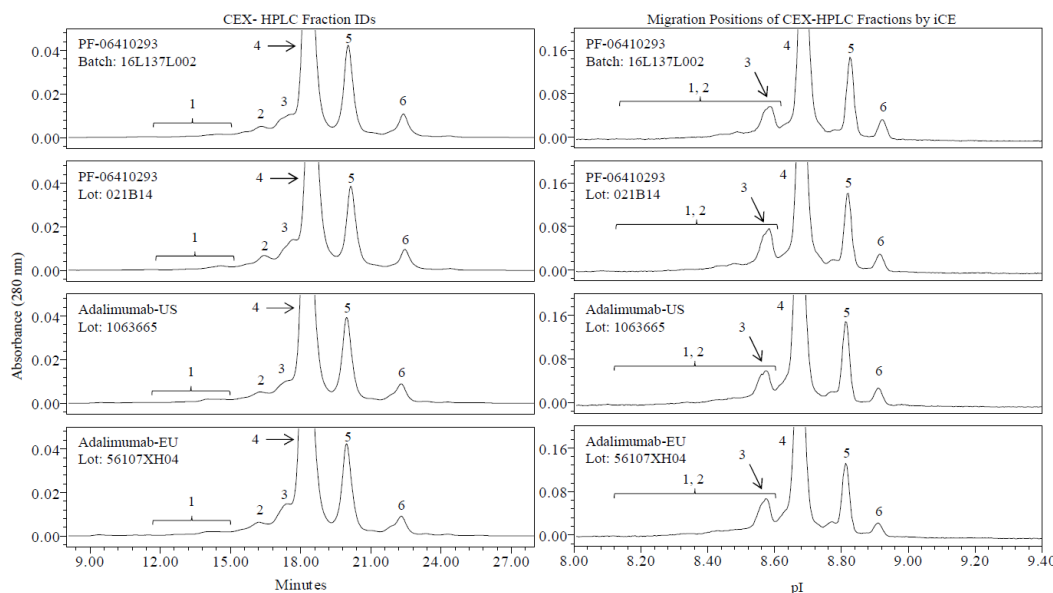
Acidic, main, and basic peaks were fractionated using preparative CEX-HPLC for detailed structural and functional characterization and biological activity assessment. The lots used for the characterization study includes aged Pfizer lot and EU lot towards the end of shelf life (see table below for lots details).

Source	Lot	Approximate Age at Time of Analysis (months) ^a	Sample Information ^b
PF-06410293	16L137L002	11	PV drug substance; PRM parent batch
	021B14	41	Aged DP
US-Humira	1063665	15	DP
EU-Humira	56107XH04	24	DP

Approximate age was determined by subtracting the date of manufacture (DOM) from the date when CEXHPLC manual peak collection was initiated for each material. DOM for innovator materials was calculated by subtracting 24 months from the expiry date.

The isolated CEX-HPLC fractions were individually analyzed using iCE. Peak number assignments are shown below (Figure 3.2.R.3.2.4-2.).

Figure 3.2.R.3.2.4-2. CEX-HPLC Individual Fraction Assignments for PF-06410293, PF-06410293 (aged), Adalimumab-US, and Adalimumab-EU and Correlation to iCE Peaks



3.2.R.3.2.4.1.1. LC/MS Characterization of Charge Isoforms

Charge fractions were evaluated by SEC/ESI MS (acetonitrile mobile phase), LC/MS/MS – Peptide Mapping (Lys-C/Trypsin) and LC/MS-subunit analysis (IdeS digestion). Results are summarized in the table shown on next page (table adapted from Table 3.2.R.3.2.4-2. of the submission).

CEX fraction Peaks	CEX-HPLC Peak Relative Abundance % ^a	Isoform Identification ^b			Results	
		Pfizer lot 021B14 16L137L002	US-Humira	EU-Humira		
Acidic	1	PF (021B14): 2.2 PF (16L137L002): 2.2 US-Humira: 2.4 EU-Humira: 2.6	Glycation ^c . Clipped between H Chain Ala105 and Ser106 Non-consensus sialylated N-linked glycosylation (G2F+2NeuAc on 1 H chain Asn163).	Glycation ^c . Clipped between H Chain Ala105 and Ser106 Non-consensus neutral N-linked glycosylation (G2F on 1 H chain Asn163).	Glycation ^c . Clipped between H Chain Ala105 and Ser106 Non-consensus neutral N-linked glycosylation (G2F on 1 H chain Asn163).	All three products contained glycation, 1 H chain clipped between Ala105 and Ser106, and various N-linked glycol-forms on Asn163 on 1 H chain.
	2	PF (021B14): 5.3 PF (16L137L002): 4.1 US-Humira: 4.8 EU-Humira: 4.4	Glycation ^c . Sialylated N-linked glycans (1 H chain with 2NeuAc on Asn301).	Glycation ^c .	Glycation ^c .	All three products contained glycation. PF-06410293 contained di-sialylated N-linked glycans on Asn301 on 1 H chain.
	3	PF (021B14): 8.0 PF(16L137L002): 6.9 US-Humira: 5.6 EU-Humira: 6.7	1 H chain with Asn388 deamidation 1 H chain with Asn393 deamidation. Sialylated N-linked glycans (1 H chain with 1NeuAc on Asn301). Glycation ^c	1 H chain with Asn388 deamidation. 1 H chain with Asn393 deamidation. Glycation ^c	1 H chain with Asn388 deamidation. 1 H chain with Asn393 deamidation. Glycation ^c .	All three products contained deamidation on 1 H chain with Asn388, 1 H chain with Asn393 deamidation, and glycation. PF-06410293 contained mono-sialylated N-linked glycans on Asn301 on 1 H chain.
Main ^b	4	PF(021B14): 58.7 PF(16L137L002): 60.5 US-Humira: 63.3 EU-Humira: 63.4	4-chain antibody with lysine absent from C termini of both H chains (G0F/G0F or G0F/G1F)	4-chain antibody with lysine absent from C termini of both H chains (G0F/G0F or G0F/G1F)	4-chain antibody with lysine absent from C termini of both H chains (G0F/G0F or G0F/G1F)	No difference, predominant isoform for all products is 4-chain antibody with lysine absent on C-termini of both H chains.

Basic	5	PF (021B14): 19.4 PF(16L137L002): 19.7 US-Humira: 18.1 EU-Humira: 17.2	1 H chain with C-terminal lysine. 1 H chain terminated with amidated proline. 1 L chain with a signal peptide sequence extension, ³ VHS ⁻¹ .	1 H chain with C-terminal lysine. 1 H chain terminated with amidated proline.	1 H chain with C-terminal lysine. 1 H chain terminated with amidated proline.	All three products contained 1 H chain with C-terminal lysine or 1 H chain terminated with amidated proline. PF-06410293 also contained 1 L chain with a signal peptide sequence extension, ³ VHS ⁻¹
	6	PF (021B14): 6.3 PF (16L137L002): 6.6 US-Humira: 5.7 EU-Humira: 5.7	2 H chains with C-terminal lysine. 2 H chains terminated with amidated proline. 1 H chain with a signal peptide sequence extension, ³ VHS ⁻¹	2 H chains with C-terminal lysine. 2 H chains terminated with amidated proline.	2 H chains with C-terminal lysine. 2 H chains terminated with amidated proline.	All three products contained 2 H chains with C-terminal lysine or 2 H chains terminated with amidated proline. PF-06410293 also contained 1 H chain with a signal peptide sequence extension, ³ VHS ⁻¹ .

a. Representative approximate relative peak area of each collected CEX-HPLC peak (i.e. based on the chromatographic UV profile).
 b. The main charge isoform in all collected fractions is a 4-chain molecule with 2 light chains and 2 heavy chains with des-Lys and two N-linked glycosylation consensus sites occupied with neutral N linked glycans (primarily G0F and G1F). All acidic and basic charge isoforms share most of these fundamental structural features with additional modifications as described in the table.
 c. Due to low abundance, it was not possible to localize glycation.

Main peak contains predominantly 4-chain antibody, both H chains without C-terminal lysine, and one H chain containing G0F and the other H chain containing either a G0F or a G1F N-linked glycan. No difference was observed among Pfizer lots, US-Humira or EU-Humira.

Basic peaks:

Peak 5 of all lots contain C-terminal lysine on one H chain as the predominant isoform, and an isoform with C-terminal amidated proline on one H chain. However, Pfizer lots also contained one L chain with a signal peptide sequence extension, ⁻³VHS⁻¹, which were not observed on the US-Humira or EU lots.

Peak 6 of all lots contain C-terminal lysine on both H chains as the predominant isoform, and an isoform with C-terminal amidated proline on both H chains. Pfizer lots also contain one H chain with a signal peptide sequence extension, ⁻³VHS⁻¹, which were not observed on the US-Humira or EU lots.

The applicant provided literature publications to support the following claims: C-Terminal lysine variants have no impact on PK or biological activity; C-terminal lysine residues of recombinant human IgG mAbs are lost in vivo, resulting in limited C-terminal heterogeneity; Amidated proline is considered a natural modification by the human immune system and does not affect antigen binding or Fc effector functions.

***Reviewer’s Comment:** Given its position away from the functional groups of the product, the signal peptide extension in PF-06410293 is unlikely to affect biological activity.*

As discussed in the following section of “3.2.R.3.2.4.1.2. Characterization by Carboxypeptidase B Treatment”, the differences seen in the percentage of basic species between PF-06410293, US-Humira and EU-Humira are mainly due to the different levels of C-terminal lysine. Published literature supports that C-terminal Lys residues of therapeutic human IgG mAbs are rapidly cleaved by endogenous serum carboxypeptidase B (CpB) in vivo and that its presence or absence does not impact in vivo efficacy of mAbs [Brorson, K, Jia, AY. Curr Opin Biotechnol. 2014;30C:140-6.]

Charged species can potentially impact product PK and bioavailability after subcutaneous injection. However, there is no definitive conclusion as limited research have conflicting results [Fathallah A.M. et al. J Pharm Sci. 2015 Feb; 104(2): 301–306].

Overall, the difference observed on the basic peak is not very likely to cause meaningful clinical impact.

Acidic peaks:

Peak 1 of all lots contains glycation, a 4-chain molecule with one H chain CDR3 clipped between Ala105 and Ser106, and various N-linked glycans on an additional non-consensus site at Asn163 on one H chain. However, Pfizer lots contained di-sialylated N-linked glycans on one H chain (Asn163), while US-Humira and EU-Humira contained neutral N-linked glycans on one H chain (Asn163).

Peak 2 of all lots contains glycation. Pfizer lots contained di-sialylated N-linked glycans on one H chain (Asn301, consensus site), which were not observed on US-Humira and EU-Humira.

Peak 3 of all lots contains Asn388 deamidation on one H chain, Asn393 deamidation on one H chain, and glycation. Pfizer lots contained mono-sialylated N-linked glycans on one H chain (Asn301, consensus site), which was not observed on US-Humira and EU-Humira.

***Reviewer’s Comment:** Acidic peak analysis indicates that acidic peaks of PF-06410293 contains sialylated N-linked glycans that are not detectable in US-Humira and EU- Humira. In the N-linked Glycan Structure Characterization (Section 3.2.R.3.2.3.), it was observed that <1% sialylated N-*

glycans in PF-06410293 (trace amount of sialylated N-glycans were also observed in US-Humira and EU-Humira during the glycan characterization study HILIC). Significance of the observed difference is discussed in the glycan characterization section.

3.2.R.3.2.4.1.2. Characterization by Carboxypeptidase B Treatment

Carboxypeptidase B is an enzyme that cleaves the basic amino acids (lysine and arginine) at the C terminus of proteins. After carboxypeptidase B treatment, the iCE profile of PF-06410293 was similar to that of US-Humira and EU-Humira and exhibit similarly low levels of basic species for all materials (mean relative area % of basic species are 5.4%, 6.0 % and 5.8% for US-Humira, Pfizer lot and EU-Humira, respectively).

Reviewer’s Comment: The results support that the predominant basic species in PF-06410293 is due to the presence of C-terminal lysine and that the difference seen in the percentage of basic species between PF-06410293, US-Humira and EU-Humira is mainly due to the different levels of C-terminal lysine.

3.2.R.3.2.4.1.3. Biological Activity of Charge Isoforms

PF-06410293, US-Humira, and EU-Humira charge fractions were evaluated for biological activity using the inhibition of apoptosis assay. Results are summarized in the table below (Table 3.2.R.3.2.4-5 of the submission),

CEX Fraction Peak Nmbers		PF-06410293 (021B14)		PF-06410293 (16L137L002)		US-Humira		EU-Humira	
		CEX Peak Relative Abundance (%) ^a	Potency (%)	CEX Peak Relative Abundance (%)	Potency (%)	CEX Peak Relative Abundance (%)	Potency (%)	CEX Peak Relative Abundance (%)	Potency (%)
Acidic	1	2.2	69	2.2	63	2.4	70	2.6	68
	2	5.3	95	4.1	90	4.8	100	4.4	93
	3	8.0	94	6.9	99	5.6	100	6.7	87
Main	4	58.7	96	60.5	97	63.3	95	63.4	87
Basic	5	19.4	93	19.7	94	18.1	100	17.2	98
	6	6.3	100	6.6	92	5.7	99	5.7	94

Reduced biological activity was observed in peak 1 of the acidic species. All other peaks, i.e., the main peak, basic peaks, as well as peak 2 and peak 3 of acidic species, showed similar level of potency. The applicant explains that, the reduced potency observed on peak1 is likely corresponding to the clipping of the H chain between Ala105 and Ser106. Because Ala105 and Ser106 are in the H chain CDR3, the clip of which could impact antigen binding and therefore result in decreased biological activity. (Note that the peak1 is at low relative abundance in all samples tested: 2.2%, 2.4% and 2.6% for PF-06410293, US-Humira and EU-Humira, respectively).

