

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761024Orig1s000

CHEMISTRY REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 22,
Silver Spring, MD 20993

Date: September 16, 2016
To: Administrative File, BLA 761024
From: Lakshmi Rani Narasimhan, Ph.D., Reviewer, CDER/OPQ/OPF/DMA
Endorsement: Patricia F. Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA
Subject: Biological License Application (BLA)
US License: # 1080
Applicant: Amgen Inc.
Facility: Amgen Manufacturing Ltd (AML), Road 31, Kilometer 24.6, Juncos, Puerto Rico 00777 USA (FEI # 1000110364) - Pre-filled syringe (PFS) and Autoinjector (AI)/Pen
Product: ABP 501 (proposed biosimilar to Humira®)
Presentation: PFS (20 mg/0.4 mL and 40 mg/0.8 mL (50mg/mL) or AI/Pen (40 mg/0.8 mL (50mg/mL) for subcutaneous injection
Indications: Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) (4 years of age and older), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps)
Due Date: September 24, 2016

Recommendation for Approvability: The drug product section of this BLA, as amended, is recommended for approval from a product quality microbiology perspective.

SUMMARY:

Amgen Inc. submitted a 351(k) application, BLA 761024 to license ABP 501, a proposed biosimilar to Humira® for the following indications: Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) (4 years of age and older), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps). Drug substance is manufactured by Amgen Inc., Thousand Oaks, CA (ATO), and drug product in pre-filled syringe and the Autoinjector (AI)/Pen are manufactured at, Amgen Manufacturing Ltd. Juncos, Puerto Rico (AML).

The application was submitted in eCTD format and included Module 1.1.2-FDA form 356h, Module 1.2-Cover letter, and Module 2 Module 3, appendices (3.2.A.1, Facilities and Equipment and 3.2.A.2, Adventitious Agents Safety Evaluation), and a regional section (3.2.R).

Letter of authorization (LOA) for (b)(4) Type III DMF (b)(4) to review the (b)(4) Syringe System was provided.

INTRODUCTION

ABP 501 is a proposed biosimilar to Humira® for the treatment of Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) (4 years of age and older), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps).. It is a fully human immunoglobulin G1 monoclonal antibody which binds and neutralizes human tumor necrosis factor alpha (TNFα), a cytokine which mediates the

inflammatory response. ABP 501 is proposed in a PFS (20 mg/0.4 mL and 40 mg/0.8 mL (50mg/mL) or AI/Pen (40 mg/0.8 mL (50mg/mL)) for subcutaneous injection.

This review covers the evaluation of the drug product aspects of the application from a product quality microbiology perspective.

DRUG SUBSTANCE

ABP 501 is a human monoclonal antibody produced in Chinese hamster ovary (CHO) cells. The drug substance manufacturing process consists of (b) (4). For the review of drug substance aspects of the application, please see review by Dr. Bo Chi.

ASSESSMENTS

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	November 25, 2015	Original
0005	February 23, 2016	Amendment
0016	May 18, 2016	Amendment
0019	June 14, 2016	Amendment
0026	July 26, 2016	Amendment
0029	August 02, 2016	Amendment
0031	August 16, 2016	Amendment
0034	August 25, 2016	Amendment

3.2.P. DRUG PRODUCT

ABP 501

The ABP 501 drug product (DP) manufacturing process consists of (b) (4). DP is supplied in two presentations, prefilled syringe (PFS) and pre-assembled autoinjector (AI). Drug product in both presentations has (b) (4) and provides 20 mg/0.4 mL or 40 mg/0.8 mL (50mg/mL) (PFS) or 40 mg/0.8 mL (50mg/mL) (AI). DP filling in PFS and AI assembly is performed at AML.

3.2.P.1 Description and Composition of the Drug Product-Pre-Filled Syringe (PFS)

Sterile, preservative-free solution of DP is supplied in a single use PFS for subcutaneous injection. The PFS contains 50 mg/mL DP in 10 mM acetate, 9.0% (w/v) sucrose, 0.10% (w/v) polysorbate 80, pH 5.2 in deliverable volume of 0.4 mL or 0.8 mL. The quantitative and qualitative composition of the DP provided in Table 1 is duplicated below:

Table 1. Quantitative and Qualitative Composition of 50 mg/mL PFS

Component	Grade	Function	Quantity (0.4 mL)	Quantity (0.8 mL)	Concentration
ABP 501	In house ^a	Active ingredient	20 mg	40 mg	50 mg/mL
Sucrose	NF, PhEur, JP	(b) (4)	36 mg	72 mg	9.0% (w/v)
Polysorbate 80	NF, PhEur, JP	(b) (4)	0.4 mg	0.8 mg	0.10% (w/v)
Glacial acetic acid ^b	USP, PhEur, JP	(b) (4)	0.24 mg	0.48 mg	10 mM
Sodium hydroxide ^c	NF, PhEur, JP	pH adjustment	qs to target pH	qs to target pH	qs to target pH
Water for injection	USP, PhEur, JP	(b) (4)			(b) (4)

qs = quantum sufficit

^a Tested to internal specifications (3.2.S.4.1. Specification)

^b Glacial acetic acid is used in the (b) (4) 10 mM represents the acetate concentration. Sodium is the counter ion upon pH adjustment with sodium hydroxide.

^c The sodium hydroxide solution may be used to adjust pH. The supplier tests sodium hydroxide (b) (4) to NF, PhEur, and JP standards.

Autoinjector (AI)

AI is a single-use, disposable, (b) (4) pre-assembled presentation used for the DP. The AI contains a 27-gauge PFS with a deliverable volume of 0.8 mL of 50 mg/mL ABP 501.

3.2.P.2 Pharmaceutical Development

Container closure integrity (CCI):

PFS

CCI of the PFS was confirmed using vacuum decay and dye ingress methods. The vacuum decay method demonstrated that the filling, plunger rod and flange extender assembly, packaging, and transportation did not impact integrity of the primary container closure system (CCS). The dye ingress method is used to monitor CCI of PFS during stability.



(b) (4)

Satisfactory

**3.2.P.3.1. MANUFACTURER(S)
PFS**

Table 1. Drug Product Facility Responsibilities

Facility	Address	Responsibility	FDA Registration Number
Amgen Manufacturing Ltd (AML)	Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777 USA	Drug product manufacture	FEI: 1000110364
		Drug product in-process, lot release, and stability testing	DUNS: 785800020
		Packaging and labeling	
		Inspection and release	
Amgen Inc. Amgen Thousand Oaks (ATO)	One Amgen Center Drive Thousand Oaks, CA 91320 USA	Drug product lot release and stability testing	FEI: 2026154 DUNS: 039976196
Amgen Technology Ireland (ADL)	Pottery Road Dun Laoghaire, LEI Ireland	Drug product lot release and stability testing	FEI: 3002808497 DUNS: 896293920

FEI = Facility Establishment Identifier
DUNS = Data Universal Numbering System

FDA Question (February 16, 2016): Please clarify if all the drug product lot release and stability tests are performed at each site where lot release and stability testing is specified in 3.2.P.3.1. Update the BLA with the specific tests to be used at each of the sites.

Firm's Response in amendment dated February 23, 2016 in sequence # 0005: Section 3.2.P.3.1 (Manufacturers) has been updated to include an additional table (Table 3). The drug product lot release and stability tests performed at each site are listed in this table.

Release sterility and endotoxin tests are performed at AML and ADL. CCI testing for stability is performed at (b) (4).

AI

The manufacture, lot release, stability testing, packaging, labeling, inspection and release of the AI are performed AML.

Satisfactory

**3.2.P.3.2. BATCH FORMULA
PFS and AI**

(b) (4)

3.2.P.3.3. DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

(b) (4)



Lakshmi Rani
Narasimhan

Digitally signed by Lakshmi Rani Narasimhan
Date: 9/20/2016 09:18:21 AM
GUID: 508da7160002976791592556d218b997



Patricia
Hughes Troost

Digitally signed by Patricia Hughes Troost
Date: 9/20/2016 09:36:01 AM
GUID: 508da717000297bcfce0919f8c09594
Comments: Signed off the review.

Recommendation:

BLA: Approval

BLA 761024 Review 1

Drug Name/Dosage Form	ABP 501 / Injection
Strength	20 mg/0.4 mL and 40 mg/0.8 mL (50 mg/mL)
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Amgen, Inc.
US agent, if applicable	Not Applicable

- a. Names
 - i. Proprietary Name: Amjevita (pending)
 - ii. Trade Name: Amjevita (pending)
 - iii. Non-Proprietary/USAN: adalimumab-xxxx (pending)¹
 - iv. INN Name: adalimumab (b) (4) (pending)
 - v. Other: None
 - vi. OBP systematic name: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [ABP501]
- b. Pharmacologic category: Therapeutic recombinant human monoclonal antibody

Product Overview

ABP 501 is an anti-TNF- α human monoclonal antibody for which Amgen is seeking approval as a biosimilar to US-licensed Humira®. The proposed dose and presentation for ABP 501 include a subset of those currently approved for US-licensed Humira®. ABP 501 is supplied as a pre-filled syringe or single-use autoinjector as a sterile liquid solution for subcutaneous injection, and Amgen is seeking approval of ABP 501 for the following indications: Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) (4 years of age and older), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn’s Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps).