3.2.R.3.2.5. PRODUCT PURITY (HMMS, Fragment)

Analytical similarity assessment of high molecular mass species (HMMS) and monomer, mAb fragment and heavy chain (HC) + light chain (LC), as well as intact IgG, are reviewed in this section.

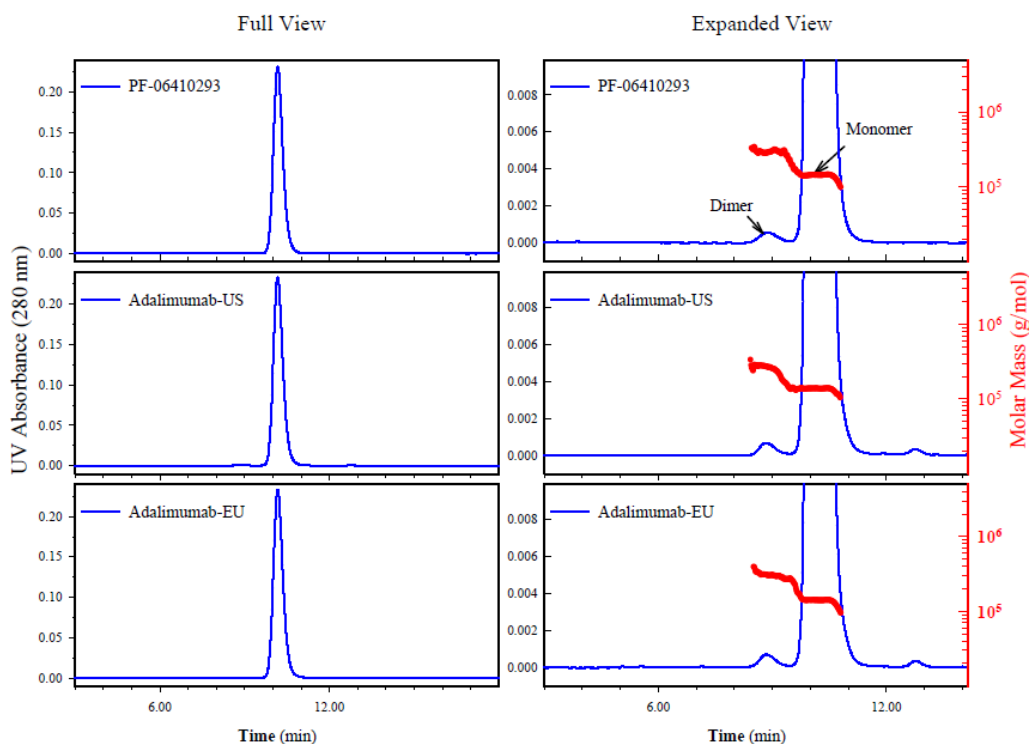
3.2.R.3.2.5.1. HMMS and Monomer (SEC, SEC-MALS and AUC)

Size exclusion chromatography with in-line multi-angle light scattering (SEC-MALS) and analytical ultracentrifugation sedimentation velocity (AUC-SV) were used to characterize HMMS in PF-06410293, US-Humira, and EU-Humira. Analytical similarity in terms of the HMMS and monomer

were evaluated by SEC on 36 lots of PF-06410293 DS and DP lots (including 10 independent lots) to 68 US-Humira and 77 EU-Humira drug product lots

SEC-MALS determines the weight-average molar mass of eluted fractionations of SE-HPLC. The weight-average molar mass for each resolved peak allows clear identification of dimer, trimer, and higher-order aggregate species. The applicant reports that the SEC-MALS system was maintained and calibrated according to the manufacturer's recommendations. Data were collected and analyzed using the manufacturer's software.

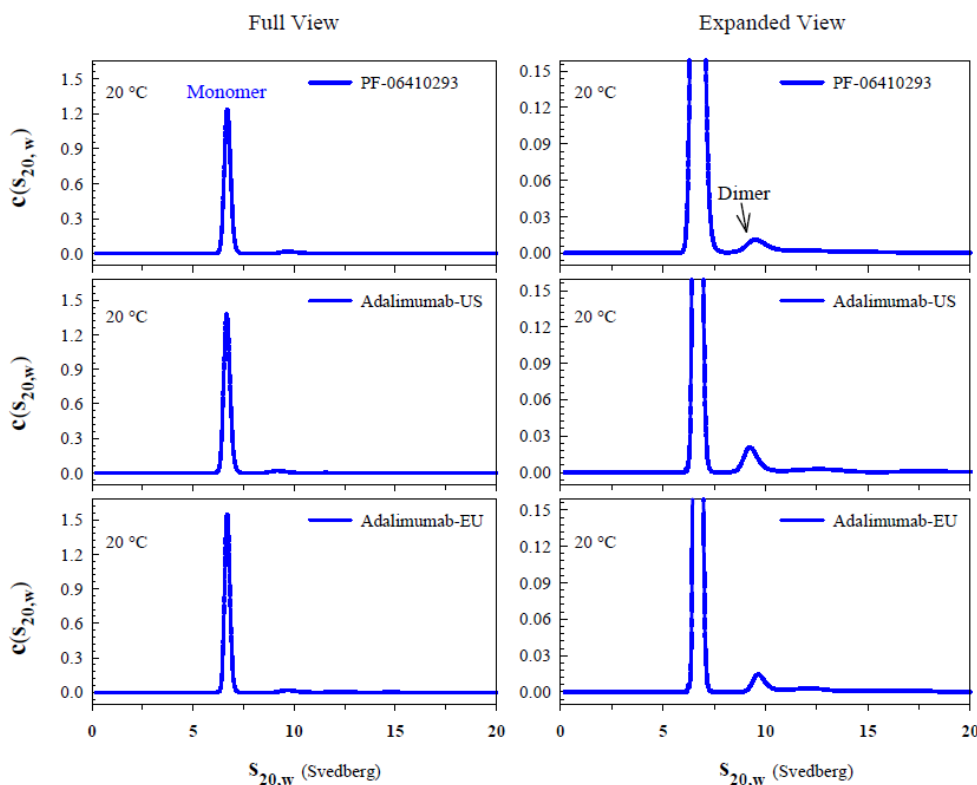
Figure 3.2.R.3.2.5-2. SEC-MALS Weight-Average Molar Mass Distribution Across SE-HPLC Profiles for PF-06410293, Adalimumab-US, and Adalimumab-EU



The applicant reports that SEC-MALS results show that the weight-average molar mass for the main peak was consistent with the monomeric four-chain adalimumab IgG1 molecule and the weight-average molar mass of the HMMS peak was consistent with that of an IgG1 dimer in PF-06410293, US-Humira, and EU-Humira samples.

AUC-SV was used to characterize HMMS. The test samples (diluted in buffer) are examined in solution in an ultracentrifuge cell, with minimal contact with solid surface, and without significant dilution during the separation by centrifugal force within the working range of the UV absorbance detector: ~0.2 - 1 mg/mL. The concentration of the final samples was determined by absorbance at 280 nm. The results are analyzed using manufacturer's recommended software and reported in the form of continuous sedimentation coefficient distribution, $c(s_{20,w})$ vs. $s_{20,w}$ profile, where raw sedimentation coefficients were corrected for the standard state of water at 20 °C. The applicant reports that the AUC instrument was maintained and calibrated according to the manufacturer's recommendations. The applicant claims that the limit of quantitation for AUC-SV is 1%.

Figure 3.2.R.3.2.5-3. AUC-SV Continuous c(s) Size Distribution Profiles of PF-06410293, Adalimumab-US and Adalimumab-EU



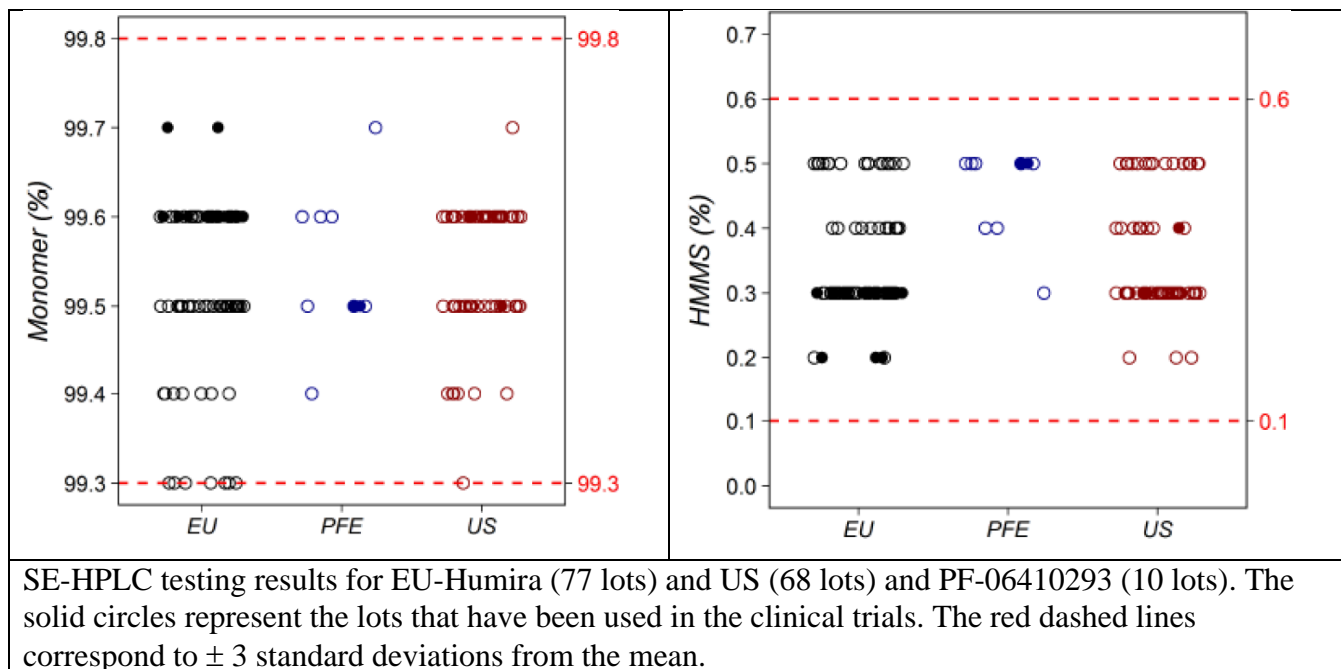
The applicant claims that AUC-SV confirmed the absence of quantifiable HMMS larger than dimer in PF-06410293, US-Humira, and EU-Humira. Similar dimer content (below quantitation limit of 1%) was observed by AUC-SV for each material.

Reviewer’s Comment: The zoomed-in AUC profiles appear to indicate that the products may contain HMMW species that are larger than dimers (see the bump centered around 12.5 Svedberg), but only trace amount exist in each product.

SEC method was used for the similarity assessment for monomer and HMMS. Thirty-six (36) lots of PF-06410293 DS and DP lots (including 10 independent lots) to 68 US-Humira and 77 EU-Humira drug product lots were compared, and the assessment results are summarized in the Table below (table modified by the reviewer):

Monomer (%)						
Region	N	Mean	SD	CV (%)	Min	Max
EU	77	99.5	0.10	0.1	99.3	99.7
Pfizer	36 (total)	99.5	0.07	0.1	99.4	99.7
	10 (Independent)	99.5	0.08	0.1	99.4	99.7
US	68	99.5	0.08	0.1	99.3	99.7
HMMS (%)						
EU	77	0.4	0.09	25.8	0.2	0.5
Pfizer	36 (total)	0.5	0.05	10.9	0.3	0.5
	10 (Independent)	0.05	0.07	15.2	0.3	0.5
US	68	0.4	0.09	25.6	0.2	0.5

Statistical analysis was performed on the monomer and HMMS peak results using 10 independent PF-06410293 lots, and all US-Humira and EU-Humira lots. The quality range derived from US licensed product lots is 0.1 – 0.6% for HMMS and 99.3 – 99.8 % for monomer, based on mean $\pm$ 3SD. As presented in Figure 3.2.R.3.2.5-5 & 6 of the submission (copied below), 100% of PF-06410293 and 91% of EU-Humira lots are within the established range for monomer, and 100% of PF-06410293 and EU-Humira lots are with the established range for HMMS. (*reviewer’s note: It appears that Pfizer consider the 99.3% monomer results for 7 EU lots not within the established range of 99.3 – 99.8 % for the monomer. Thus, only 91% of EU-Humira lots are within the established range for monomer*). Thus, both PF-06410293 and EU-Humira lots meet the acceptance criteria for high similarity to US-Humira product.



The applicant reports that SE-HPLC showed similar results amount the PF-06410293, US-Humira and 77 EU-Humira lots in terms of relative percentage of monomer peak, levels of HMMS, and trace levels of low molecular mass species (LMMS, consistently below 0.2%).

Reviewer’s Comment: *The characterization results by SEC-MALS indicates that the SE-HPLC HMMS fraction contains dimers for all samples. The SEC monomer and HMMS results comparison conclude that the PF-06410293, US-Humira and EU-Humira are similar to each other. The AUC results confirm that the products contain no or trace amount of HMMS that are larger than dimers.*

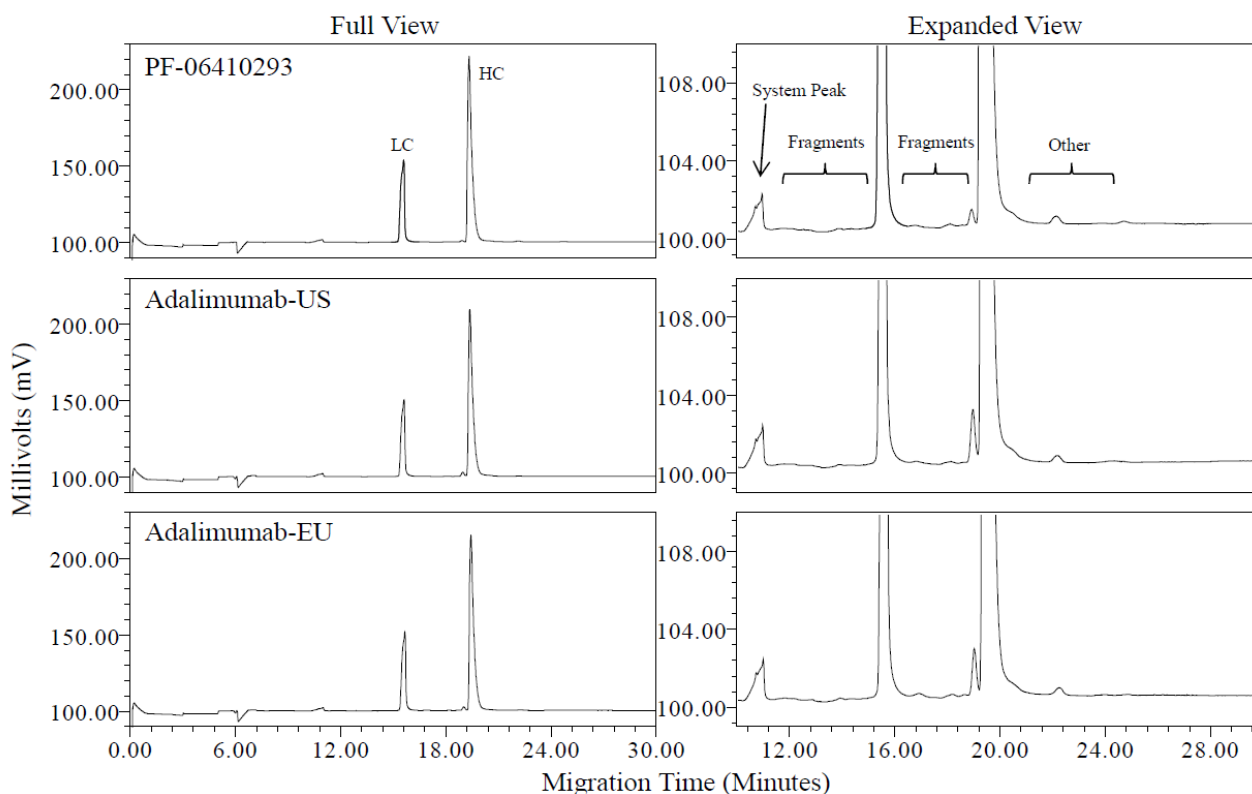
The SE-HPLC method used for the analytical similarity assessment is the same as the release testing method for the DS and DP. It was validated for quantifying monomer and HMMS and reviewed by Dr. Nailing Zhang.

The applicant did not provide method qualification reports for SEC-MALS and AUC test. Considering the results were not used for quantitative comparison and these two methods are common analytical methods used in protein characterization, the risk is low and assay qualification data were not requested.

3.2.R.3.2.5.2. Fragments and Heavy Chain ± Light Chain - rCGE

The level of product-related fragments presented in PF-06410293, US-Humira, and EU-Humira was analyzed by capillary gel electrophoresis performed under reducing conditions (rCGE). As shown in the representative r-CGE profiles (see Figure below), all peaks eluting prior to the HC (except for the LC peak) combined is reported as the fragment, and “other” are all peaks eluting after HC combined. The “other” species are believed to be non-reducible HH and HL species. The trace amount of the “Other” species is not reported but included in calculation of the reported results.

Figure 3.2.R.3.2.5-7. CGE (Reducing) Profiles of PF-06410293, Adalimumab-US and Adalimumab-EU



The similarity assessment for HC+LC and fragment were conducted using 36 PF-06410293 lots, 68 US-Humira and 77 EU-Humira drug product lots. The study results are summarized in the table below (modified from Table 3.2.R.3.2.5-4, -5, -6).

Region	N	Mean	SD	CV (%)	Min	Max
Heavy + Light Chain (%)						
EU	77	98.9	0.23	0.2	98.3	99.3
Pfizer	36	99.4	0.21	0.2	98.7	99.7
US	68	98.7	0.19	0.2	98.1	99.0
Fragment (%)						
EU	77	1.0	0.15	15.0	0.7	1.3
Pfizer	36 (total)	0.4	0.05	14.2	0.3	0.4
	10 (independent)	0.4	0.05	15.1	0.3	0.4
US	68	1.2	0.13	11.1	1.0	1.6

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

A “Tier 2” statistical analysis was performed on the fragment results using 10 independent PF-06410293 lots, and all US-Humira and EU-Humira lots. The quality range derived from US licensed product lots is 0.8 – 1.6% based on the mean $\pm$ 3SD. As presented in Figure 3.2.R.3.2.5-9 (see below), 95% of EU lots are within the established range, indicating that EU lots meet the acceptance criteria for high similarity to US lots. However, lower level of fragment was observed in PF-06410293 lots, and none fall within the established range.

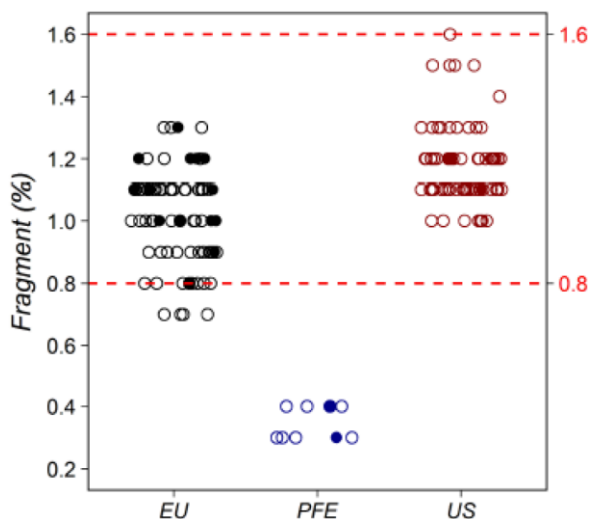


Figure 3.2.R.3.2.5-9: Testing results from 77 adalimumab EU lots, and 68 US-Humira lots and 10 independent PF-06410293 lots. The red dashed lines correspond to $\pm$ 3 SD from the mean. The solid circles represent the lots that have been used in the clinical trials.

In addition, the applicant also evaluated PF-06410293, US-Humira, and EU-Humira using reduced SDS-PAGE analysis (Coomasie Blue stain) as an orthogonal method. Similar major band patterns HC (Heavy Chain) and LC (Light Chain) were observed on all three products (*reviewer’s note: as shown in Figure 3.2.R.3.2.5-10 of the submission, there were no detectable fragment bands on the gel*). Since this method is less resolving and not quantitative thus only applied to one lot each of PF-06410293, US-Humira, and EU-Humira as a confirmatory measure.

Reviewer’s Comment: *The reduced CGE method used for the analytical similarity assessment is the same as the release testing method for the DS and DP. The method and validation are found acceptable by Dr. Nailong Zhang (See DS review). During the similarity assessment evaluation, slightly lower levels of fragments were observed in PF-06410293 lots than those in the US-Humira and EU-Humira lots. However, the observed minor difference by rCGE is not likely to be clinically meaningful, as all products contained high levels of HC + LC (98.1- 99.7%) and low levels of fragments (0.3-1.3%).*

3.2.R.3.2.5.3. Intact IgG - nrCGE

The level of intact IgG was analyzed by capillary gel electrophoresis performed under non-reducing conditions (nrCGE). The intact IgG is shown as the predominant peak on the nrCGE electropherograms (*representative profiles of PF-06410293, US-Humira, and EU-Humira are provided in Figure 3.2.R.3.2.5.-11 of the submission*). Some small peaks eluted before the main peak are believed to be fragments/partial antibody molecules.

The similarity assessment for intact IgG were conducted on 36 PF-06410293 lots, 68 US-Humira and 77 EU-Humira drug product lots. The results are summarized in the table below (modified from Table

3.2.R.3.2.5-7 and Table 3.2.R.3.2.5-8), while the individual lot data are displayed in Figure 3.2.R.3.2.5-12 below.

Region	N	Mean	SD	CV (%)	Min	Max
EU	77	97.2	0.83	0.9	91.1	98.1
Pfizer	36 (total)	97.3	0.47	0.5	96.5	98.0
	10 (independent)	97.2	0.40	0.4	96.7	98.0
US	68	97.5	0.86	0.9	91.7	98.3

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

A “Tier 2” statistical analysis was performed on the intact IgG results using 10 independent PF-06410293 lots, and all US-Humira and EU-Humira lots. The quality range derived from US licensed product lots is 94.9 – 100.1% for intact IgG based on the mean $\pm$ 3SD. As presented in Figure 3.2.R.3.2.5-13, the intact IgG results indicate that 97% of EU-Humira lots and 100% of independent PF-06410293 lots are within the established range, meeting the acceptance criteria for high similarity.

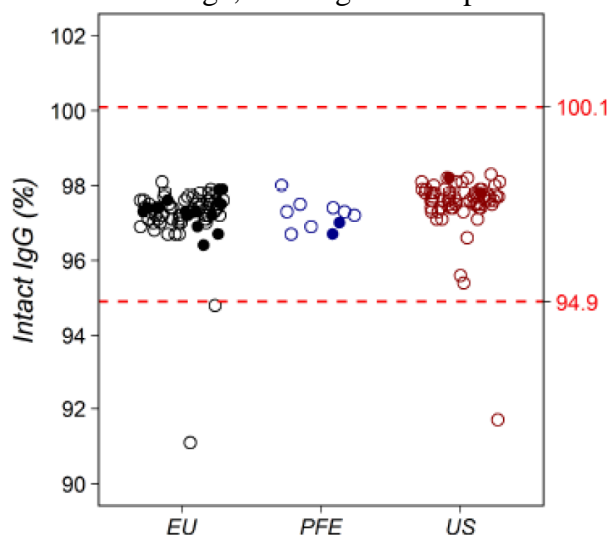


Figure 3.2.R.3.2.5-13: Testing results from 77 adalimumab EU lots, and 68 US-Humira lots and 10 independent PF-06410293 lots. The red dashed lines correspond to $\pm$ 3 SD from the mean. The solid circles represent the lots that have been used in the clinical trials.

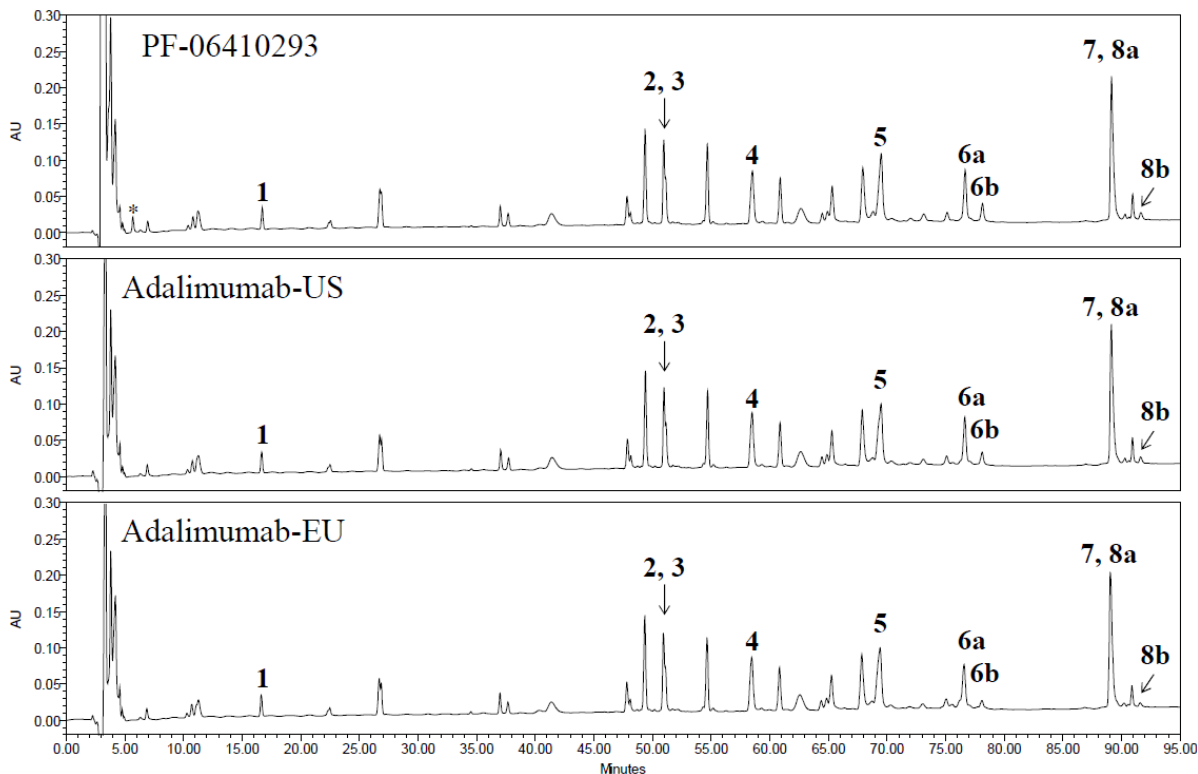
Reviewer’s Comment: The nrCGE method used for the analytical similarity assessment is the same as that used for release testing of the DS and DP. The method and validation are found acceptable by Dr. Nailing Zhang (See DS review). Study results support a determination that PF-06410293 is highly similar to US-Humira in terms of in terms of the intact IgG by nrCGE. The data also support the analytical portion of the scientific bridge.