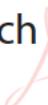
¹ ABP 501 has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). Since the proper and non-proprietary names for ABP 501 have not yet been determined, ABP 501 is used throughout this review.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance and Drug Product	Jun Park	Division of Biotechnology Review and Research - II
Drug Substance and Drug Product and ATL	Joel Welch	Division of Biotechnology Review and Research – II
Microbiology Drug Substance	Bo Chi	Division of Microbiology Assessment
Microbiology Drug Product	Lakshmi Narasimhan	Division of Microbiology Assessment
Facility	Steven Fong	Division of Inspectional Assessment
Immunogenicity	Jun Park	Division of Biotechnology Review and Research - II
Regulatory Business Process Manager	Keith Olin	OPRO
Application Technical Lead	Joel Welch	Division of Biotechnology Review and Research – II
Microbiology Team Lead (Drug Substance)	Patricia Hughes	Division of Microbiology Assessment
Microbiology Team Lead (Drug Product)	Patricia Hughes	Division of Microbiology Assessment
Facilities Team Lead	Peter Qiu	Division of Inspectional Assessment

Cross-Discipline Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
RPM	Sadaf Nabavian	DPARP
CDTL	Nikolay Nikolov	DPARP
Medical Officer	Keith Hull	DPARP
Clinical Pharmacology	Jiangmen Chen	DCPV
Statistics	Kathleen Fritsch	DBV
Statistics	Yongmin Kim	DBV
CMC Stats	Meiyu Shen	DBVI

NAME AND TITLE	ELECTRONIC SIGNATURE
Joel Welch, PhD Acting Review Chief CDER/OPQ/OBP/DBRR II	 <p>Joel T. Welch -S</p> <p><small>Digitally signed by Joel T. Welch -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joel T. Welch -S, 0.9.2342.19200300.100.1.1=2000443745 Date: 2016.09.07 13:33:43 -04'00'</small></p>
David Frucht, M.D. Acting Division Director CDER/OPQ/OBP/DBRR II	 <p>David M. Frucht -S</p> <p><small>Digitally signed by David M. Frucht -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13001686 94, cn=David M. Frucht -S Date: 2016.09.08 10:22:27 -04'00'</small></p>

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(k)

2. RELATED/SUPPORTING DOCUMENTS:

B. Submissions Reviewed:

Submission	Date Received	Review Completed (Yes/No)
Original Application	November 25, 2015	Yes
Amendment 02	December 31, 2015	Yes
Amendment 11	March 21, 2016	Yes
Amendment 17	June 07, 2016	Yes
Amendment 20	June 27, 2016	Yes
Amendment 23	July 05, 2016	Yes
Amendment 24	July 13, 2016	Yes
Amendment 25	July 14, 2016	Yes
Amendment 27	July 26, 2016	Yes
Amendment 28	July 29, 2016	Yes
Amendment 29	August 02, 2016	Yes
Amendment 30	August 11, 2016	Yes

C. DMFs:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)	(b) (4)	(b) (4) Syringe System	Yes	Sufficient as Leachables and Extractables data and primary stability program in BLA. Not reviewed as DMA reviewed on Jun 21 2016.
		Needle Shields	Yes	Sufficient Leachables and Extractables data and primary stability program in BLA. Not Reviewed.
		(b) (4) Auto Injector	Yes	Reviewed by CDRH

D. Other Documents: None

3. CONSULTS:

Center/Topic	Date Requested	Status	Recommendation	Reviewer
CDRH – PFS	Feb 16 2016	Pending	Pending	Pending
CDRH - AI	Feb 16 2016	Pending	Pending	Pending

4. Review

I. Recommendations

The Office of Pharmaceutical Quality recommends approval of BLA 761024 for ABP 501 manufactured by Amgen. The data and information submitted in this application, including the analytical similarity assessment, are adequate to support the conclusion that:

- The biological product, ABP 501, is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components;
- A sufficiently robust analytical bridge was established to support the use of EU-Approved Humira as a comparator in clinical trial 20120263.

It is recommended that this product be approved for human use under conditions specified in the package insert.

A. Recommendation and Conclusion on Approvability

a. Recommendation:

The DS and DP manufacturing process is well controlled and should consistently deliver DS and DP of desired quality. The analytical similarity assessment was considered sufficient to support a determination of highly similar.

A PMC is recommended to perform a confirmatory shipping study to evaluate the impact of actual shipping conditions on the product quality of drug product. (b) (4)

A PMC is recommended to perform additional validation in support of the introduction of a non-reduced CE-SDS method into the integrated control strategy for drug substance. While this method was qualified as a portion of the similarity assessment, additional experiments are recommended to be conducted in accordance with ICH Q2.

b. Action letter language

Manufacturing locations:

- o Drug substance – Amgen Inc. Amgen Thousand Oaks (ATO) One Amgen Center Drive, Thousand Oaks, CA 91320
- o Drug product – Amgen Manufacturing Ltd (AML) Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777
- o Fill size and dosage form – single-use, 1 mL prefilled glass syringe (40 mg/ 0.8 mL or 20 mg/0.4 mL) or as a single-use, prefilled SureClick® autoinjector (40 mg/ 0.8 mL)
- o Dating period:
 - o Drug product – 30 months at 2-8°C
 - o Drug substance – (b) (4) months at (b) (4) °C
- o Stability option:

We have approved the stability protocol(s) in the license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.
- o Exempt from lot release
 - o Yes
 - o Rationale if exempted – ABP 501 is exempted from lot release because it is a specified product per 601.2 (a).

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

Below are the draft PMC/PMRs to be proposed to the sponsor should approval be the recommendation.

- 1) Perform a drug product shipping study using the actual approved commercial shipping lane to evaluate the impact of shipment on product quality.
- 2) Perform supplemental method validation to support the introduction of a non-reduced CE-SDS test into the integrated control strategy for drug substance manufacture. Submit the analytical procedure, validation report, the proposed acceptance criterion, and the data used to set the acceptance criterion that will be provided in a CBE-0 supplement.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Management

Table 1 below is a summary of critical quality attributes and their control strategy that are relevant to both drug substance and drug product. For additional information see the primary review for the Drug Substance and Drug Product Quality Review: OBP Assessment, the primary review for Drug Substance Microbiology Review: Division of Microbiology Assessment, and the primary review for Drug Product Microbiology Review: Division of Microbiology Assessment.

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

CQA	Risk	Origin	Control Strategy	Other
Potency	Efficacy	Changes to protein composition during manufacture or storage	(b) (4)	N/A
HMW Species	Efficacy, Pharmacokinetics, and Immunogenicity	Affected by production conditions. HMW species formed due to temperature, light, and agitation.		N/A
LMW Species	Efficacy and Pharmacokinetics	Affected by production conditions. Degradation product formed due to temperature, light, and agitation.		nrCE-SDS will be added as part of the DS IPC testing as a PMC
Charge Variant Profile (deamidation, C-terminal and N-terminal variants and oxidation)	Efficacy, Pharmacokinetics, and Potency	Bioreactor conditions and degradation		N/A
Osmolality	Safety	Controlled during formulation		N/A
Endotoxin	Safety	Contamination during manufacturing process		Reviewed by OPF and considered adequate.

B. ABP 501 Drug Substance Quality Summary

Table 2 below is a summary of critical quality attributes and their control strategy that are relevant to only drug substance. For additional information see the primary review for for the Drug Substance and Drug Product Quality Review: OBP Assessment and see the primary review for Drug Substance Microbiology Review: Division of Microbiology Assessment.

Table 2: Drug Substance CQA Identification, Risk and Lifecycle Knowledge Management				
CQA	Risk	Origin	Control Strategy	Other
Bioburden	Safety; product quality due to degradation or modification of product	Contamination during manufacturing process	(b) (4)	Reviewed by OPF and considered adequate.
Endotoxin	Safety	Endotoxin introduction during manufacturing process		N/A
Host Cell Proteins	Safety and Immunogenicity	Process-related impurity introduced during manufacture from host cell line		N/A
Host Cell DNA	Safety	Process-related impurity introduced during manufacture from host cell line		N/A
pH	Safety and Efficacy	Controlled by formulation ingredients during process		N/A

Residual Protein A	Safety and Immunogenicity	Process related impurity (b) (4)	(b) (4)	N/A
Virus Contamination	Safety	Contamination during manufacture		N/A
Protein Content	Efficacy	Controlled by the step. (b) (4)		N/A
Appearance	Safety	Controlled by the manufacturing process		N/A
Identity	Safety and Efficacy	Not Applicable		N/A
Polysorbate 80	Safety	Controlled during formulation		N/A
Leachables	Safety	Process-related impurities due to contact with container closure		N/A

1. Description

ABP 501 is a human monoclonal antibody based on a human immunoglobulin G1 (IgG1) framework. It is produced in Chinese hamster ovary (CHO) cells and consists of two heavy chains (448 amino acid residues each) and two light chains (214 amino acid residues each).

(b) (4)

For additional information see the primary review from the Office of Biotechnology Products.

2. Mechanism of action

ABP 501 binds specifically to TNF- α and blocks its interaction with the p55 and p75 cell surface TNF receptors. ABP 501 does not bind or inactivate lymphotoxin (TNF beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF- α are found in the synovial fluid of patients with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Additionally, antibody dependent cell mediated cytotoxicity, complement dependent cytotoxicity, and mediation of transmembrane TNF- α expressing cells have been implicated in IBD indications, though the level of contribution of each of these individual mechanisms is considered unknown (based on literature review). For additional information see the primary review from the Office of Biotechnology Products.

3. Potency Assay

The potency assay of ABP 501 DS serves as a quantitative *in vitro* assay to determine the biological activity of both ABP 501 Drug Substance and Drug Product. The *in vitro* biological activity of ABP 501 is assessed by analyzing its ability to inhibit the biological activity of TNF- α using the human histiocytic lymphoma cell line U-937. TNF- α induces U-937 cells to undergo apoptosis through caspase activation that is detected by Caspase-Glo[®] 3/7 Assay System. The Caspase-Glo[®] system provides a luminogenic substrate containing the DEVD amino acid sequence (Asp-Glu-Val-Asp), which is recognized by these caspases. Once the caspases are activated, they cleave the DEVD sequence from the luminogenic substrate, which results in light (luminescence) production. The amount of luminescence generated is proportional to the amount of caspase activation and is quantified in a luminometer after reaction with a Caspase-Glo[®] 3/7 luciferase substrate. ABP 501 causes a dose dependent inhibition of TNF- α induced apoptosis. Test sample biological activity is determined by comparing test sample response to the response obtained with the Reference Standard as a percentage. For additional information see the primary review from the Office of Biotechnology Products.

4. Reference material(s)

A primary reference standard system was characterized and is considered sufficiently well qualified. A working reference standard is undergoing qualification.

Amgen provided a qualification protocol for future working reference standards that will be prepared and fully qualified (b) (4)

For additional information see the primary review from the Office of Biotechnology Products.

5. Manufacturing process summary

(b) (4)

For additional information see the primary review from the Office of Biotechnology Products and primary review for Drug Substance Microbiology Review: Division of Microbiology Assessment.

6. Container closure

ABP 501 DS is formulated in (b) (4) prior to being filled into (b) (4) containers. The closure is manufactured from (b) (4). The drug substance is stored at (b) (4) °C. There is minimal drug substance degradation in the CCS during the (b) (4) month dating period. See the primary review from the Office of Biotechnology Products.