3.2.R.3.2.6. DISULFIDE BONDS

There are 32 cysteine (Cys) residues in adalimumab, all are expected to be present as disulfide bonds: two disulfide bonds in each light chain, four in each heavy chain, one inter-chain disulfide between each light and heavy chain, and two inter-chain disulfides between the heavy chains forming the hinge region. Orthogonal analytical methods, LC/MS–non-reduced peptide mapping (Lys-C), and sulfhydryl analyses, were used to evaluate the disulfide bonds of the adalimumab.

3.2.R.3.2.6.1. Characterization of Disulfide Bonds

To determine the presence and location of disulfide bonds, samples of PF-06410293, US-Humira, and EU-Humira were initially denatured and alkylated (to prevent disulfide bond scrambling), digested using Lys-C endoprotease, and then analyzed by reversed-phase high performance liquid chromatography with UV detection at 214 nm and identified by on-line electrospray ionization mass spectrometry (LC/MS). The chromatographic profiles of PF-06410293, US-Humira, and EU-Humira were essentially superimposable:



The observed masses for the respective peaks representing disulfide bonded peptides were highly consistent with the expected non-reduced Lys-C peptides from adalimumab as shown in Table 3.2.R.3.2.6-1 of the submission. In addition, no Cys-containing peptides with mis-paired disulfide bonds were detected. The LC/MS – non-reduced peptide mapping (Lys-C) results for PF-06410293, US-Humira, and EU-Humira confirms that the disulfide linkages for each product were identical and consistent with the IgG1-kappa antibody structure.

Name ^a	Peak #	Peptides		Disulfide Bond Linkage	Theoretical Mass (Da)	Observed Mass Differences (Da) ^b			Results
		1	2			PF-06410293	Adalimumab-		
							US	EU	
Intrachain									
VL	6a	L1L2 [1-42]	L4 [46-103]	C23-C88	10908.3716	0.0080	0.0098	0.0091	All predicted disulfide bonds were detected in all three products.
	6b	L1 [1-39]	L4 [46-103]		10626.2024	0.0105	0.0027	0.0129	
CL	4	L7 [127-145]	L13 [191-207]	C134-C194	3883.9237	-0.0022	-0.0014	-0.0006	
VH	5	H1 [1-43]	H3 [77-98]	C22-C96	7169.4685	-0.0031	-0.0006	0.0044	

Name ^a	Peak #	Peptides		Disulfide Bond Linkage	Theoretical Mass (Da)	Observed Mass Differences (Da) ^b			Results
		1	2			PF-06410293	Adalimumab-		
							US	EU	
CH1	7	H6 [138-151]	H7H8 [152-214]	C148-C204	7916.9193	-0.0034	-0.0076	0.0050	
CH2	2	H15 [253-278]	H20 [325-326]	C265-C325	3144.5141	-0.0021	-0.0018	-0.0006	
CH3	3	H26 [365-374]	H30 [419-443]	C371-C429	4087.9567	-0.0020	-0.0020	0.0000	
Interchain									
L-H	1	L14 [208-214]	H12 [223-226]	L C214-H C224	1260.4863	0.0007	0.0003	0.0005	
H=H	8a	H13H14 [227-252]	H13H14 [227-252]	C230-C230 and C233-C233	5454.7834	-0.0043	-0.0051	-0.0027	
	8b	H13 [227-250]	H13H14 [227-252]		5229.6356	-0.0053	-0.0029	0.0007	

3.2.R.3.2.6.1. Sulfhydryl Analyses

Side-by-side sulfhydryl analysis was performed on PF-06410293, US-Humira, and EU-Humira by UV/VIS spectroscopy using Ellman’s reagent. All three products exhibited low levels of sulfhydryls (0.2 ± 0.02, 0.3 ± 0.02 and 0.3 ± 0.03 mol SH/ mol mAb for PF-06410293, US-Humira, and EU-Humira, respectively) indicating that very few unpaired cysteine residues were present. This is consistent with the presence of primarily disulfide bonds as determined by the LC/MS method.

Reviewer’s Comment: *The analytical similarity assessment results support a determination that PF-06410293 is highly similar to US-Humira in terms of in terms disulfide bonds structure. The data also support the analytical portion of the scientific bridge.*

3.2.R.3.2.6. HIGH ORDER STRUCTURE

Structural characterization for proteins in the native state in solution were evaluated by far-ultraviolet circular dichroism (far-UV CD) and Fourier transform infrared (FTIR) spectroscopy for the secondary structure, and the near-ultraviolet circular dichroism (near-UV CD) and intrinsic fluorescence emission spectroscopy for the tertiary structure. Differential scanning calorimetry (DSC) was used to characterize the thermal unfolding of adalimumab domains, which is indicative of overall integrity of the higher order structure. X-ray crystallography was collected for the visualization of the secondary and the tertiary structure of proteins at high resolution.

Closely matching spectra by all spectroscopic methods and superimposable crystal structures indicates that PF-06410293, US-Humira and EU-Humira have similar higher order structures.

Reviewer’s comment: *No differences were identified in the high order structure among the three products.*

3.2.R.3.2.6. PROTEIN CONCENTRATION

The protein concentration is determined by the UV spectroscopy method which is also used for product release and stability test.

A “Tier 2” statistical analysis was done based on the results from 13 PF-06410293 lots, 68 US-Humira and 77 EU-Humira lots, using quality range derived from the 68 US-Humira lots (mean± 3 SD). As illustrated in the plot below (*Figure 3.2.R.3.2.8-1 from the submission*), 92% PF-06410293 and 99 %

EU-Humira lots met the “tier 2” acceptance criteria when compared with US-Humira. *These results support that PF-06410293, US-Humira, and EU-Humira drug product have similar protein concentrations.*

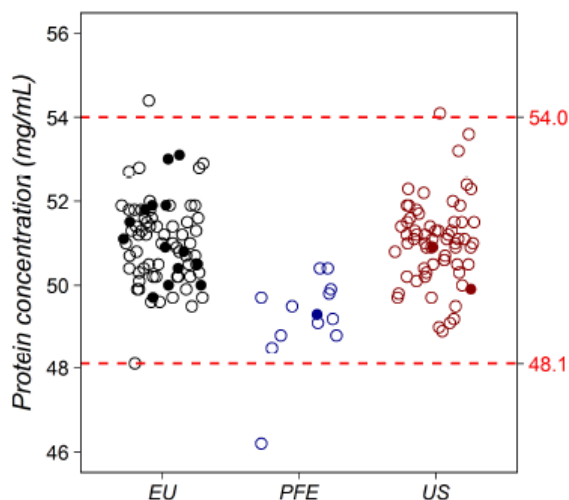


Figure 3.2.R.3.2.8-1. The results of protein concentration. The red dashed lines represent the upper and lower limits of the quality range. Solid circles represent the lots used in the clinic.

3.2.R.3.3. COMPARATIVE FORCED DEGRADATION STUDIES

Forced degradation studies were carried out to support similarity of PF-06410293, US-Humira and EU-Humira. Product quality attribute changes were evaluated under thermal stress (40°C for 3 months), light exposure (8.0 klux, 25°C for 7 days), forced deamidation (50mM phosphate buffer, pH7.5, 40°C, 3 weeks) and forced oxidation (peracetic acid) conditions. The forced degradation studies results indicate that the relative changes in stability-indicating quality attributes are similar regardless of the age and formulation buffer of the starting products. The applicant explains that obtaining lots of US-Humira and EU-Humira that represent initial time of manufacture (release or “time zero”) is not possible. Thus, a comparison of the relative changes is more meaningful than the absolute value at each time point during the forced degradation study.

3.2.R.3.3.1. Elevated Temperature

Forced degradation at elevated temperature was split into three studies. The lots used and the purpose of these three studies are summarized in the table below:

Study	Source	Configuration	Number of lots	Comparison
Initial study for Adult Configuration (40 mg/0.8 mL PFS)	Pfizer	40 mg/0.8 mL PFS	3	Compare PF-06410293 manufactured drug product to licensed products to assess similarity. Compare licensed products to one another to assess similarity of US-Humira to EU-Humira
	US	40 mg/0.8 mL PFS	3	
	EU	40 mg/0.8 mL PFS	3	
Initial study for Pediatric Configuration (PFS, vial)	Pfizer	20 mg/0.4 mL PFS	1	Compare all pediatric configurations of PF-06410293 to all pediatric configurations of reference product to assess comparability of configurations.
	US	20 mg/0.4 mL PFS	2	
	Pfizer	10 mg/0.2 mL PFS	1	
	US	10 mg/0.2 mL PFS	2	
	Pfizer	40 mg/0.8 mL Vial	1	
	EU	40 mg/0.8 mL Vial	2	

Study	Source	Configuration	Number of lots	Comparison
Final study for Adult and Pediatric Configuration (PFS, Vial)	Pfizer	40 mg/0.8 mL Vial	1	Compare and perform heightened characterization on multiple PF-06410293 lots of various ages to reference products to assess similarity.
	Pfizer	40 mg/0.8 mL PFS	2 (1 aged lot)	
	US	40 mg/0.8 mL PFS	1	
	EU	40 mg/0.8 mL PFS	1 (aged lot)	

The initial adult and pediatric configuration studies included lots covering all drug product configurations from PF-06410293, US-Humira and EU-Humira. The final study was performed to study thermal degradation impact on aged lots. Appearance, pH, protein concentration, HMMS, Monomer and LMMS by SEC, charge variants by iCE, fragments by rCGE, intact IgG by nrCGE, potency by cell-based assay, methionine oxidation by Limited Lysyl Endopeptidase Peptide and primary structure by LC/MS/MS-Peptide Mapping (Lys- C/Trypsin) were compared during the forced thermal degradation studies. Testing results for samples at time zero and at end of 3 months were reported. All results including the differences observed between time zero and at the end of 3 months, are provided in Table 3.2.R.3.3-4 to Table 3.2.R.3.3-13 of the submission. The following changes were observed over the thermal stress at 40°C for 3 months:

- Increase in acidic species with a corresponding decrease in main species by iCE were observed in all lots studied
- Decrease in monomer, increase in HMMS and increase in LMMS by SEC were observed in all lots studied.
- Increase in fragments by CGE were observed in all lots studied
- Increase in methionine oxidation were observed in all lots studied by Limited Lysyl Endopeptidase Peptide Mapping.
- LC/MS/MS – peptide mapping (Lys-C/trypsin) showed small increases in H Chain N-terminal glutamic acid cyclization at Glu1, oxidation of the Met256 and Met432, isomerization of Asp284, and deamidation of Asn388 and Asn393
- Apparent potency decreases were observed in all lots (95-107% potency range was observed at time zero potency range: and 76-97% were observed at 3 months). However, the applicant does not consider the observed as change in potency because all results were within acceptance criteria.

No new degraded species were observed in PF-06410293 as compared to US-Humira and EU-Humira. No meaningful changes were observed in other quality attributes after 3 months storage at 40°C.

The applicant compared the difference between the results obtained at 3 months at time zero and claims that the observed degradation profiles were similar for PF-06410293, US-Humira, and EU-Humira.

Comparison of representative chromatograms and electropherograms (SEC, iCE, CGE) and peptide mapping profiles, at time zero- and 3-months testing point, were also provided.

Reviewer’s Comment: *The testing results difference between time zero and 3 months at 40°C were comparable for all quality attributes except that the PF-06410293 appears to show less change by SEC results than those observed in US-Humira and EU-Humira (more decrease in % main peak and less increase in %HMMS and %LMMS). The decrease of %main peak by SEC during the thermal stress studies are 4.6 – 6.5%, 8.4 -12.7% and 8.2-11.7% for PF-06410293, US-Humira and EU-Humira, respectively. This slightly better apparent stability profile in terms of dimer and fragment formation observed in PF-06410293 is likely caused by formulation difference between the PF-06410293 and US-Humira and EU- Humira.*

3.2.R.3.3.2. Light Exposure

Three lots of PF-06410293 drug product (2 PFS lots one vial lot) and 2 lots each of US-Humira (2 PFS lots) and EU-Humira Lots (1 PFS lot and 1 vial lot) were exposed to approximately 8.0 klux of light for 7 days at a controlled temperature of 25 °C. Samples were tested at time zero and after 7 days of light exposure. Appearance, pH, protein concentration, HMMS, Monomer and LMMS by SEC, charge variants by iCE, fragments by rCGE, intact IgG by nrCGE, potency by cell-based assay, methionine oxidation by Limited Lysyl Endopeptidase Peptide and primary structure by LC/MS/MS-Peptide Mapping (Lys- C/Trypsin) were compared. No significant changes were detected by appearance, pH and protein concentration for all lots and all configurations of PF-06410293, US-Humira, and EU-Humira lots after 7 days of light exposure at 25 °C. The following changes after 7 days of light exposure at 25 °C were observed:

- Significant increase in acidic species and decrease in main species, as well as minor decrease in basic species, were observed for all product lots.
- Increase in HMMS were observed in all lots studied, and the increases are more significant in US-Humira and EU-Humira. Minor increase in LMMS were also observed in all lots.
- Increase in fragments and significant reduction in intact IgG were observed by CGE in all lots and the changes are more significant in US-Humira and EU-Humira lots.
- An increase in methionine oxidation (oxidation of H chain Met256 and Met432) are observed in all lots and the changes are more significant in US-Humira and EU-Humira lots
- Apparent potency decreases were observed in all lots, but all results were within acceptance criteria.

Reviewer's Comment: *The differences in degradation rate under light stress are most likely due to the formulation difference between the PF-06410293 and US- and EU-Humira. The forced light degradation study indicates that the PF-06410293 formulation may provide better protection of the product from light degradation.*

3.2.R.3.3.3. Forced Deamidation

To conduct forced deamidation study, the product solution is removed from the primary container, dialyzed into 50 mM phosphate buffer, pH 7.5, then normalized to a protein concentration of approximately 50 mg/mL, and incubated for 3 weeks at 40 °C. The materials were tested at time zero and after 3 weeks of incubation. One PF-06410293 DS lot, one US-Humira lot and one EU-Humira lot were studied. Appearance, pH, protein concentration, HMMS, Monomer and LMMS by SEC, charge variants by iCE, fragments by rCGE, intact IgG by nrCGE, potency by cell-based assay, and primary structure by LC/MS/MS-Peptide Mapping (Lys- C/Trypsin) were compared. No measurable changes were detected by appearance, pH, protein concentration or relative potency for all lots. The following changes after 3 weeks of forced degradation were observed:

- Significant increase in acidic species and decrease in main species, as well as some decrease in basic species, were observed for all product lots. The degree of change in acidic species are comparable among PF-06410293 and US-Humira and EU-Humira. However, more change in basic species was observed in US-Humira (the change in basic species after 3 weeks of forced deamination was -4.1%, -5.9% and -10% for PF-06410293, EU-Humira and US-Humira, respectively).
- Increase in HMMS and LMMS were observed in all lots studied. The degrees of increase were comparable among PF-06410293 and US-Humira and EU-Humira.
- Increase in fragments and reduction in intact IgG were observed by CGE in all lots. The degrees of change are comparable among PF-06410293 and US-Humira and EU-Humira lots.

- LC/MS – peptide mapping (Lys-C) showed an increase in deamidation of the H chain peptide 152DYF...NTK214, Asn388 and Asn393, isomerization of Asp284, and H chain N-terminal glutamic acid cyclization.

Comparison of representative chromatograms and electropherograms (SEC, iCE, CGE) and peptide mapping, at time zero- and 3-week testing point, were also provided.

3.2.R.3.3.4. Forced Oxidation with Peracetic Acid

PF-06410293 pre-excipient spike drug substance was formulated without methionine. Such formulated PF-06410293, US-Humira and EU-Humira were then incubated with increasing concentrations of peracetic acid to determine the most susceptible sites for oxidation. An acetic acid control was also included and demonstrated that the acetic acid found in the peracetic acid solution does not induce degradation. The treated samples were tested by LC/MS – peptide mapping (Lys-C), limited lysyl endopeptidase peptide mapping, cell-based potency assay, and binding to FcRn by SPR.

- Major oxidation sites are H chain Met256 and Met432 [by LC/MS – peptide mapping (Lys-C)]
- Met256 oxidation increases as peracetic acid concentration increases (by limited lysyl endopeptidase peptide mapping). The changes are comparable among PF-06410293 and US-Humira and EU-Humira.
- No change in relative potency up to the highest Peracetic acid level (258 µm) studied.
- Reduced FcRn binding was observed at 258µm Peracetic acid level for all lots studied ($\geq 58.0\%$ Met₂₅₆ oxidation was observed at 258µm Peracetic acid):

***Reviewer's Comment:** Forced degradation comparison results indicate that the PF-06410293 and US-Humira and EU-Humira follows the same degradation pathway. Although some apparent differences in degradation rates were observed, they may be explained by the different formulation used for PF-06410293 and Humira products. Overall, the Pfizer formulation appears to provide a slightly better protection of the product under the forced degradation conditions, specifically, the thermal, light and deamidation stresses. The minor differences observed in the forced degradation studies do not preclude a determination that PF-06410293 and US-Humira are highly similar or the establishment of the analytical portion of the scientific bridge.*



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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewer: Aimee L. Cunningham, Ph.D., M.P.H.
Quality Assessment Lead: Reyes Candau-Chacon, Ph.D.
Branch Chief: Patricia Hughes, Ph.D

BLA: 761118/0
Applicant: Pfizer
US License Number: 2060
Submission Reviewed: Original BLA
Product: PF-06410293 / Abrilada (adalimumab-xxxx)
Indication: rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, plaque psoriasis
Dosage Form: 50 mg/mL solution for s.c. injection
Manufacturing Sites: DS: Wyeth BioPharma, Andover, MA (FEI: 1222181)
DP: (b) (4) (FEI: (b) (4))
FDA Receipt Date: 11/16/2018
Action Date: 11/16/2019

Conclusion and Approvability Recommendation

This BLA was reviewed for microbial control, product quality microbiology, and sterility assurance and is recommended for approval.

Product Quality Microbiology Assessment

Pfizer has submitted BLA 761118 to license PF-06410293 (adalimumab-xxxx) and its associated drug substance and drug product manufacturing processes. The BLA was submitted via eCTD on 11/16/2018. This review contains the assessment of the drug substance and drug product manufacturing processes from a microbiological quality perspective.

Quality Microbiology Information Reviewed

Sequence number	Date	Description
0001	11/16/2018	Original BLA

Sequence number	Date	Description
0003	12/31/2018	IR responses
0004	01/04/2019	IR responses
0005	01/17/2019	IR responses
0015	06/24/2019	IR responses

The following Drug Master Files (DMFs) were referenced in support of this BLA. The status of each DMF is summarized below.

DMF #	DMF Holder	Type	Date Reviewed	Finding	Document Name
	(b) (4)	3	04/05/2018	Adequate	(b) (4)
		3	02/03/2017	Adequate	
			01/24/2019	Adequate	
		3	04/10/2018	Adequate	
		3	10/10/2018	Adequate	
		3	12/07/2017	Adequate	
		2	01/08/2018	Adequate	

Module 1

LABEL

The following dosage forms and strengths are described in the label:

- Injection: 40 mg/0.8 mL in a single-dose prefilled pen (ABRILADA Pen)
- Injection: 40 mg/0.8 mL in a single-dose prefilled glass syringe
- Injection: 20 mg/0.4 mL in a single-dose prefilled glass syringe
- Injection: 10 mg/0.2 mL in a single-dose prefilled glass syringe
- Injection: 40 mg/0.8 mL in a single-dose glass vial for institutional use only

Single-use PF-06410293 drug product is to be administered subcutaneously; dosages vary based on indication. The drug product can be left at room temperature for 15-30 prior to administration. Vials are to only be administered institutionally (hospital or clinic). Any unused portions should be discarded.

Reviewer's Comment: No studies are needed to support the label as written, as drug product is not reconstituted or diluted for administration.

SATISFACTORY

Module 3.2

DRUG SUBSTANCE

S.1 General Information

PF-06410293 is a proposed biosimilar to Humira (adalimumab). It is a recombinant IgG1κ monoclonal antibody which binds and neutralizes human tumor necrosis factor (TNF) in a dose-dependent fashion. It is produced from Chinese hamster ovary (CHO) cells.

SATISFACTORY

S.2 Manufacture

S.2.1 Manufacturers

Site	FEI	Responsibilities
Wyeth BioPharma LLC Division of Wyeth Pharmaceuticals One Burt Rd Andover, MA 01810	1222181	Cell bank manufacture and storage, DS manufacture, DS in-process control, release, and stability testing, DS storage
(b) (4)		In-process DS testing (b) (4)
Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin Dublin 22 Ireland	3004145594	Cell bank storage
(b) (4)		DS storage
(b) (4)		DS storage
(b) (4)		DS storage

Reviewer's Comment: Refer to Panorama for the updated status of all facilities.

SATISFACTORY

S.2.2 Description of the Manufacturing Process and Process Controls

Description of Process Steps

PF-06410293 DS manufacturing occurs at Wyeth BioPharma and uses CHO cells. A flow diagram documenting the manufacturing process is provided within the submission (Figure 3.2.S.2.2-1).

Batch and Scale Definition

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

DESCRIPTION IS SATISFACTORY

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SATISFACTORY

DRUG PRODUCT

Reviewer's Comment: The drug product portion of the BLA is organized into 3 DP sections in eCTD: vial, pre-filled syringe (PFS), and pre-filled pen (PFP). For ease of review assessment, this memo is organized by eCTD and all presentations will be covered together in each section so as to avoid repetition of identical sections.

P.1 Description and Composition of Drug Product

Regardless of presentation, PF-06410293 solution for s.c. injection is supplied at 50 mg/mL, pH 5.5. It is intended for single use and does not contain preservative. Different excipients are used compared to the reference product. The composition of PF-06410293 is outlined below.

Ingredient	Function	Unit Formula (mg/syringe or vial)			Unit Formula (mg/mL)
		10 mg	20 mg	40 mg	
PF-06410293	Active ingredient	10	20	40	50
L-histidine	(b) (4)	0.157	0.314	0.63	0.786
L-histidine HCl monohydrate		0.626	1.253	2.51	3.132
Edetate disodium dihydrate		0.01	0.02	0.04	0.05
Sucrose		17	34	68	85
L-methionine		0.04	0.08	0.16	0.2
Polysorbate 80		0.04	0.08	0.16	0.2
WFI		q.s. to 0.2 mL	q.s. to 0.4 mL	q.s. to 0.8 mL	q.s. to 1 mL

There are five DP presentations (outlined in the table below). Pictures of the PFP device before and after use are provided in Figure 3.2.P.1-1 with an exploded view in Figure 3.2.P.1-2. The final assembly includes the PFS, syringe clip, power pack subassembly and front subassembly. The label wraps around the outer housing.

Presentation	Dosage	Fill Volume	Container Closure System
Vial	40 mg	0.8 mL	2 mL vial, 13 mm stopper, aluminum seal and flip-off cap
PFS	40 mg	0.8 mL	1 mL long (b) (4) glass PFS with a 29-gauge thin walled ½ inch staked needle
	20 mg	0.4 mL	
	10 mg	0.2 mL	
PFP	40 mg	0.8 mL	PFS assembled into PFP autoinjector

SATISFACTORY

P.2 Pharmaceutical Development

(b) (4)

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(b) (4)

P.3 Manufacture

P.3.1 Manufacturers

Site	FEI	Responsibilities
[Redacted]	(b) (4)	DS storage, DP manufacture, primary packaging, sterility & endotoxin release testing, assembly of PFS, secondary packaging & labeling
Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin, Dublin 22 IRELAND	3004145594	DP release & stability testing
[Redacted]	(b) (4)	Assembly of PFP, labeling, release and stability testing, secondary packaging
[Redacted]	[Redacted]	Manufacture of PFP subassemblies

Reviewer's Comment: Refer to Panorama for the updated status of all facilities.

SATISFACTORY

P.3.2 Batch Formula



(b) (4)

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Patricia
Hughes Troost

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**Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum**

Date: 06/23/2019

From: Amy A. Devlin, OPQ/OPF/DIA

To: BLA File, STN 761118/0

Through: Thuy T. Nguyen, QAL, OPQ/OPF/DIA Branch 1

Subject: Inspection waiver memo for manufacture of ABRILADA™ (PF-06410293, adalimumab-xxxx) drug product (b) (4)

Applicant : Pfizer, Inc.

Facility : (b) (4)
FEI: (b) (4)

Product: ABRILADA™ (adalimumab-xxxx)

Dosage: Sterile liquid solution for injection, 40 mg/ 0.8 mL PFP, PFS; 20 mg/ 0.4 mL, 10 mg/ 0.2 mL PFS; 40 mg/ 0.8 mL vial, subcutaneous.

Indication: All indications approved for US-Humira except the indications protected under orphan drug exclusivity.

Waiver Recommendation

The ABRILADA™ (PF-06410293, adalimumab-xxxx) DP is a sterile liquid solution for injection. The DP is supplied as a single-dose syringe, vial, or pre-filled pen. All 5 presentations contain 50 mg/ mL PF-06410293 (b) (4); water for injection, EDTA, L-methionine, Polysorbate 80, Sucrose and L-Histidine.

This original biosimilar application was submitted to provide for drug product vial and syringe filling lines for final vial and syringe products for subcutaneous administration (b) (4). The proposed commercial manufacturing process for ABRILADA™ (vial) utilizes (b) (4)

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Signed:

Amy Devlin, Ph.D., OPF/DIA Reviewer _____

Haoheng Yan, Ph.D., OPQ/OBP ATL _____

Aimee Cunningham, Ph.D., OPF/DMA Reviewer _____

Patricia Hughes, Ph.D., OPF/DMA Branch Chief _____

Thuy T. Nguyen, MPH, OPF/DIA QAL _____



STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA #	761118
Related IND #:	114729
Product Name:	PF-06410293(adalimumab-Pfizer)
Strength	adalimumab, 50 mg/mL concentration
Indication(s):	the same as the approved Humira indications that are not currently protected under regulatory exclusivity provisions: rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA) 4 years and older, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease (CD), ulcerative colitis (UC), plaque psoriasis.
Applicant:	Pfizer
Dates:	11/16/2018
Statistical reviewer	Tianjiao Dai
Second reviewer	Chao Wang
Project Manager	Colette Jackson

Concur: _____

Meiyu Shen, Ph.D., Lead Mathematical Statistician, CDER/OTS/OB/DB VI
 Permutt, Thomas J, Ph.D., Associate Director, CDER/OTS/OB

CC List:

Yi Tsong, Ph.D., Division Director, CDER/OTS/OB/DB VI
 Leah S. Her, MS, PMP, OMPT/CDER/OND/OHOP/DOPII

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VI. APPENDIX 16

I. EXECUTIVE SUMMARY AND RECOMMENDATION

The CMC statistical reviewer, Tianjiao Dai, in the Office of Biostatistics reviewed the lot independence and the corresponding selection criteria used by sponsor for Tier 1 quality attributes (QA). An IR was sent to sponsor on April 23, 2019 for detailed justification of lot selection. After reviewing the response received on April 30, 2019, the reviewer thinks the lot selection process and criteria are appropriate and acceptable. Statistical analysis with equivalence test based on the assay results from these selected batches should lead to valid conclusion of Tier 1 QA similarity.