7. Dating period and storage conditions:

The sponsor conducted real-time, accelerated, and stressed stability studies to support their proposed dating period of (b) (4) months when stored at (b) (4) °C.

C. ABP 501 Drug Product Quality Summary

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that are derived from the drug product manufacturing process and general drug product attributes. For additional information on the characterization of ABP 501, see the primary review from the Office of Biotechnology Products and the primary review for Drug Product Microbiology Review: Division of Microbiology Assessment.

Table 3: ABP 501 Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management				
CQA	Risk	Origin	Control Strategy	Other
Sterility	Safety (infection) Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination could be introduced during manufacturing process or through a container closure integrity failure.	(b) (4)	Reviewed by OPF and considered adequate.
Endotoxin	Safety	Contamination could be introduced throughout DP manufacturing or through a container closure integrity failure.		Reviewed by OPF and considered adequate
Particulate Matter	Occlusion of blood vessels	Product- or Process-Related Impurities		N/A
Appearance	Safety	Controlled by the		N/A



Secondary Quality Review BLA 761024



		manufacturing process.	(b) (4)	
Identity	Safety and Efficacy	Not Applicable		N/A

Summary of Drug Product Intended Use

a. Potency and Strength

Potency is considered, for the purposes of this review, as the percent activity relative to the current ABP 501 reference standard. The potency assay is the same as described in the DS section B3 of this memo. ABP 501 DP is available as 40 mg/0.8mL and 20 mg/0.4mL strengths.

Based on comparative data between ABP 501 and US-licensed Humira for protein content and deliverable volume, the 40 mg/0.8 mL and 20 mg/0.4 mL pre-filled syringe presentations, and the 40 mg/0.8 mL autoinjector presentation, of ABP 501 have the same total content of drug substance and the same concentration of drug substance as the respective presentations of US-licensed Humira. These presentations meet the statutory same strength requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.

b. Summary of Product Design

A single-use prefilled syringe ((b) (4) 29G needle) and a single-use prefilled syringe in a SureClick autoinjector will be available as a sterile single-use (b) (4) for subcutaneous injection.

c. Excipients

Excipients include glacial acetic acid, sodium hydroxide, sucrose, polysorbate 80, and water for injection. The excipients used in manufacturing are acceptable as they are compliant with compendial quality standards. The excipients are safe for use since they are not of human or animal origin and therefore are of little risk for viral or TSE contamination. For additional information see primary review from the Office of Biotechnology Products.

d. Reference standard(s)

There is no drug product specific reference standard. The primary reference standard is drug substance. Please see drug substance reference standard for information.

e. Manufacturing Process

The manufacturing process for drug product include the following steps: (b) (4)

The control strategy includes (b) (4)

(b) (4) Critical parameters selected for routine monitoring support (b) (4)

(b) (4) rocess validation studies included manufacture of three consecutive commercial scale lots. Additional validation studies included:

- Validation of sterilization and (b) (4) manufacturing process

- Shipping qualification study
- Process simulation (media fills)

f. Container Closure System

The primary container closure system consists of a 1 mL Type I glass syringe with a staked-in-place stainless steel needle (27-gauge or 29-gauge), (b) (4) needle shield, and a (b) (4) plunger-stopper.

g. Expiration Date & Storage Conditions

The sponsor conducted real-time, accelerated, and stressed stability studies on finished drug product, to support a dating period of 30 months when stored at 2-8°C. If needed, ABP 501 DP may be stored at room temperature up to a maximum of 25°C for a period of up to 14 days, with protection from light. For further information see primary review from the Office of Biotechnology Products.

h. List of co-packaged components N/A

D. Novel Approaches

N/A

E. Any Special Product Quality Labeling Recommendations

Store ABP 501 DP in both the prefilled syringe and autoinjector presentations under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light

Do not freeze

Do not shake.

Administer immediately once prepared. If needed, for example when traveling, ABP 501 DP may be stored at room temperature up to a maximum of 25°C for a period of up to 14 days.

F. Establishment Information

G. Facilities

The subject BLA proposes manufacture, testing, and storage of ABP 501 Drug Substance and Drug Product at the following facilities:

DS Manufacturers for ABP 501

Site Name	Address	FEI #	Responsibility
Amgen Inc. Amgen Thousand Oaks (ATO)	One Amgen Center Drive, Thousand Oaks, CA 91320 USA	2026154	Drug substance manufacture Drug substance in-process, lot release, and stability testing Master cell bank and working cell bank manufacture and storage

Amgen Manufacturing Ltd (AML)	Road 31, Juncos, Puerto Rico 00777 USA	1000110364	Drug substance lot release and stability testing
(b) (4)			(b) (4)
			Mycoplasma and adventitious viral testing
			(b) (4)
(b) (4)			Mycoplasma and adventitious viral testing
			(b) (4)
(b) (4)			Mycoplasma testing

DP Manufacturers for ABP 501

Site Name	Address	FEI #	Responsibility
Amgen Manufacturing Ltd (AML)	Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777 USA	1000110364	Drug product manufacture Drug product in-process, lot release, and stability testing Packaging and labeling inspection and release
Amgen Inc. Amgen Thousand Oaks (ATO)	One Amgen Center Drive, Thousand Oaks, CA 91320 USA	2026154	Drug product lot release and stability testing
Amgen Technology Ireland (ADL)	Pottery Road Dun Laoghaire, LEI Ireland	3002808497	Drug product lot release and stability testing
(b) (4)			Container closure integrity testing for stability

For a complete summary see the: Drug Substance Facilities Review: Division of Inspectional Assessment.

H. Lifecycle Knowledge Management

a. Drug Substance

i. Protocols approved:

- annual stability protocol
- qualification of new working reference standard
- concurrent validation protocol for (b) (4)
- (b) (4) reuse

- ii. Outstanding review issues/residual risk - see sections 1A and 1B of this memo for post-marketing commitments.
- iii. Future inspection points to consider – Follow up on 483 citation.

b. Drug Product

- i. Protocols approved:
 - annual stability protocol,
 - Comparability protocol for AML (b) (4) product introduction
- ii. Outstanding review issues/residual risk – None
- iii. Future inspection points to consider – none at this time.

Quality Assessment Summary Table:

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
2.	Botanical ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.	Naturally-derived Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.	PET Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.	PEPFAR Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.	Sterile Drug Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
8.	Transdermal ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Pediatric form/dose ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Locally acting drug ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
11.	Lyophilized product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	First generic ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
13.	Solid dispersion product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
14.	Oral disintegrating tablet ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Modified release product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
16.	Liposome product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Biosimilar product ¹	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Biosimilar product to Humira® (adalimumab)
18.	Combination Product _____	<input checked="" type="checkbox"/>	<input type="checkbox"/>	ABP 501 fomulation in PFS and autoinjector
19.	Other _____	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Regulatory Considerations					
20.	USAN Name Assigned		<input checked="" type="checkbox"/>	<input type="checkbox"/>	Adalimumab (b) (4)
21.	End of Phase II/Pre-NDA Agreements		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
22.	SPOTS (Special Products On-line Tracking System)		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		<input type="checkbox"/>	<input type="checkbox"/>	Not available
24.	Comparability Protocol(s) ²		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
25.	Other _____		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Quality Considerations					
26.	Drug Substance Overage		<input type="checkbox"/>	<input checked="" type="checkbox"/>	The autoinjector contains a prefilled syringe which is filled to ensure a deliverable volume of 0.8 mL.
27.	Design Space	Formulation	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
28.		Process	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
29.		Analytical Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
30.		Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
31.	Real Time Release Testing (RTRT)		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
33.	Alternative Microbiological Test Methods		<input checked="" type="checkbox"/>	<input type="checkbox"/>	Container closure integrity
34.	Process Analytical Technology ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
36.		Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
37.		Microbial	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
38.	Unique analytical methodology ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
39.	Excipients of Human or Animal Origin		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
40.	Novel Excipients		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Nanomaterials ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Hold Times Exceeding 30 Days		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
43.	Genotoxic Impurities or Structural Alerts		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
44.	Continuous Manufacturing		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
45.	Other unique manufacturing process ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
47.	New delivery system or dosage form ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
48.	Novel BE study designs		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
49.	New product design ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
50.	Other _____		<input type="checkbox"/>	<input checked="" type="checkbox"/>	

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

Analytical Assessment Summary:

The totality of the analytical data provided is sufficient to conclude that ABP 501 is "highly similar" to US-licensed Humira.

The analytical similarity of ABP 501, US-licensed Humira, and EU-approved Humira was evaluated using multiple drug product lots of each of the three products. The expiration dates of the US-licensed Humira and EU-approved Humira lots was sufficiently broad and ranged over a span of approximately 4 - 5 years. The number of lots that were analyzed was chosen by the Applicant based on their assessment of the variability of the analytical method and availability of material. A minimum of 10 lots of each product were analyzed for product quality attributes that were evaluated using equivalency testing. For attributes that are known to change slightly over the course of shelf life, the applicant also provided an additional comparison with estimated values based on extrapolation to the initial proposed end of shelf life for ABP 501 and the applicant's presumed shelf life for US-licensed Humira.

Clinical study 20120263 used a non-US-licensed comparator product [European Union (EU)]-approved Humira. To justify the use of these comparative clinical data to support a demonstration of biosimilarity of ABP 501 to US-licensed Humira, the Applicant performed an analytical study to establish an adequate scientific bridge for the products. The results of these comparisons show that the three products (ABP 501, US-licensed Humira, and EU-Approved Humira) met expectations for analytical similarity.

The analytical similarity assessment of ABP 501, US-licensed Humira and EU-Approved Humira was assessed using a comprehensive set of assays as listed below.