The reviewer analyzed the comparative results of two critical quality attributes: % Relative Potency as assessed by Inhibition of Apoptosis Assay and Binding to sTNF Target Antigen by ELISA, which were recommended for equivalence testing analysis by the Office of Biotechnology. Tier 1 statistical equivalence testing was conducted using equivalence margins of $\pm 1.5\sigma_R$, where R represents the reference product US-licensed Humira (referred to as adalimumab-US), and EU-approved Humira (referred to as adalimumab-EU). 10 PF-06410293 lots (3 DS batches and 7 DP lots), 68 adalimumab-US drug product lots, and 77 adalimumab-EU drug product lots were used for equivalence testing for % Relative Potency as assessed by Inhibition of Apoptosis Assay. The results are summarized in Table 1.

Table 1: Equivalence testing results for Inhibition of Apoptosis Assay (% Relative Potency)

Comparison	# of lots	Mean Difference, %	90% Confidence Interval for Mean Difference, %	Equivalence Margin, %	Pass the Equivalence Testing?
PF-06410293 vs. US	(10, 68)	1.95	(-3.57, 7.47)	(-8.78, 8.78)	Yes
PF-06410293 vs. EU	(10, 77)	-1.16	(-7.01, 4.68)	(-11.36, 11.36)	Yes
EU vs. US	(77, 68)	3.11	(1.26, 4.96)	(-8.78, 8.78)	Yes

*The 90% confidence interval is adjusted by the sample size imbalance.

Ten PF-06410293 lots (3 DS batches and 7 DP lots), 10 adalimumab-US drug product lots and 10 adalimumab-EU drug product lots were used for equivalence testing for Binding to sTNF Target Antigen by ELISA. The results are summarized in Table 2.

Table 2: Equivalence testing results for the Binding to sTNF Target Antigen by ELISA

Comparison	# of lots	Mean Difference, %	90% Confidence Interval for Mean Difference, %	Equivalence Margin, %	Pass the Equivalence Testing?
PF-06410293 vs. US	(10,10)	-0.7	(-6.01, 4.61)	(-12.02, 12.02)	Yes
PF-06410293 vs. EU	(10,10)	-2.1	(-7.73, 3.53)	(-13.0, 13.0)	Yes
EU vs. US	(10,10)	1.4	(-5.07, 7.87)	(-12.02, 12.02)	Yes

*The 90% confidence interval is adjusted by the sample size imbalance.

As shown in Tables 1 and 2, the results from the statistical equivalence testing of % Relative Potency as assessed by Inhibition of Apoptosis Assay and Binding to sTNF Target Antigen by ELISA support a demonstration that the proposed biosimilar PF-06410293 is highly similar to adalimumab-US. The results also support the analytical portion of the scientific bridge to justify the use of adalimumab-US or adalimumab-EU in the PF-06410293 development program, in that the comparative results obtained for the adalimumab-EU can be applied to the adalimumab-US, and vice versa.

II. INTRODUCTION

On November 16, 2018, Pfizer Inc. submitted to the U.S. Food and Drug Administration (FDA) a 351(k) BLA which included an analytical similarity assessment of comparing the Tier 1 quality attributes for PF-06410293, US-licensed Humira (referred to as adalimumab-US), and EU-approved Humira (referred to as adalimumab-EU).

A total of 9 DS batches and 26 DP lots were produced at the commercial scale and 1 development scale DS batches of PF-06410293 were included in the similarity assessment. These batches were demonstrated to be representative and comparable to the commercial scale batches through their quality attributes and assessment of the manufacturing process details. However, independent lots for PF-06410293 were chosen resulting in 3 DS batches and 7 DP lots for a Tier 1 statistical analysis. The lot genealogy and independent lot selected for Tier 1 statistical analysis are shown in Table 3. In the response to IR sent on April 23, 2019, sponsor addressed the request for detailed justification of the selection of independent lot selection. See Table C in appendix with additional discussion of the selection of particular lots.

A total of 145 licensed product lots (68 adalimumab-US drug product lots, 40 mg/0.8 mL PFS or PFP and 77 adalimumab-EU drug product lots, 40 mg/0.8 mL PFS or PFP) were purchased on the open market at set intervals with no predetermined criteria, and each lot was considered equally relevant in terms of reflecting a licensed product profile established to be safe and efficacious. These licensed product lots represent the final 18 months of the full 24-month expiry period; at the start of the individual lot testing, they had between < 1 month and 18 months remaining prior to expiry. For statistical analysis of % Relative Potency, all of the reference lots are used. For statistical analysis of sTNF binding activity by ELISA, A subset of 10 adalimumab-US and 10 adalimumab-EU drug product lots were selected randomly from available lots. In the response to IR sent on April 23, 2019, sponsor ensured that the 10 lots of adalimumab-US and adalimumab-EU were selected without consideration of any test or characterization results..

Lots information and data of Inhibition of Apoptosis and sTNF binding used in Statistical Analysis of PF-06410293, adalimumab-US, and adalimumab-EU Lots are shown in Table A and Table B respectively in Appendix.

Table 3: PF-06410293 Lots Used to Demonstrate Analytical Similarity

Drug Substance Batch	Drug Product	Drug Product
12L137L002	40 mg/0.8 mL	MJP1-01-
12L137L003	40 mg/0.8 mL	008A13 ^a
	40 mg/0.8 mL	021B14 ^{a, b}
12L137L005	10 mg/0.2 mL	ENG16017
	10 mg/0.2 mL	082B16
	20 mg/0.4 mL	079B16
	40 mg/0.8 mL	ENG16046
	40 mg/0.8 mL	003C13
	40 mg/vial	ENG16013
	40 mg/vial	068B16
13L137L006	10 mg/0.2 mL	083B16
	10 mg/0.2 mL	ENG16048
	20 mg/0.4 mL	080B16
	40 mg/0.8 mL	004C13
	40 mg/vial	ENG16047
	40 mg/vial	069B16
14P137K605	N/A	N/A
15L137L001	10 mg/0.2 mL	081B16
	20 mg/0.4 mL	078B16
	40 mg/0.8 mL	007F15 ^b
	40 mg/vial	067B16
16L137L001	10 mg/0.2 mL	029M16
	20 mg/0.4 mL	026M16
	40 mg/0.8 mL	023M16
	40 mg/vial	020M16
16L137L002	10 mg/0.2 mL	030M16
	20 mg/0.4 mL	027M16
	40 mg/0.8 mL	024M16
	40 mg/vial	021M16
16L137L003	10 mg/0.2 mL	031M16
	20 mg/0.4 mL	028M16
	40 mg/0.8 mL	025M16
	40 mg/vial	022M16
16L137L004	N/A	N/A

a. Lot used in comparative PK study

b. Lot used in comparative safety and efficacy study

Bold, DS batches and DP lots were selected as independent lots for statistical analyses.

N/A = No drug product made from the drug substance

The Agency carefully evaluated the data for the % Relative Potency as assessed by Inhibition of Apoptosis Assay and sTNF Binding by ELISA provided in the BLA submission. Our comments regarding Pfizer, Inc.'s equivalence testing (Tier 1 approach) is provided in Section 3. and our independent statistical equivalence testing analyses are presented in section 4.

III. APPLICANT'S STATISTICAL EQUIVALENCE TESTING

In this submission, Pfizer, Inc. conducted Tier 1 statistical equivalence testing with the margin defined as $(-1.5\sigma_R, 1.5\sigma_R)$ for % Relative Potency as assessed by Inhibition of Apoptosis Assay and sTNF Binding by ELISA. Pairwise comparisons were used for the assessment of the Tier 1 quality attributes. Similarity is demonstrated if all the two-sided 90% confidence intervals of the difference between means for PF-06410293 vs. adalimumab-US, PF-06410293 vs. adalimumab-EU, and adalimumab-EU vs. adalimumab-US are within the equivalence acceptance criteria of $(-1.5\sigma_R, 1.5\sigma_R)$, where R represents the reference product adalimumab-US or adalimumab-EU in each of the 3 pairwise comparisons. Pfizer, Inc. presumed unequal variances and used adjusted effective sample size to calculate the two-sided 90% confidence interval of the mean difference.

FDA CMC statistics reviewer's comments on Pfizer, Inc.'s equivalence testing are:

- 1) Pfizer, Inc.'s statistical approach is appropriate for Tier 1 analytical similarity assessment.
- 2) Pfizer, Inc.'s statistical analysis results matches with the results of the independent study conducted by FDA CMC statistical reviewer. The independent study conducted by FDA CMC statistical reviewer is present in section 4 below.

IV. FDA STATISTICAL ANALYSES

A Tiered approach is recommended by the Agency to evaluate analytical similarity. That is, product quality attributes are assigned to three tiers based on their criticality. The quality attributes with potential highest risk in product quality, efficiency, safety and PK/PD are assigned to Tier 1, in which analytical similarity is assessed by statistical equivalence test. This review focuses on the equivalence testing in Tier 1.

IV.I Statistical method

Let μ_T and μ_R be respectively the population means of the quality attribute for the test product and the population mean of the quality attribute for the adalimumab-US product. Let σ_R be the standard

deviation of the quality attribute of interest for the adalimumab-US. In order to conclude the equivalence in the quality attribute of interest between the test product and the adalimumab-US product, we aim to test the following null and alternative hypotheses:

$$H_0: \mu_T - \mu_R \leq \theta_1 \text{ or } \mu_T - \mu_R \geq \theta_2$$

$$H_1: \theta_1 < \mu_T - \mu_R < \theta_2$$

Here $\theta_1 = -1.5\sigma_R$, $\theta_2 = 1.5\sigma_R$, θ_1 and θ_2 are equivalence margins.

We reject H_0 if 90% confidence interval for the mean difference in the quality attribute of interest falls within $(-1.5\sigma_R, 1.5\sigma_R)$. In other words, we conclude that the equivalence in the quality attribute of interest between the test product and the reference product if 90% confidence interval for the mean difference in the quality attribute of interest falls within $(-1.5\sigma_R, 1.5\sigma_R)$. This specific equivalence margin was set as 1.5 times the standard deviation of the quality attribute for the reference product to ensure an adequate power for the case in which a small but sufficient number of lots are available for testing. For example, the probability of rejecting H_0 in the above two one-sided tests procedure with the equivalence margin being $(-1.5\sigma_R, 1.5\sigma_R)$ is 87% if the true mean difference is $0.125\sigma_R$ for a sample size of 10 test product lots and 10 reference lots. First, we estimate σ_R by the sample variability of the reference product and then in the statistical analysis, θ_1 and θ_2 are treated as a constant, not a random variable.

Let X_{Tj} be the observed value of the quality attribute of interest for Batch j of the test product and X_{Rj} be the observed value of the quality attribute of interest for Batch j of the reference product.

Since the two products are manufactured by two manufacturers, two groups are independent. $\bar{X}_i =$

$$\frac{\sum_{j=i}^{n_j} X_{ij}}{n_i} \text{ and } S_i^2 = \frac{\sum_{j=i}^{n_j} (X_{ij} - \bar{X}_i)^2}{(n_i - 1)}, \text{ where } n_j \text{ is the number of lots for the } i\text{th product, } i = T, R.$$

Under the unequal variances of the test product and the reference product, the $(1 - 2\alpha) \times 100\%$ confidence interval of the mean difference in the quality attribute of interest can be calculated as:

$$(\bar{X}_T - \bar{X}_R - t_\alpha(v) \sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}}, \bar{X}_T - \bar{X}_R + t_\alpha(v) \sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}}) \quad (1)$$

Here $t_\alpha(v)$ is the $(1 - \alpha)$ quantile of the student's t distribution with v degree of freedom and v is

CMC Statistical Review of BLA761118

calculated by Satterthwaite's approximation.

If $n_R > 1.5n_T$, the $(1 - 2\alpha) \times 100\%$ confidence interval of the mean difference in the quality attribute of interest can be calculated as:

$$(\bar{X}_T - \bar{X}_R - t_\alpha(v^*) \sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R^*}}, \bar{X}_T - \bar{X}_R + t_\alpha(v^*) \sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R^*}}) \quad (2)$$

Here $n_R^* = \min(n_R, 1.5n_T)$ and $v^* = \frac{(\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R^*})^2}{\frac{1}{n_T-1}(\frac{S_T^2}{n_T})^2 + \frac{1}{n_R-1}(\frac{S_R^2}{n_R^*})^2}$.

If the number of biosimilar lots, n_T , is 50% more than the number of reference lots, n_R , we can apply a similar approach as above with $n_T^* = \min(n_T, 1.5n_R)$ for the confidence interval calculation. In the following analyses, we use $\alpha = 0.05$.

IV.II FDA statistical equivalence testing for Inhibition of Apoptosis Assay

The Inhibition of Apoptosis Assay data of PF-06410293, adalimumab-US and adalimumab-EU are displayed in Figure 1. 10 PF-06410293 lots, 68 adalimumab-US lots, and 77 adalimumab-EU lots are included in the inhibition of apoptosis assay dataset for statistical equivalence testing.

Descriptive statistics for the Inhibition of apoptosis assay data of PF-06410293 lots, adalimumab-US and adalimumab-EU are listed in Table 4.

Figure 1: Scatter plots of inhibition of apoptosis assay for adalimumab-US, PF-06410293 and adalimumab-EU

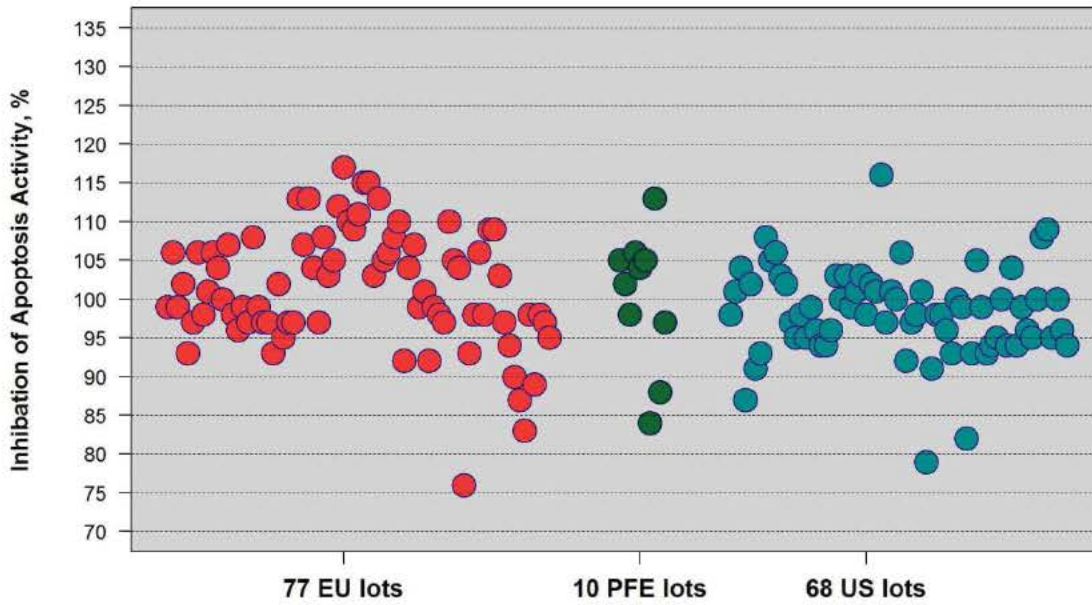


Table 4: Descriptive statistics for Inhibition of Apoptosis Assay data

Product	Number of lots	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
PF-06410293	10	100.2	8.74	84	113
adalimumab-US	68	98.25	5.85	79	116
adalimumab-EU	77	101.36	7.58	76	117

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Table 5 shows that the 90% confidence interval for the mean difference in the Inhibition of Apoptosis assay between PF-06410293 and adalimumab-US is (-3.57, 7.47)%. It falls entirely within the equivalence margin (-8.78, +8.78)%. Hence, the results of the Inhibition of Apoptosis Assay for PF-06410293 are equivalent to those for adalimumab-US.

It also shows that the 90% confidence interval for the mean difference in Inhibition of Apoptosis Assay between PF-06410293 and adalimumab-EU is (-7.01, 4.68)%. It falls within the equivalence margin (-11.36, + 11.36)%. Therefore, the results of the Inhibition of Apoptosis Assay for PF-06410293 are equivalent to those for adalimumab-EU.

The 90% confidence interval for the mean difference in Inhibition of Apoptosis Assay between adalimumab-EU and adalimumab-US is (1.26, 4.96)%, which falls entirely within the equivalence margin (-8.78, +8.78)%. Therefore, the results of the Inhibition of Apoptosis Assay for adalimumab-EU are equivalent to those for adalimumab-US.

The statistical equivalence analyses support that relative potency as measured by the Inhibition of Apoptosis Assay of PF-06410293 is similar to that of adalimumab-US. The results of all three pairwise comparisons support the analytical portion of the scientific bridge to justify the relevance of the data obtained from clinical studies that compared adalimumab-EU and the PF-06410293 product to support a demonstration of biosimilarity to adalimumab-US.

Table 5: Results of equivalence testing for Inhibition of Apoptosis Assay

Comparison	# of lots	Mean Difference, %	90% Confidence Interval for Mean Difference, %	Equivalence Margin, %	Pass the Equivalence Testing?
PF-06410293 vs. US	(10, 68)	1.95	(-3.57, 7.47)	(-8.78, 8.78)	Yes
PF-06410293 vs. EU	(10, 77)	-1.16	(-7.01, 4.68)	(-11.36, 11.36)	Yes
EU vs. US	(77, 68)	3.11	(1.26, 4.96)	(-8.78, 8.78)	Yes

IV.III FDA statistical equivalence testing for sTNF Binding Activity by ELISA

Scatter plots of the sTNF Binding by ELISA for PF-06410293, adalimumab-US and adalimumab-EU are shown in Figure 2. Ten batches of PF-06410293, 10 batches of adalimumab-US, and 10 batches of adalimumab-EU are included in the sTNF Binding by ELISA dataset for statistical equivalence testing. Descriptive statistics for the sTNF Binding by ELISA data of PF-06410293, adalimumab-US, and adalimumab-EU are listed in Table 6.

Figure 2: Scatter plots of sTNF Binding by ELISA for PF-06410293, adalimumab-US and adalimumab-EU

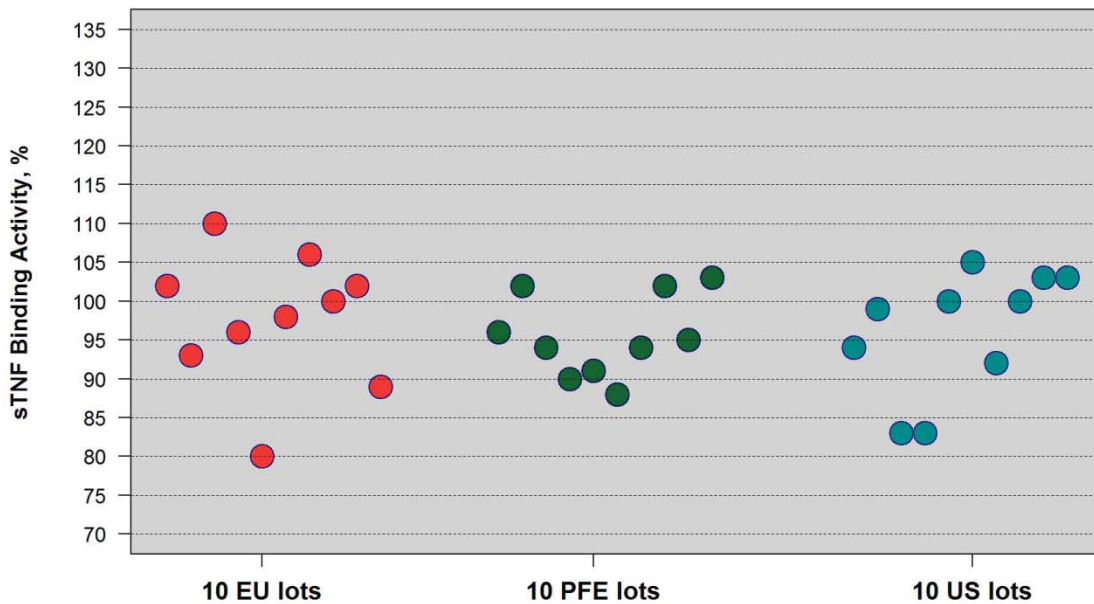


Table 6: Descriptive statistics for the sTNF binding by ELISA data

Product	Number of lots	Sample mean, %	Sample standard deviation, %	Min, %	Max, %
PF-06410293	10	95.5	5.30	88	103
adalimumab-US	10	96.2	8.01	83	105
adalimumab-EU	10	97.6	8.67	80	110

Table 7 shows that the 90% confidence interval for the mean difference in the sTNF Binding by ELISA between PF-06410293 and adalimumab-US is (-6.01, 4.61)%. It falls entirely within the equivalence margin (-12.02, +12.02)%. Hence the sTNF binding by ELISA of PF-06410293 is equivalent to the sTNF binding by ELISA of adalimumab-US.

It also shows that the 90% confidence interval for the mean difference in the sTNF binding by ELISA between PF-06410293 and adalimumab-EU is (-7.73, 3.53)%. It falls within the equivalence margin (-13.0, +13.0)%. Therefore, the sTNF binding by ELISA of PF-06410293 is equivalent to the sTNF binding by ELISA of adalimumab-EU.

The 90% confidence interval for the mean difference in sTNF binding by ELISA between adalimumab-EU and adalimumab-US is (-5.07, -7.87)%, which falls entirely within the equivalence margin (-12.02, +12.02)%. Therefore, the sTNF binding by ELISA of adalimumab-EU is equivalent to the sTNF binding by ELISA of adalimumab-US.

The statistical equivalence analyses support that sTNF binding measured by ELISA of PF-06410293 is similar to that of adalimumab-US. The results of all three pairwise comparisons support the analytical portion of the scientific bridge to justify the relevance of the data obtained from clinical studies that compared adalimumab-EU and the PF-06410293 product to support a demonstration of biosimilarity to adalimumab-US.

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Table 7: Equivalence testing results for the sTNF Binding by ELISA

Comparison	# of lots	Mean Difference, %	90% Confidence Interval for Mean Difference, %	Equivalence Margin, %	Pass the Equivalence Testing?
PF-06410293 vs. US	(10,10)	-0.7	(-6.01, 4.61)	(-12.02, 12.02)	Yes
PF-06410293 vs. EU	(10,10)	-2.1	(-7.73, 3.53)	(-13.0, 13.0)	Yes
EU vs. US	(10,10)	1.4	(-5.07, 7.87)	(-12.02, 12.02)	Yes

V. CONCLUSION AND RECOMMENDATION

The statistical equivalence analyses shown above regarding sTNF binding and the inhibition of apoptosis of PF-06410293 support a demonstration that PF-06410293 is highly similar to adalimumab-US. They also support the analytical portion of the scientific bridge to justify the use of adalimumab-US or adalimumab-EU in the PF-06410293 development program.

VI. APPENDIX

Table A. Lot Information and Data of Inhibition of Apoptosis (Relative potency, %) used in Statistical Analysis for Adalimumab-US, and Adalimumab-EU Lots

Methodology				Inhibition of Apoptosis
BATCH/ LOT NAME	SOURCE	TESTING START DATE ^a	EXPIRY DATE	RELATIVE POTENCY (%)
6033341	EU	17-OCT-2013	30-NOV-2014	99
6033404	EU	17-OCT-2013	30-NOV-2014	106
6033772	EU	17-OCT-2013	31-DEC-2014	99
272382E	US	19-FEB-2014	31-DEC-2014	98
280172E	US	19-FEB-2014	31-DEC-2014	101
281242E	US	20-FEB-2014	30-NOV-2014	104
1004012	US	19-FEB-2014	31-DEC-2014	87
1009147	US	27-AUG-2014	31-MAY-2015	102
1010534	US	02-MAY-2014	31-MAY-2015	91
1010535	US	27-AUG-2014	31-MAY-2015	93
1010537	US	27-AUG-2014	31-MAY-2015	108
1010847	US	27-AUG-2014	31-MAY-2015	105
1014235	US	26-MAY-2015	31-AUG-2015	106
1014236	US	26-MAY-2015	31-AUG-2015	103
1014237	US	05-JUN-2015	31-AUG-2015	102
1017235	US	05-JUN-2015	31-OCT-2015	97
1017238b	US	12-AUG-2014	31-OCT-2015	95
1017698	US	26-MAY-2015	31-OCT-2015	98
1017699	US	26-MAY-2015	30-NOV-2015	95
1017700	US	26-MAY-2015	30-NOV-2015	99
1017701	US	29-MAY-2015	31-OCT-2015	96
1021485	US	29-MAY-2015	31-JAN-2016	94
1021487	US	29-MAY-2015	28-FEB-2016	94
1021488	US	29-MAY-2015	28-FEB-2016	96
1021489	US	01-JUN-2015	28-FEB-2016	103
1021490	US	01-JUN-2015	28-FEB-2016	100
1024661	US	01-JUN-2015	30-APR-2016	103
1024662	US	01-JUN-2015	30-APR-2016	99
1024663	US	01-JUN-2015	30-APR-2016	101
1028009	US	01-JUN-2015	30-JUN-2016	103
1028010	US	21-MAY-2015	30-JUN-2016	98
1028011	US	21-MAY-2015	30-JUN-2016	102
1029648	US	10-SEP-2015	31-AUG-2016	101
1029650	US	10-SEP-2015	31-AUG-2016	116
1032716	US	10-SEP-2015	31-OCT-2016	97
1032718	US	10-SEP-2015	30-NOV-2016	101
1035454	US	10-SEP-2015	30-NOV-2016	100
1039179	US	08-FEB-2016	28-FEB-2017	106
1039181	US	08-FEB-2016	31-JAN-2017	92
1039182	US	08-FEB-2016	28-FEB-2017	97
1041999	US	08-FEB-2016	31-MAR-2017	98
1042000	US	01-FEB-2016	31-MAR-2017	101
1063507	US	14-JUL-2017	30-APR-2018	79
1063665	US	02-MAY-2017	31-MAY-2018	91
1064080	US	14-JUL-2017	30-APR-2018	98
1069685	US	14-JUL-2017	30-AUG-2018	98