Quality Attribute	Methods
Primary Structure	<ul style="list-style-type: none"> • Peptide mapping with ultraviolet (UV) and mass spectrometry (MS) detection • Intact Molecular Mass (LC-MS) • Reduced and Deglycosylated Molecular Mass (LC-MS)
Bioactivity	<ul style="list-style-type: none"> • Apoptosis Inhibition (Bioassay) • sTNF-α binding (ELISA)
Purity	<ul style="list-style-type: none"> • Reduced/non-reduced CE-SDS
Fc Receptor Binding	<ul style="list-style-type: none"> • FcγRIIIa V type binding affinity (AlphaLISA) • FcγRIIIa F type binding affinity (AlphaLISA) • FcγR Ia, IIa binding affinity (AlphaLISA) • FcRn binding affinity (cell-based)
Protein Content	<ul style="list-style-type: none"> • Concentration (UV₂₈₀)
Sub-visible Particles	<ul style="list-style-type: none"> • Micro Flow Imaging • Light Obscuration
Higher Order Structure	<ul style="list-style-type: none"> • 2^o Structure (Fourier Transform-IR; Circular Dichroism)
Biologic Analysis and mechanism of action exploration	<ul style="list-style-type: none"> • CDC • ADCC of NK cells • C1q binding (ELISA) • Specificity against Lta • Inhibition of sTNF-α-induced IL-8 in HUVEC • Binding to tmTNF-α • Reverse Signaling (apoptosis of mbTNF-α) • Inhibition of T-Cell proliferation (MLR)
High molecular weight variants/aggregates	<ul style="list-style-type: none"> • Size exclusion chromatography (SEC) • SEC- Multi Angle Laser Light Scatter • SEC- Analytical Ultracentrifugation • Field Flow Fractionation
Physicochemical Analysis	<ul style="list-style-type: none"> • Glycan Profiling • Thermal stability (DSC) • pI (cIEF) • Charge variant Dist.(cIEF and CEX-HPLC) • Disulfide Bond Structure
General Properties	<ul style="list-style-type: none"> • Deliverable Volume • Osmolality • Polysorbate 80 • pH • Appearance

The following attributes for ABP 501 are similar or matched (i.e., amino acid sequence) the reference product (with the exceptions described later in this section):

- Primary Structure
- Bioactivity
- Purity
- Fc Receptor Binding
- Protein Content
- Sub-visible Particles
- Higher Order Structure
- Biologic Analysis and Mechanism of Action Exploration
- High Molecular Weight Variants/Aggregates
- Physicochemical Analysis
- General Properties

Tier 1 statistical equivalence was performed by the CMC Stats reviewer for the Tier 1 assays, sTNF-binding and potency (sTNF- α apoptosis inhibition). For the TNF- α binding assay, 10 batches of ABP 501, 10 batches of US-licensed Humira, and 10 batches of EU-approved Humira were evaluated. For the TNF- α apoptosis inhibition, 10 batches of ABP 501, 21 batches of US-licensed Humira, and 18 batches of EU-approved Humira were included in the analysis. The statistical analysis using equivalence testing met the pre-determined equivalence margin of $\pm 1.5 \sigma_R$.

While the TNF binding and neutralization assessed by Tier 1 assays is generally regarded by literature as the main mechanism of action by adalimumab, other mechanism have also been proposed. These include reverse signaling of mTNF- α positive cells, antibody dependent cell-mediated cytotoxicity of mTNF- α positive cells and/or complement dependent cytotoxicity of mTNF- α positive cells, and induction of regulatory macrophages in mucosal healing. It is possible that the relative role and importance of adalimumab activity for each of these mechanisms may differ from indication to indication. The sponsor developed functional assays to assess each potential mechanism of action for ABP 501. A summary of the potential mechanisms is presented in the table below. In each case, results support a conclusion of highly similar for ABP 501 relative to US-licensed Humira.

MOA of Humira	RA, JIA	AS	PsA	PsO	CD	UC	Criteria Met
Mechanisms involving the Fab (antigen binding) region:							
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF	Known	Known	Known	Known	Likely	Likely	Yes
Reverse (outside-to-inside) signaling via binding to tmTNF	-	-	-	-	Likely	Likely	Yes
Mechanisms involving the Fc (constant) region:							
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible	Yes
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible	Yes
Induction of regulatory macrophages in mucosal healing	-	-	-	-	Plausible	Plausible	Yes
ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's disease; CDC: complement-dependent cytotoxicity; JIA: juvenile idiopathic arthritis; MOA: mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; UC: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF							

Source: FDA Advisory Committee briefing materials for Arthritis Advisory Committee, July 12, 2016.

Each general antibody protein biochemistry attribute in the two pairwise comparisons for ABP 501 (versus US-licensed Humira and EU-Approved Humira) met the pre-determined criteria with the following exceptions:

- Glycosylation profile relative to both US-licensed Humira and EU-Approved Humira (% high mannose, % sialylation, % galactosylation, % afucosylation, and % total afucosylation [EU-Approved Humira only])
- Purity (rCE-SDS) relative to both US-licensed Humira and EU-Approved Humira for NGHC (non-glycosylated heavy chain) and relative to US-licensed Humira for %LC+%HC (light chain + heavy chain).
- Purity (nrCE-SDS) relative to US-licensed Humira for % pre-peaks and % main peak.
- Charge Variant profile (% acidic peak [age-adjusted only], % main peak and % basic peak) relative to both US-licensed Humira and EU-Approved Humira.

In each case, the impact of the slight differences in the attributes and resultant residual uncertainty is mitigated by additional information and analysis provided by the applicant. Specifically, functional assays that assess biological activity known to be influenced by the attributes were evaluated in each case. These functional data unanimously demonstrate that the modest changes do not correspond to a change in product performance and do not preclude a determination of highly similar for ABP 501 relative to US-licensed Humira.

In summary, the totality of evidence supports a conclusion:

- That ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components.

- That a sufficiently robust analytical bridge was established to support the use of EU-Approved Humira as a comparator in clinical trial 20120263.
- That ABP 501 and US-licensed Humira share an identical primary sequence.
- That ABP 501 demonstrates statistical equivalence of *in vitro* measures of TNF- α binding and TNF- α neutralization relative to US-licensed Humira.
- That an appropriate panel of functional assays were employed that measure potential secondary mechanisms of action of anti-TNF monoclonal antibodies and that results meet quality range criteria.
- That based on comparative data between ABP 501 and US-licensed Humira for protein content and deliverable volume, the 40 mg/0.8 mL and 20 mg/0.4 mL pre-filled syringe presentations, and the 40 mg/0.8 mL autoinjector presentation, of ABP 501 have the same total content of drug substance and the same concentration of drug substance as the respective presentations of US-licensed Humira. These presentations meet the statutory same strength requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.
- That while some modest shifts were noted in biochemical attributes noted above, these were within the commercial experience range for bioreactor produced antibodies and were shown by the applicant to not impact either the primary or potential secondary mechanisms of action of adalimumab products.



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

Date: 8/5/2016
To: Administrative File, **STN 761024/0**
From: Bo Chi, Ph.D., CDER/OPQ/OPF/DMA/Branch IV
Endorsement: Patricia Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA/Branch IV
Subject: New 351(k) Biologic License Applications (BLA)
Applicant: Amgen Inc.
US License: 1080
Facility: Amgen, Inc. (Amgen Thousand Oaks or ATO)
One Amgen Center Drive
Thousand Oaks, CA
FEI: 2026154
Product: anti-TNF α monoclonal antibody (ABP 501)
Dosage: 20 mg/0.4 mL, 40 mg/0.8 ml (50 mg/ml), liquid, subcutaneous injection
Indications: Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) (4 years of age and older), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps)
BsUFA date: September 25, 2016

Recommendation: The drug substance part of this BLA is recommended for approval from quality microbiology perspective.

Review Summary

Amgen has submitted this Biologics License Application (BLA) under 351(k) of the Public Health Service Act for ABP501 to seek licensure for a subset of indications for which the US-licensed Humira is approved. The drug substance (DS) is manufactured at Amgen Thousand Oaks (ATO). The drug product (DP) is manufactured at Amgen Manufacturing Ltd (AML). The application contains CMC information in an eCTD format.

This review contains an assessment of the ABP501 drug substance section of the BLA from microbiology perspective.

Assessment

Drug Substance (3.2.S)

General Information (3.2.S.1)

ABP501 is a recombinant fully human monoclonal antibody binds to human tumor necrosis factor alpha (TNF α), a cytokine mediates the inflammatory response, and prevents it from binding to TNF α receptor 1 and TNF α receptor 2. ABP501 is manufactured using Chinese hamster ovary (CHO) cells. The formulation of DS contains (b) (4)

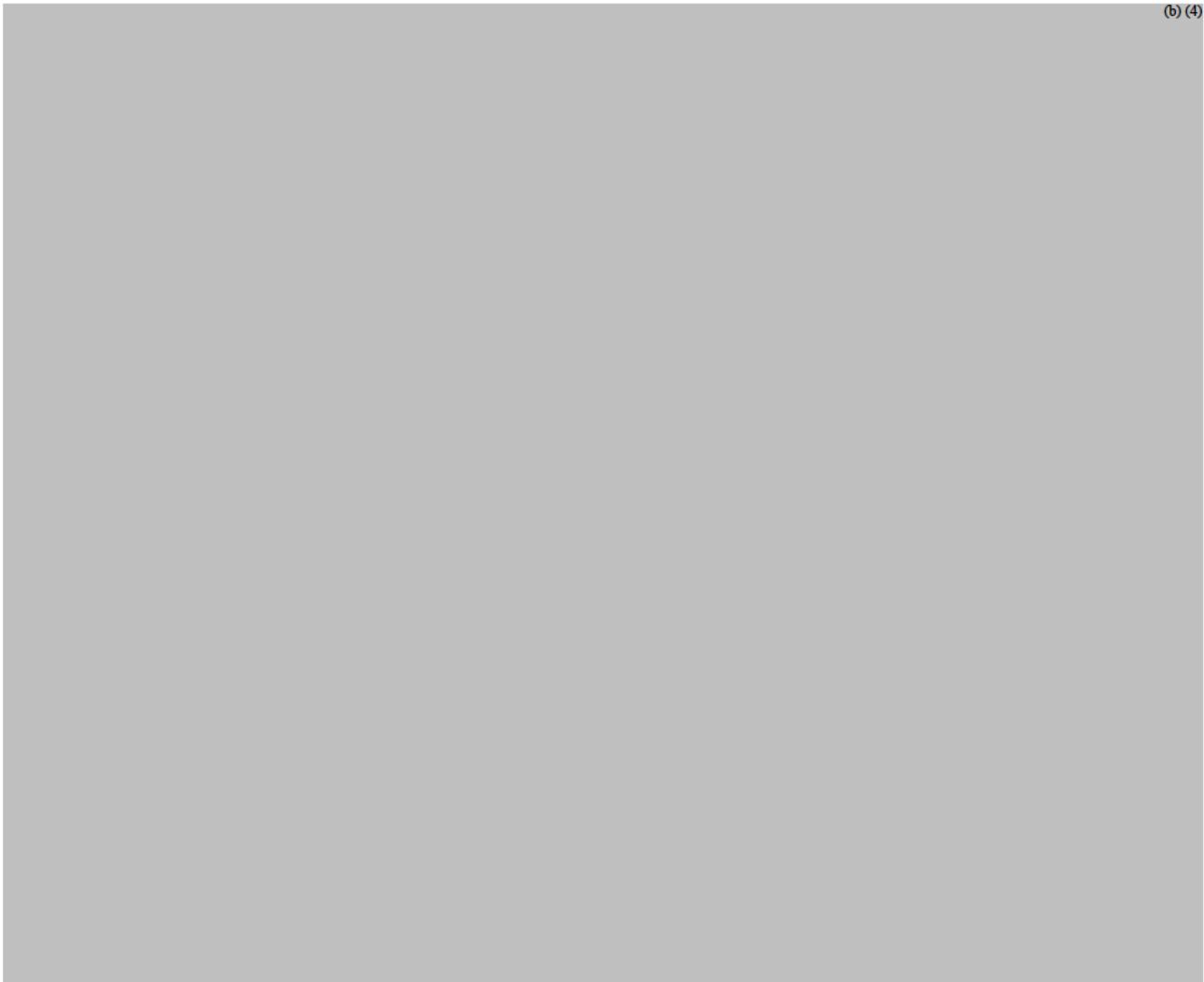
Manufacture (3.2.S.2)

Manufacturer(s) (3.2.S.2.1)

Drug substance (DS) manufacturing, Drug substance in-process, lot release, and stability testing, Master cell bank and working cell bank manufacture and storage, Drug product lot release and stability testing

Amgen Thousand Oaks (ATO)
One Amgen Center Drive
Thousand Oaks, CA 91320
FEI: 2026154

Description of Manufacturing Process and Process Controls (3.2.S.2.2) and Controls of Critical Steps (3.2.S.2.4)



Stability (3.2.S.7)

A (b) (4) months expiry period has been proposed for the (b) (4) drug substance stored at (b) (4) (b) (4). C. A minimum of 1 lot of drug substance will be added to the post-approval stability program annually if ABP501 DS is manufactured. No bioburden or endotoxin test is conducted on the (b) (4) on the stability program, which is acceptable.

Reviewer comment: The stability program and data should be further reviewed by the OBP reviewer.

Satisfactory

Conclusion

- I. The drug substance part of this BLA is recommended for approval from quality microbiology perspective.
- II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the OBP reviewer.
- III. See Panorama for compliance status of the facilities.

Primary reviewer signature

Bo Chi -S



Digitally signed by Bo Chi-S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Bo Chi-S,
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Secondary reviewer signature

Patricia F.
Hughestroost -S



Digitally signed by Patricia F.
Hughestroost -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
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47, cn=Patricia F. Hughestroost -S
Date: 2016.08.31 13:46:23 -04'00'



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

Date: 08/29/2016
To: Administrative File, STN 761024/0
From: Steven Fong, Ph.D., Quality Assessment Lead, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
US License: 1080
Applicant: Amgen Inc.
Mfg Facility: Drug Substance: Amgen Inc., Thousand Oaks, CA
FEI #2026154
Drug Product: Amgen Manufacturing Ltd., Juncos, Puerto Rico
FEI #1000110364
Product: ABP 501
Dosage: 20 mg or 40 mg of ABP 501 delivered in prefilled syringes containing, respectively, 0.4 mL or 0.8 mL of 50 mg/mL DP formulation. The prefilled syringes are inserted into autoinjectors.
Indication: Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) (4 years of age and older), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps)
Due Date: 08/26/2016

RECOMMENDATION: The BLA is recommended for approval from a facilities assessment standpoint.

SUMMARY

The subject BLA proposes manufacture of ABP 501 DS and DP, respectively, at Amgen, Inc., Thousand Oaks CA (FEI 2026154), and Amgen Manufacturing Ltd, Juncos, Puerto Rico (FEI 1000110364). API release testing will be conducted at (b) (4)
 DP release and stability testing will be conducted at Amgen Technology Ireland, Dun Laoghaire, Ireland (FEI 3002808497).

ABP 501 is an IgG1 mAb expressed in CHO cells that is proposed as a treatment for rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, and plaque psoriasis. The DP is provided in prefilled syringes containing 0.4 mL or 0.8 mL of a formulation with 50 mg/mL of ABP 501 protein, 10 mM

acetate, 9.0% (w/v) sucrose, and 0.10% (w/v) polysorbate 80. The 0.4 mL and 0.8 mL presentations deliver 20 mg and 40 mg, respectively, of ABP 501 protein. Following fill and labeling the syringes are inserted into autoinjectors.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

• 3.2.S.2.1 DS Manufacturers.

The sites proposed for ABP 501 DS manufacture, cell banking operations, and testing are presented below in Table 1.

TABLE 1. Proposed Sites for (b) (4) DS Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
Amgen, Inc. (ATO)	1 Amgen Center Drive Thousand Oaks, CA 91320	2026154	DS manufacture. DS IPC testing. DS release testing. DS stability testing. Raw materials testing. Master and working cell bank manufacture and storage.
Amgen Manufacturing Ltd (AML)	Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777	1000110364	DS lot release and stability testing.
(b) (4)			Mycoplasma and adventitious viral testing of (b) (4) DS.
			Mycoplasma and adventitious viral testing of (b) (4) DS.
			Storage of master and working cell bank.

Reviewer Comment 1: *The facilities for manufacture of ABP 501 DS manufacture and testing were adequately described.*

• Prior Inspection History for DS Manufacturing and Testing Sites

- Amgen, Inc., Thousand Oaks, CA (ATO, FEI 2026154). *Responsibility: DS manufacture and testing.*
 - Inspection Conducted 05/04-22/2015 by LOS-DO. CPGM 7356.002-, 7356.002A-, and 7346.832-based PAI and cGMP inspection that covered PAC codes 56002M and 46832M. The PAI portion was conducted for BLA (b) (4) at ATO. Quality, facilities/equipment, materials, production, laboratory controls, and packaging/labeling systems were covered. The inspection resulted in issuance of a 3-item FDA Form 483 for inadequate investigations into unexplained discrepancies, inadequate environmental monitoring of aseptic processing areas, and inadequate test method documentation for laboratory operations. The firm’s responses were determined to be adequate and the inspection was classified VAI.
 - Inspection Conducted 08/12-27/2013 by LOS-DO. CPGM 7356.002-based CGMP surveillance inspection conducted as a follow-up to an Untitled Letter issued after an

11/13/2012 - 12/12/2012 Postmarketing Adverse Drug Experience (PADE) inspection, a Warning Letter (#11-14) issued after an 06/04-17/2013 combination products inspection, and previous Form FDA 483 observations. Quality, facilities/ equipment, materials, production, laboratory controls, and packaging/labeling systems were covered. The deficiencies raised in the 2012 PADE and 2012 combination products inspections were determined to have been adequately addressed. No Form FDA 483 was issued and the inspection was classified NAI.

- Inspection Conducted 11/13/2012 – 12/12/2012 by LOS-DO. CPGM 7356.002M-based cGMP inspection for manufacture of noncommercial, clinical products. Training, Manufacturing/Design Operations, and Change Management were examined. No Form FDA 483 was issued and the inspection was classified NAI.

Reviewer Comment 2. *PADE and Risk Evaluation and Mitigation Strategy (REMS) investigations of ATO were conducted concomitantly with the 11/13/2012 – 12/12/2012 cGMP inspection. The PADE investigation led to issuance of an 8-item Form FDA 483 for failure to report adverse events, late reporting of adverse events, and lack of procedures. From 06/04-17/2013 a combination device inspection was conducted that led issuance of a Warning Letter (#11-14) dated 01/27/2014 and an OAI classification. The deficiencies identified during the PADE and device investigations were determined to have been adequately addressed during the 08/12-27/2013 inspection.*

- Amgen Manufacturing Ltd, Juncos, Puerto Rico (AML-, FEI 1000110364). *Responsibility: DS lot release and stability testing.* In addition to DS testing, the AML site is also proposed for DP manufacture. The facility is assessed below in the DP portion of this Review.
- (b) (4). *Responsibility: Mycoplasma and adventitious viral testing of (b) (4) DS.* The most recent inspection of this facility was conducted (b) (4) by the (b) (4) DO. This CPGM 7348.808-based surveillance GLP investigation covered a CTL profile and PAC code 48808, and included an assessment of training, operations, SOPs, facilities, equipment, quality assurance, validation studies, archives, contractors, vendors, and electronic records. No FDA Form 483 was issued and the inspection was classified NAI. Previous inspections conducted in the last four years consisted of surveillance investigations performed by the (b) (4) -DO from (b) (4) and (b) (4). The latter covered training, quality, laboratory, materials, facilities, equipment, and processes (receiving, storage and testing). Both resulted in VAI conclusions.
- (b) (4). *Responsibility: Mycoplasma and adventitious viral testing of (b) (4) DS.* The most recent inspection of this facility was conducted (b) (4) by the (b) (4) DO. This CPGM 7356.002M-based surveillance inspection covered a CTL profile and PAC code 56002M, and included an assessment of quality, laboratories, facility/equipment systems, cell bank operations, environmental/personnel monitoring, training records, sanitation, cleaning, HVAC, and change controls. No FDA Form 483 was issued and the inspection was classified NAI. Previous to the 2016 inspection, a CPGM 7356.002M-based surveillance investigation was

performed by the (b) (4) DO from (b) (4). No FDA Form 483 was issued and the inspection was classified NAI.

- (b) (4) *Responsibility: Mycoplasma and adventitious viral testing of* (b) (4) DS. The most recent inspection of this facility was conducted (b) (4) by CDER DIA, CDER-DMA, and CDER-OBP. This CPGM 7356.002M-, 7346.832-, and ICH Q7A-based PAI was performed in support of the review of BLA (b) (4). Quality, materials, production, laboratory control, facilities, and equipment systems were assessed for bioreactor and purification areas. The inspection resulted in the issuance of a 3-item FDA Form 483 regarding deficiencies in microbial control. The firm's responses were considered adequate and the inspection was classified VAI. Recent inspections conducted prior to the 2016 investigation included a PAI performed (b) (4) by CDER-DIA, -DMA, and -OBP for BLA (b) (4) that resulted in a VAI conclusion, and a surveillance inspection conducted (b) (4) by the (b) (4) DO that resulted in an NAI conclusion.