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02129XH03	EU	21-NOV-2012	31-JAN-2013	102
02129XH07	EU	29-NOV-2012	31-JAN-2013	93
02136XH02	EU	21-NOV-2012	31-JAN-2013	97
02136XH05	EU	29-NOV-2012	31-JAN-2013	106
03138XH05	EU	21-NOV-2012	28-FEB-2013	98
032482E	US	30-NOV-2012	28-FEB-2013	96
04151XD14	EU	21-NOV-2012	28-FEB-2013	101
042212E	US	30-NOV-2012	31-DEC-2012	93
043112E	US	30-NOV-2012	31-JAN-2013	100
061582E	US	26-NOV-2012	30-JUN-2013	99
062242E	US	30-NOV-2012	30-APR-2013	82
07182XD03	EU	29-NOV-2012	30-JUN-2013	106
090482E	US	30-NOV-2012	31-MAY-2013	93
102322E	US	03-DEC-2012	30-JUN-2013	105
122542E	US	30-NOV-2012	30-SEP-2013	99
131072E	US	30-NOV-2012	31-AUG-2013	93
131142E	US	03-DEC-2012	30-SEP-2013	94
13251XH10	EU	23-APR-2013	31-DEC-2013	104
13257XD08	EU	01-FEB-2013	31-DEC-2013	100
13257XD14	EU	23-APR-2013	31-DEC-2013	107
141442E	US	03-JAN-2013	31-JAN-2014	95
14270XD14	EU	01-FEB-2013	31-JAN-2014	98
151432E	US	03-JAN-2013	30-APR-2014	100
151442E	US	03-JAN-2013	31-JAN-2014	94
170192E	US	03-DEC-2012	30-JUN-2013	104
17292XH02	EU	01-FEB-2013	30-APR-2014	96
17297XD13	EU	01-FEB-2013	30-APR-2014	99
200622E	US	14-OCT-2013	30-APR-2014	94
200642E	US	03-JAN-2013	31-MAR-2014	99
20321XH04	EU	15-OCT-2013	31-JUL-2014	97
21327XH07	EU	16-JUL-2013	31-AUG-2014	108
21327XH10b	EU	23-APR-2013	31-AUG-2014	99
23342XH04	EU	16-JUL-2013	31-OCT-2014	97
240462Eb	US	20-MAY-2013	31-JUL-2014	96
241442E	US	14-OCT-2013	30-SEP-2014	95
250942E	US	16-JUL-2013	30-SEP-2014	100
25361XD01	EU	16-JUL-2013	31-DEC-2014	97
25361XD09	EU	21-OCT-2013	31-DEC-2014	93
260972E	US	16-JUL-2013	30-SEP-2014	108
260982E	US	16-JUL-2013	31-OCT-2014	109
261502E	US	19-FEB-2014	31-OCT-2014	95
261512E	US	14-OCT-2013	31-OCT-2014	100
26370XD05	EU	15-OCT-2013	31-JAN-2015	102
26370XD15	EU	19-FEB-2014	31-JAN-2015	95
271882E	US	19-FEB-2014	30-NOV-2014	96
28387XD04	EU	19-FEB-2014	31-MAR-2015	97
28390XH09	EU	19-FEB-2014	31-MAR-2015	97
29396XH15	EU	27-AUG-2014	30-APR-2015	113
30402XH02	EU	27-AUG-2014	31-MAY-2015	107
31413XH03	EU	27-AUG-2014	30-JUN-2015	113
32419XD07	EU	27-AUG-2014	31-JUL-2015	104
33425XD08	EU	02-MAY-2014	31-AUG-2015	97
33428XD07	EU	27-AUG-2014	31-AUG-2015	108
35442XD03	EU	21-MAY-2015	31-OCT-2015	103
35442XD10b	EU	05-AUG-2014	31-OCT-2015	105
36452XH01	EU	21-MAY-2015	30-NOV-2015	112
37456XD13b	EU	05-AUG-2014	31-DEC-2015	117
37461XD07	EU	21-MAY-2015	31-DEC-2015	110
37461XD08	EU	21-MAY-2015	31-DEC-2015	109

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38468XD03b	EU	12-SEP-2014	31-JAN-2016	111
38468XD05	EU	21-MAY-2015	31-JAN-2016	115
39474XH03	EU	21-MAY-2015	28-FEB-2016	115
39474XH05	EU	21-MAY-2015	29-FEB-2016	103
40478XD08	EU	21-MAY-2015	31-MAR-2016	113
40483XD10	EU	21-MAY-2015	31-MAR-2016	105
41494XH05	EU	21-MAY-2015	30-APR-2016	106
42497XD14	EU	21-MAY-2015	31-MAY-2016	108
42498XD01	EU	21-MAY-2015	31-MAY-2016	110
43012XD06b	EU	26-MAY-2015	30-JUN-2016	92
43012XD07	EU	05-JUN-2015	30-JUN-2016	104
45018XD05b	EU	26-MAY-2015	31-AUG-2016	107
46033XD07	EU	14-SEP-2015	30-SEP-2016	99
46033XD09b	EU	02-JUL-2015	30-SEP-2016	101
47039XH09b	EU	14-SEP-2015	31-OCT-2016	92
47041XH01	EU	10-SEP-2015	31-OCT-2016	99
48048XH07	EU	14-SEP-2015	30-NOV-2016	98
49056XD01b	EU	02-JUL-2015	31-DEC-2016	97
49057XH03	EU	01-FEB-2016	31-DEC-2016	110
50059XH01	EU	10-SEP-2015	31-JAN-2017	105
50062XD05	EU	14-SEP-2015	31-JAN-2017	104
50062XD09b	EU	14-SEP-2015	31-JAN-2017	76
50064XD06	EU	01-FEB-2016	31-JAN-2017	93
51069XH01	EU	01-FEB-2016	28-FEB-2017	98
51070XD07b	EU	07-MAR-2016	28-FEB-2017	106
52077XH04b	EU	01-FEB-2016	31-MAR-2017	98
53087XH01	EU	01-FEB-2016	30-APR-2017	109
53087XH13b	EU	01-FEB-2016	30-APR-2017	109
55098XH10	EU	07-MAR-2016	30-JUN-2017	103
56107XH04b	EU	31-MAR-2016	31-JUL-2017	97
58122XD08	EU	16-JUN-2016	30-SEP-2017	94
68204XH04	EU	14-JUL-2017	31-JUL-2018	90
68213XD10	EU	14-JUL-2017	31-JUL-2018	87
69216XD06	EU	14-JUL-2017	31-AUG-2018	83
70226XD06	EU	14-JUL-2017	30-SEP-2018	98
71236XD01	EU	14-JUL-2017	31-OCT-2018	89
72245XD14	EU	14-JUL-2017	30-NOV-2018	98
85470LJ40e	US	29-NOV-2012	31-DEC-2011	94
87010XD06e	EU	26-NOV-2012	28-FEB-2011	97
96110XD01	EU	29-NOV-2012	30-NOV-2012	95

- a. Testing start date is the date the testing was initiate
- b. Lots used in the comparative clinic studies
- c. Pfizer independent batch/lots for statistical analysis
- d. Due to a deviation during original sample analysis, release testing result is invalid; the 1 month timepoint at the intended storage condition is reported as the release result.
- e. Lot was frozen prior to expiry but tested after expiry, therefore excluded from assessment of lot age in [Section 3.2.R.3.1.2 Lots Enrolled in Similarity Assessment](#)

NMT= Not more than, N/A= Not Applicable, NT= Not Tested

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Table B. sTNF Binding ELISA Data of Adalimumab-US, and Adalimumab-EU Lots used in statistical analytical similarity analysis

Source	Lot/Batch Number	sTNF Binding ELISA	
		Assay Date ^a	Relative Potency (%)
US	061582E	8-May-17 ^b	94
US	1063665	8-May-17	99
US	1035454	8-May-17 ^b	83
US	1029650	8-May-17 ^b	83
US	1032716	8-May-17 ^b	100
US	1028011	8-May-17 ^b	105
US	1021487	8-May-17 ^b	92
US	1028009	8-May-17 ^b	100
US	1028010	8-May-17 ^b	103
US	1029648	8-May-17 ^b	103
EU	87010XD06	8-May-17 ^b	102
EU	55098XH10	8-May-17	93
EU	56107XH04 ^d	8-May-17 ^b	110
EU	47041XH01	8-May-17 ^b	96
EU	50059XH01	8-May-17 ^b	80
EU	48048XH07	8-May-17b	98
EU	40478XD08	8-May-17b	106
EU	36452XH01	8-May-17b	100
EU	40483XD10	8-May-17b	102
EU	43012XD06 d	8-May-17b	89

- a. Assay date is the date the material was tested in the assay.
- b. Sample tested in this assay was a -70 °C stored frozen aliquot that was frozen within expiry, but date of use was beyond the manufacturer's expiry date.
- c. Pfizer independent batch/lot for statistical
- d. Lot used in the comparative clinical study

Table C. Lot Genealogy and Discussion of Independent Lot Selection

Drug Substance Batch	Drug Product Presentation	Drug Product Lot	Discussion
12L137L002	40 mg/0.8 mL	MJP1-01-004	DP Lot MJP1-01-004 was an engineering lot produced in 2012. This lot expired and was not available for heightened characterization activities and therefore the parent DS was selected as an independent lot for use in the similarity assessment.
12L137L003	40 mg/0.8 mL	008A13 ^a	DP lots 008A13 and 021B14 were both used in clinical studies. 021B14 was selected as an independent lot as it was manufactured later than 008A13. While 021B14 was beyond the final proposed commercial expiry (3 years) at the time of heightened characterization, its continued use is supported by stability studies extending to 4 years in which no significant changes were observed.
	40 mg/0.8 mL	021B14 ^{a, b}	
12L137L005	10 mg/0.2 mL	ENG16017	DP lots 082B16, 079B16 and 068B16 were all considered representative and were unexpired at the time of heightened characterization activities. 082B16 was selected to ensure a 10 mg/0.2 mL PFS strength was included in the independent lot set.
	10 mg/0.2 mL	082B16	
	20 mg/0.4 mL	079B16	
	40 mg/0.8 mL	ENG16046	
	40 mg/0.8 mL	003C13	
	40 mg/vial	ENG16013	
13L137L006	40 mg/vial	068B16	DP lots 0873B16, 080B16 and 069B16 were all considered representative and were unexpired at the time of heightened characterization activities. 069B16 was selected to ensure a 40 mg/vial strength was included in the independent lot set.
	10 mg/0.2 mL	083B16	
	10 mg/0.2 mL	ENG16048	
	20 mg/0.4 mL	080B16	
	40 mg/0.8 mL	004C13	
	40 mg/vial	ENG16047	
14P137K605	N/A	N/A	DS batch 14P137K605 is a representative, pilot-scale DS that was not manufactured into DP, therefore the DS was selected as an independent lot for use in the similarity assessment.
15L137L001	10 mg/0.2 mL	081B16	DP lots 081B16, 078B16, 007F15 and 067B16 were all considered representative and were unexpired at the time of heightened characterization activities. 007F15 was selected as a lot that was used in clinical studies.
	20 mg/0.4 mL	078B16	
	40 mg/0.8 mL	007F15 ^b	
	40 mg/vial	067B16	
16L137L001	10 mg/0.2 mL	029M16	All DS and DP lots in this group were manufactured as part of manufacturing process validation, and were unexpired at the time of heightened characterization. Two lots were considered potentially non-representative at the time of independent lot selection due to open investigations and were excluded from consideration. 026M16 was under investigation (b) (4) that was subsequently confirmed, and 023M16 was under investigation (b) (4) that was subsequently deemed to have no product impact. 027M16 was selected to ensure a 20
	20 mg/0.4 mL	026M16	
	40 mg/0.8 mL	023M16	
	40 mg/vial	020M16	
16L137L002	10 mg/0.2 mL	030M16	(b) (4) that was subsequently deemed to have no product impact. 027M16 was selected to ensure a 20
	20 mg/0.4 mL	027M16	

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Drug Substance Batch	Drug Product Presentation	Drug Product Lot	Discussion
16L137L003	40 mg/0.8 mL	024M16	mg/0.4 mL PFS strength was included in the independent lot set. Among the remaining lots, one lot each of the 40 mg/vial and 40 mg/0.8 mL PFS were arbitrarily selected for inclusion in the independent lots set.
	40 mg/vial	021M16	
	10 mg/0.2 mL	031M16	
	20 mg/0.4 mL	028M16	
	40 mg/0.8 mL	025M16	
	40 mg/vial	022M16	
16L137L004	N/A	N/A	DS batch 16L137L004 was not manufactured into DP therefore the DS was selected as an independent lot for use in the similarity assessment.

- a. Lot used in comparative PK study
- b. Lot used in comparative safety and efficacy study are selected as independent lots for statistical analyses.

N/A = No drug product made from the drug substance

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/s/

TIANJIAO DAI
05/06/2019 12:05:56 PM

CHAO WANG
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MEIYU SHEN
05/06/2019 01:06:45 PM

THOMAS J PERMUTT
05/06/2019 02:21:38 PM
I concur.