- **Current Prior Approval Inspection Decisions**

- Amgen, Inc., Thousand Oaks, CA (ATO, FEI 2026154). *DS manufacture and testing*. Inspection Conducted 05/31/2016 - 06/06/2016 by CDER DIA, CDER-DMA, CDER-OBP, and LOS-DO. CPGM 7346.832- and ICH Q7A-based PAI performed in support of the DS review of the subject BLA that covered PAC code 46832M and profile CBI. Quality, materials, production, laboratory control, facilities, and equipment systems were assessed for bioreactor and purification areas. The inspection resulted in the issuance of a 2-item FDA Form 483 regarding inadequate risk assessment for potential contamination (b) (4) and inadequate controls for preventing microbial contamination of the (b) (4) centrifuge. The firm's responses were considered adequate and the inspection was classified VAI.
- Amgen Manufacturing Ltd, Juncos, Puerto Rico (AML-, FEI 1000110364). *DS lot release and stability testing*. Facility approved based on the recommendation of the SJN-DO. The inspectional file assessment for this site is presented below in the DP portion of this Review.
- (b) (4). *Mycoplasma and adventitious viral testing of* (b) (4) DS. Facility approved based on profile.
- (b) (4) *Mycoplasma and adventitious viral testing of* (b) (4) DS. Facility approved based profile.
- (b) (4). *Mycoplasma and adventitious viral testing of* (b) (4) DS. Facility approved based on profile.

Reviewer Comment 3: *The sites proposed for ABP 501 DS manufacture and testing are adequate from the standpoint of inspectional assessment. As noted a PAI was conducted in support of the subject BLA for the ATO site proposed for DS manufacture. The inspection resulted in a VAI conclusion.*

- **3.2.S.2.2. Overview of ABP 501 DS Manufacturing Operations Conducted at ATO.**

(b) (4)



- **3.2.A.1.1. ATO Design and Site Plan, and ABL 501 Manufacturing Areas.**

(b) (4)



CONCLUSION

Adequate descriptions were provided for the ATO (FEI 2026154) and AML (b) (4) (FEI 1000110364) facilities proposed for ABP 501 DS and DP manufacture. The descriptions were verified by inspection. These manufacturing sites, the proposed testing facilities, (b) (4) (b) (4), and the proposed cell bank preparation/storage facility, (b) (4) (b) (4), are currently in a state of compliance. The subject BLA is recommended for approval from the standpoint of facilities assessment.

Steven E. Fong, M.S., Ph.D.
Microbiologist
OPF Division of Inspectional Assessment
Branch 1

Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1



Steven
Fong

Digitally signed by Steven Fong
Date: 8/29/2016 09:31:20AM
GUID: 508da717000297d4c049faedea31f7c1



Zhihao Peter
Qiu

Digitally signed by Zhihao Peter Qiu
Date: 8/29/2016 09:27:31AM
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BLA STN 761024

Product name: ABP 501

Amgen, Inc.

**Jun Park, Ph.D. Reviewer
Joel Welch, Ph.D., Acting Review Chief**

**Office of Biotechnology Products
Division of Biotechnology Review and Research II**

OBP CMC Review Data Sheet

1. **BLA#:** STN 761024
2. **REVIEW DATES:** August 15, 2016
3. **PRIMARY REVIEW TEAM:**

CDTL:	Nikolay Nikolov
Medical Officer:	Keith Hull
Product Quality Team:	Jun Park
	Joel Welch (Application Technical Lead)
Immunogenicity:	Jun Park
Microbiology Drug Substance:	Bo Chi
Microbiology Drug Product:	Lakshmi Narasimhan
Facilities:	Steven Fong
CMC Statistics:	Meiyu Shen
Clinical Pharmacology:	Jiangmen Chen
OBP Labeling:	Jibril Abdus-Samad
RPM:	Sadaf Nabavian
	Keith Olin

4. **MAJOR 21st Century Review DEADLINES**

Filing 74 Day letter:	February 07, 2016
Mid-Cycle Meeting:	April 05, 2016
AC Meeting:	July 12, 2016
Primary Review Due:	August 19, 2016
Secondary Review Due:	August 26, 2016
Wrap-Up Meeting:	August 29, 2016
PDUFA Action Date:	September 23, 2016

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

Communication/Document	Date
Information Request 1 (74-day letter)	December 24, 2015
Information Request 2	February 16, 2016
Information Request 3	March 04, 2016
Information Request 4	March 08, 2016
Information Request 5	March 15, 2016
Information Request 6	May 09, 2016
Information Request 7	May 19, 2016
Information Request 8	June 07, 2016
Teleconference	June 16, 2016
Information Request 9	June 22, 2016
Information Request 10	June 30, 2016
Information Request 11	July 01, 2016
Information Request 12	July 27, 2016

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

Submission	Date Received	Review Completed (Yes/No)
Original Application	November 25, 2015	Yes
Amendment 02	December 31, 2015	Yes
Amendment 11	March 21, 2016	Yes
Amendment 17	June 07, 2016	Yes
Amendment 20	June 27, 2016	Yes
Amendment 23	July 05, 2016	Yes
Amendment 24	July 13, 2016	Yes
Amendment 25	July 14, 2016	Yes
Amendment 27	July 26, 2016	Yes
Amendment 28	July 29, 2016	Yes
Amendment 29	August 02, 2016	Yes
Amendment 30	August 11, 2016	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**

- a. Code Name: ABP 501
- b. Trade Name: Amjevita (pending)
- c. Non-Proprietary/USAN: adalimumab-xxxx (pending)
- d. CAS name: 1446410-95-2
- e. INN Name: adalimumab-xxxx (pending)
- f. Compendial Name: not applicable
- g. OBP systematic name: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [ABP 501]

8. **PHARMACOLOGICAL CATEGORY:** Therapeutic recombinant human monoclonal antibody

9. **DOSAGE FORM:** Injection

10. **STRENGTH:** 0.8 mL/40 mg in PFS and AI
0.4 mL/20 mg PFS

11. **ROUTE OF ADMINISTRATION:** Subcutaneous injection

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
	(b) (4)	(b) (4)	Yes	Sufficient Leachables and Extractables data and primary stability program in BLA. Reviewed by DMA Jun 2016
		Syringe System		
		Needle Shields	Yes	Sufficient Leachables and Extractables data and primary stability

				program in BLA. Not Reviewed.
	(b) (4)	(b) (4)	Yes	Reviewed by CDRH
	Auto Injector			

13. INSPECTIONAL ACTIVITIES:

A PAI was conducted from March 8, 2016 through March 14, 2016. Information about the facility and FDA personnel involved is described below:

Firm: Amgen Inc.
 Location: Thousand Oaks, CA 91320
 Telephone: 805-447-7140

Dates of inspection: May 31 to June 06, 2016
 Days in the facility: 5
 FDA Participants: Bo Chi

Steven Fong
 Joel Welch
 Jun Park
 Marcus Yambot

CDER/OPQ/OPF/DMA
 CDER/OPQ/OPF/DIA
 CDER/OPQ/OBP/DBRRII
 CDER/OPQ/OBP/DBRRII
 ORA/LOS-DO

This pre-license inspection of the drug substance manufacturing facility at Amgen Inc., Thousand Oaks, CA (ATO) was conducted on 5/31-6/6/2016 following a request by Branch IV of Division of Microbiology Assessment, Office of Process and Facilities, Office of Pharmaceutical Quality, CDER under FACTS assignment #11644466. The inspection was conducted to support the approval of Amgen’s BLA STN761024/0 for ABP 501. The inspection covered drug substance manufacturing areas in Building (b) (4), QC laboratories in Building (b) (4), warehouse in Building (b) (4), and Building (b) (4) for the storage of both US-licensed Humira and EU-licensed Humira.

This inspection was system-based and covered Quality, Facilities and equipment, Production, Materials, and Laboratories systems. This inspection was limited to the manufacturing of ABP501 drug substance. No refusals were encountered during the inspection. No sample collection was needed.

A two-item Form FDA 483 was issued to the firm at the end of the inspection on June 6, 2016 with the following observation summaries:

- 1) The information provided does not support that existing procedural controls and process containment are adequate to prevent cross-contamination of ABP 501 drug substance by a potent biological product.
- 2) Equipment is not stored appropriately after cleaning to prevent potential microbial contamination of the ABP 501 (b) (4).

14. CONSULTS REQUESTED BY OBP:

Center/Topic	Date Requested	Status	Recommendation	Reviewer
CDRH – PFS	Feb 16 2016	Pending	Pending	Pending
CDRH - AI	Feb 16 2016	Pending	Pending	Pending

15. QUALITY BY DESIGN ELEMENTS

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

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

16. PRECEDENTS:

None

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
<p>Jun Park, Ph.D. Product Quality Reviewer Division of Biotechnology Review and Research II Office of Biotechnology Products Office of Pharmaceutical Quality, FDA</p>	<p>Jun T. Park -S</p>  <p>Digitally signed by Jun T. Park -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jun T. Park -S, 0.9.2342.19200300.100.1.1=2000596611 Date: 2016.08.23 16:16:21 -04'00'</p>
<p>Joel Welch, Ph.D. Acting Review Chief Division of Biotechnology Review and Research II Office of Biotechnology Products Office of Pharmaceutical Quality, FDA</p>	<p>Joel T. Welch -S</p>  <p>Digitally signed by Joel T. Welch -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joel T. Welch -S, 0.9.2342.19200300.100.1.1=2000443 745 Date: 2016.08.23 16:30:05 -04'00'</p>

B. CC Block

Recipient	Date
Clinical Division BLA RPM	

Division of Biotechnology Review and Research II File/BLA STN 761024	
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SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

We recommend approval of the BLA. The data submitted in this Biologics License Application support the conclusion that the manufacture of ABP 501 is well controlled and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. It is recommended that ABP 501 be approved for human use (under conditions specified in the package insert).

We recommend an expiration dating period of (b) (4) months for ABP 501 drug substance when stored at - (b) (4) °C.

We recommend an expiration dating period of 30 months for ABP 501 drug product when stored at 2-8°C.

We recommend approval of the proposed release and shelf-life specifications for ABP 501 drug substance and drug product.

The similarity assessment performed support that:

- ABP 501 is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components;
- A sufficiently robust analytical bridge was established to support the use of EU-Approved Humira as a comparator in clinical trial 20120263.

II. List of Deficiencies To Be Communicated

There are no CMC deficiencies precluding approval of this BLA.

III. List of Post-Marketing Commitments/Requirement

- 1) Perform a drug product shipping study using the actual approved commercial shipping lane to evaluate the impact of shipment on product quality.
- 2) Perform supplemental method validation to support the introduction of a non-reduced CE-SDS test into the integrated control strategy.

IV. Review of Common Technical Document-Quality Module 1

A. Environmental Assessment or Claim Of Categorical Exclusion

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

V. Primary Container Labeling Review

A separate primary container labeling review was performed by Jibril Abdus-Samad and reviewed by Jun Park and Joel Welch.

VI. Review of Common Technical Document-Quality Module 3.2

The review of module 3.2 is provided below. A review of the product immunogenicity assays is included at the end of the primary review document.

VII. Review of Immunogenicity Assays – Module 5.3.1.4

The anti-drug antibody immunogenicity assay has sufficient sensitivity (< 10 ng/ml) and demonstrates sufficient drug tolerance (detects 250 ng/ml ADA in the presence of up to 250 μ g/ml of ABP 501). Equivalent sensitivity was demonstrated for ABP 501, US-licensed Humira, and EU-Approved Humira.

The current neutralizing antibody assay is a competitive ligand binding assay that possesses lower, but sufficient sensitivity (0.6 to 0.7 μ g/ml) and demonstrates sufficient drug tolerance (5 μ g/ml in the presence of up to 10 μ g/ml adalimumab).

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DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

Reviewer Note: Unless otherwise specified, data tables are copied from the original submission.

S. DRUG SUBSTANCE**3.2.S.1.2 Structure**

ABP 501 is a fully human IgG1 monoclonal antibody expressed in the Chinese hamster ovary (CHO) cell line and consists of 2 heavy chains (HC), and 2 light chains (LC) of the kappa subclass. ABP 501 contains 32 total cysteine residues involved in both intra-chain and inter-change disulfide bonds. Each HC contains 451 amino acids with 4 intra-chain disulfides. Each LC contains 214 amino acids with 2 intra-chain disulfides. Each HC contains an N-linked glycan at the consensus glycosylation site on Asn301. The sequence is presented in the BLA in section 3.2.S.1.2.

Reviewer Comment: The applicant noted that the experimentally determined predominant ABP 501 mass is 148,083 Da, in agreement with the theoretical value of 148,081 Da containing 2 N-linked glycans (1 per heavy chain).

3.2.S.1.3 General Properties

The physical and chemical properties of ABP 501 are summarized in Table 1.

Table 1. Physical and Chemical Properties of ABP 501

Property	Results
Immunoglobulin subclass	IgG1
Biological target	Specific binding to tumor necrosis factor α
Molecular mass ^a	145,194 Da for deglycosylated molecule 148,083 Da including glycosylation (major)
Cysteines	32
Number of disulfide bonds	16
Glycosylation	N-linked: Asn ³⁰¹ at each heavy chain
Extinction coefficient	Theoretical: 1.46 cm ⁻¹ (mg/mL) ⁻¹ at A ₂₈₀ Experimental: 1.39 cm ⁻¹ (mg/mL) ⁻¹ at A ₂₈₀
Isoelectric point (pI)	Theoretical: 8.7 Experimental: 8.5 (main species)
T _m (melting temperatures) ^a	T _{m1} = 74°C (C _{H2} and Fab) T _{m2} = 85°C (C _{H3})

^a Experimentally determined

ABP 501 is a fully human monoclonal immunoglobulin IgG1 that specifically binds to human tumor necrosis factor α (TNF α) and prevents it from binding to tumor necrosis factor alpha receptor 1 (TNFR1, p55TNFR, or TNFRSF1A) and tumor necrosis factor alpha receptor 2 (TNFR2, p75TNFR, or TNFRSF1B). ABP 501 also binds Fc γ Rs and induces both antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) *in vitro*. Additional mechanisms of action are proposed specifically for irritable bowel indications. Specifically, the induction of regulatory macrophages in mucosal healing, and the initiation of reverse signaling (cell apoptosis or inhibition of inflammatory cytokines) are considered to be likely or plausible mechanisms in these indications.

Reviewer Note: A summary of the proposed mechanisms of action have summarized in the table below (adapted from the FDA Briefing Document to the Arthritis Advisory Committee, July 12, 2016).

MOA of Humira	RA, JIA	AS	PsA	PsO	CD	UC
Mechanisms involving the Fab (antigen binding) region:						
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF	Known	Known	Known	Known	Likely	Likely
Reverse (outside-to-inside) signaling via binding to tmTNF	-	-	-	-	Likely	Likely
Mechanisms involving the Fc (constant) region:						
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible
Induction of regulatory macrophages in mucosal healing	-	-	-	-	Plausible	Plausible
ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn’s disease; CDC: complement-dependent cytotoxicity; JIA: juvenile idiopathic arthritis; MOA: mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; UC: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF						

The release and stability test potency assay (evaluated in the similarity section 3.2.R. and the characterization section 3.2.S.3.1, and section 3.2.S.4.3) is an apoptosis inhibition bioassay used to assess the ability of ABP 501 to inhibit TNF α activity. The assay uses a human histiocytic lymphoma cell line. In the assay, a luminogenic substratum with a DEVD sequence is recognized by caspases and cleaved. The amount of luminescence is proportional to caspase activation. Caspase activation is inhibited by ABP 501.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Facility	Address	Responsibility	FDA Registration Number
Amgen Inc. Amgen Thousand Oaks (ATO)	One Amgen Center Drive Thousand Oaks, CA 91320 USA	Drug substance manufacture Drug substance in-process, lot release, and stability testing Master cell bank and working cell bank manufacture and storage	FEI: 2026154 DUNS: 039976196
Amgen Manufacturing Ltd (AML)	Road 31, Kilometer 24.6 Juncos, Puerto Rico 00777 USA	Drug substance lot release and stability testing	FEI: 1000110364 DUNS: 785800020

FEI = Facility Establishment Identifier
DUNS = Data Universal Numbering System

Table 2. Contract Testing Laboratories

Facility	Address	Type of Testing	FDA Registration Number
		(b) (4) mycoplasma and adventitious viral testing	(b) (4)
		(b) (4) mycoplasma and adventitious viral testing	
		(b) (4) mycoplasma testing	

FEI = Facility Establishment Identifier
DUNS = Data Universal Numbering System

Reviewer Comment: *The steps in this section are considered to provide sufficient control to the manufacturing process to recommend licensure.*

3.2.S.2.2 Description of Manufacturing Process and Process Controls



174 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

3.2.R.4 Analytical Similarity

The ABP 501 clinical program includes 3 studies to support the application (Table 1).

Table 1. ABP 501 Clinical Studies

Study Number	Subject Population	Type	Investigational Products
20110217	Healthy subjects	PK similarity, safety, tolerability, immunogenicity	ABP 501, adalimumab (US), adalimumab (EU)
20120262	Rheumatoid arthritis	Efficacy, safety, immunogenicity	ABP 501, adalimumab (US)
20120263	Plaque psoriasis	Efficacy, safety, immunogenicity	ABP 501, adalimumab (EU)

To support the use of clinical data generated using EU-Approved Humira, Amgen has established a scientific bridge between US-licensed Humira and EU-Approved Humira, which is based on 3-pair wise analytical and PK comparisons.

- ABP 501 to US-licensed Humira
- ABP 501 to EU-Approved Humira
- EU-Approved Humira to US-licensed Humira

The table below includes lots of ABP 501 used in the similarity assessment. In total, 24 lots of US-Approved Humira and 18 lots EU-Approved Humira were used in the similarity assessment. For the clinical studies, Amgen used five lots for each of the three products that were included in the similarity assessment.

Table 2. ABP 501 Lots Included in the Analytical Similarity Assessment

Drug Product Lot Number	Drug Product Date of Manufacture	Drug Product Intended Use	Drug Substance Lot Number	Drug Substance Date of Manufacture	Drug Substance Intended Use
0010085288 ^a	Jun 2011	Development, toxicology, stability	30052311 ^b	May 2011	Development, toxicology, stability, primary reference standard
0010085295 ^a	Aug 2011	Development	30071211 ^b	Jul 2011	Development
0010085297 ^a	Sep 2011	Development	30080811 ^b	Aug 2011	Development
0010095541 ^a	Dec 2011	Clinical, stability	0010094220 ^c	Nov 2011	Clinical, stability
0010112898 ^a	Feb 2012	Clinical	0010094219 ^c	Nov 2011	Clinical
0010134483 ^a	Oct 2012	Development, stability	30080811 ^b	Aug 2011	Development
0010156727 ^a	Apr 2013	Clinical, stability	0010094219 ^c	Nov 2011	Clinical
0010155776 ^a	May 2013	Clinical, stability	0010140760 ^c	May 2013	Clinical, stability
0010155784 ^a	Jun 2013	Clinical	0010140761 ^c	May 2013	Clinical, stability
0010178757 ^a	Nov 2013	Clinical, stability	0010140761 ^c	May 2013	Clinical, stability

Page 1 of 2

NA = not applicable. The corresponding drug product lots were not included in the similarity assessment.

^a Drug product lot manufactured at Amgen Thousand Oaks Building (b) (4)

^b Drug substance lot manufactured at Amgen Thousand Oaks Building (b) (4)

^c Drug substance lot manufactured at Amgen Thousand Oaks Building

^d Drug product lot manufactured at Amgen Manufacturing Limited, Building (b) (4) Only deliverable volume and subvisible particles data from these lots are included in analytical similarity assessment.

^e Analytical similarity data (except deliverable volume and subvisible particles) for these lots were generated on drug substance material.

Table 2. ABP 501 Lots Included in the Analytical Similarity Assessment

Drug Product Lot Number	Drug Product Date of Manufacture	Drug Product Intended Use	Drug Substance Lot Number	Drug Substance Date of Manufacture	Drug Substance Intended Use
0010237900 ^d	Feb 2015	Process validation, stability	0010140761 ^c 0010194222 ^c	May 2013 Jun 2014	Clinical, stability Development
0010237902 ^d	Feb 2015	Process validation, stability	0010140761 ^c 0010194222 ^c	May 2013 Jun 2014	Clinical, stability Development
0010237901 ^d	Feb 2015	Process validation, stability	0010194222 ^c	Jun 2014	Development
NA	NA	NA	0010235980 ^{c,e}	Jun 2015	Process validation, stability
NA	NA	NA	0010235981 ^{c,e}	Jun 2015	Process validation, stability
NA	NA	NA	0010235982 ^{c,e}	Jun 2015	Process validation, stability

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NA = not applicable. The corresponding drug product lots were not included in the similarity assessment.

^a Drug product lot manufactured at Amgen Thousand Oaks Building (b) (4)

^b Drug substance lot manufactured at Amgen Thousand Oaks Building (b) (4)

^c Drug substance lot manufactured at Amgen Thousand Oaks Building

^d Drug product lot manufactured at Amgen Manufacturing Limited, Building (b) (4) Only deliverable volume and subvisible particles data from these lots are included in analytical similarity assessment.

^e Analytical similarity data (except deliverable volume and subvisible particles) for these lots were generated on drug substance material.

Reviewer Comments:

The results of the similarity assessment support the following conclusions:

- ABP 501 is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components;
- A sufficiently robust analytical bridge was established to support the use of EU-Approved Humira as a comparator in clinical trial 20120263.
- Method qualification results for methods used in the analytical similarity assessment are considered sufficient, and the proposed quality ranges based on a 3 standard deviation range for Tier 2 attributes are considered appropriate acceptance criteria for each attribute.

A summary of the analytical similarity results are presented in the following table. Throughout the similarity assessment, the number of lots analyzed will be represented as ABP501:US-Licensed Humira: EU-Approved Humira.

Reviewer Comment on Summary Table:

1. For some attributes that are evaluated by multiple Tier comparisons (e.g., a visual view of a CEX-HPLC or SE-HPLC profile is assessed by Tier 3, and numerical values assessed by Tier 2), the higher Tier number is reported in the table below.
2. Some attributes (e.g., orthogonal measures of aggregates) were evaluated using a quality range provided by the applicant. In instances where our review suggests that Tier 3 visual criteria would be more appropriate, the FDA tier assignment is provided in the table below and used in our analysis.
3. Method qualification/verification was considered for all methods used in the assessment. Those methods proposed for specification or inclusions in the integrated control strategy are presented in section 3.2.S.4.3. Functional assays and those assays assigned to Tier 2 had method specific qualification provided by information requests during the course of the BLA review. Tier 3

assays that are general characterization tests (e.g., FTIR or peptide map) do not require product-specific qualification. The in vitro pharmacology assays (denoted below as “Additional Characterization”) that were evaluated by Tier 3 assays included the full study report in module 2.6 of the BLA. Each method has sufficient replicates to consider the values reported to be appropriately precise for use in comparison.

- 4. As noted in the summary assessment table, a pairwise comparison was performed between all three products. EU-Approved Humira failed the acceptance criteria for charge variants (main peak) and non-glycosylated heavy chain (NGHC) and % HC+% LC relative to US-licensed Humira. These slight differences (and consequently failure of the Tier 2 criteria) were also observed in greater magnitude for ABP 501 relative to US-licensed Humira. As with the analysis of the pairwise comparison of ABP 501 to US-licensed Humira, functional assays were used to evaluate the impact of any observed differences. Data from these assays support the conclusion that a sufficiently robust analytical bridge is established to justify the use of EU-Approved Humira in trial 20120263.*
- 5. The numerical ranges provided in the table below reflect the span of the measured values for each attribute, rather than the “Quality Range” used to assess Tier 2 attributes.*
- 6. Several assays included a set of “age-adjusted” values for attributes known to change over the course of shelf life. In these experiments, the applicant extrapolated individual values to the proposed shelf life (ABP 501) and the presumed shelf life (US-licensed Humira and EU-Approved Humira) and used those estimates in the similarity assessment. This review considered both the non-extrapolated values and the extrapolated ones. The non-extrapolated values are reflected in the ranges presented in the table below.*

Similarity Assessment Results								
Category	Test		Tier	Number of Lots (ABP 501: US Licensed Humira: EU-Approved Humira)	US-Licensed Humira Range	ABP 501 Range	EU-Approved Humira Range	ABP 501:US-Licensed Humira/ ABP 501:EU-Approved Humira/ EU-Approved Humira:US-Licensed Humira
Primary Structure	Molecular Mass	Intact mass	3	4:4:4	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass
		Reduced/ Deglycosylated Mass	3	4:4:4	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass
		Reduced Peptide Map	3	9:7:7	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass (No new peptides observed)
		Non-reduced peptide Map	3	2:2:2	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass (Correct disulfide linkages confirmed)
	Glycan Map	% Total Afucosylation	2	10:24:18	9.9 – 12.4	6.6 - 10.8	9.0 – 10.9	Pass/Fail/Pass (ABP 501 Slight trend toward lower level)

		% High Mannose	2	10:24:18	7.5 – 9.7	5.0 – 8.5	6.8 – 8.6	Fail/Fail/Pass (ABP 501 Slight trend toward lower level)
		& Afucosylation	2	10:24:18	1.3 - 1.7	1.6-2.4	1.2-1.7	Fail/Fail/Pass(ABP 501 slight trend toward higher level)
		% Galactosylation	2	10:24:18	18.7 - 21.6	19.9-39.2	17.7-21.5	Fail/Fail/Pass (ABP 501 higher levels)
		% Sialylation	2	10:24:18	0.2 - 0.3	0.5 - 1.3	0.1 - 0.3	Fail/Fail/Pass (ABP 501 higher levels)
	cIEF : Isoelectric point		3	3:3:3	8.45-8.46	8.43-8.44	8.45-8.46	Pass/Pass/Pass
	Extinction coefficient (mg ⁻¹ cm ⁻¹)		3	1:1:1	1.38	1.45	1.45	Pass/Pass/Pass
	Identity by ELISA		3	10:3:3	All positive	All positive	All positive	Pass/Pass/Pass
Higher Order Structure	FTIR		3	6:6:6	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass
	Near UV		3	6:6:6	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass
	DSC		3	6:6:6	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass
Particles and Aggregates	HIAC	≥ 2 μm particles	3	15:7:7	Visually Similar to ABP	Visually Similar to US-Licensed Humira and	Visually Similar to US-Licensed Humira and	
		≥ 5 μm particles		15:7:7				

		≥ 10 µm particles		15:7:7	501 and EU-Approved Humira	EU-Approved Humira	ABP 501	Pass/Pass/Pass
		≥ 25 µm particles		15:7:7				
	MFI:	≥ 5 µm particles	2	15:7:7	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass
		≥ 5 µm non-spherical particles	3	15:7:7	0-192	24-172	18-139	Pass/Pass/Pass
	FFF: Submicron particles		3	3:3:3	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass
	DLS: Submicron particles		3	3:3:3	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass
	AUCSV: Monomer (%)		3	6:6:6	97.4-99.8%	98.4%-99.9%	97.5%-99.5%	Pass/Pass/Pass
	SE-HPLC-LS: Molar mass		3	3:3:3	145 -146 KDa (main) 307-320 KDa (Pre-Peak)	145 -145 KDa (main) 318-322 KDa (Pre-Peak)	145 -146 KDa (main) 310-318 KDa (Pre-Peak)	Pass/Pass/Pass
Product Related Impurities	SEHPLC: % HMW		2	10:23:18	0.3-0.4%	0.1-0.5%	0.3%-0.5%	Pass/Pass/Pass
	rCE-SDS:	% HC+ LC	2	10:23:18	97.8-98.5%	98.3-99.0%	97.9-98.9%	Fail/Pass/Pass
		% NGHC	2	10:23:18	1.1-1.7%	0.5-0.6%	0.9-1.6%	Fail/Fail/Fail
		LMW + MMW	2	10:23:18	<0.4-0.6%	<0.5-0.8%	<0.4-0.9%	Pass/Pass/Pass
	nrCE-SDS:	% Main peak	2	10:23:18	98.1-99.2%	96.7-98.7%	97.3-98.6%	Fail/Pass/Pass
% Pre peaks		2	10:23:18	1.0-2.0%	1.3-3.2%	1.4%-2.7%	Fail/Pass/Pass	

	CEX-HPLC:	% Acidic peaks	2	10:23:18	12.8-15.7%	13.6-20.5%	13.3-16.9%	Pass/Pass/Pass
		% Main peak	2	10:23:18	57.0-63.5%	66.0-69.7%	57.4-67.4%	Fail/Fail/Fail
		% Basic peaks	2	10:23:18	22.3-28.2%	14.0-18.5%	16.2-28.9%	Fail/Fail/Pass
Thermal Degradation	50°C (2 weeks)	SE-HPLC rCE-SDS CEX-HPLC Potency (Bioassay)	3	3:3:3	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass (Lower HMW Species for ABP 501)
	40°C (3 months)	SE-HPLC rCE-SDS CEX-HPLC Potency (Bioassay)	3	2:1:1	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass
	25°C (6 months)	SE-HPLC rCE-SDS CEX-HPLC Potency (Bioassay)	3	2:1:1	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass
General Properties	Protein concentration (mg/mL)		2	10:23:18	48.1 to 52.3	47.9 to 52.6	49.6-53.7	Pass/Pass/Pass
	Deliverable volume (mL)		2	15:14:10	0.80 to 0.81	0.79 to 0.84	0.79 to 0.81	Pass/Pass/Pass
	Osmolality (mOsm/kg)		3	10:3:3	312-313	311-320	298-303	Pass/Pass/Pass
	pH		3	10:3:3	5.2-5.3	5.1-5.2	5.3	Pass/Pass/Pass
	Appearance		3	10:3:3	Pass	Pass	Pass	Pass/Pass/Pass
	Color		3	10:3:3	Pass	Pass	Pass	Pass/Pass/Pass
	Clarity		3	10:3:3	Colorless to Slightly Yellow	Colorless	Colorless	Pass/Pass/Pass
Polysorbate 80		3	10:1:1	0.09%	0.09-0.10%	0.09%	Pass/Pass/Pass	
Process-Related Impurities	HCP-ELISA		3	10:3:3	129-168 ppm	5-46 ppm	87-171 ppm	Pass/Pass/Pass
	HCP-2D DIG		3	10:3:3	Visually Similar to ABP 501 and EU-	Visually Similar to US-Licensed	Visually Similar to US-Licensed	Pass/Pass/Pass

				Approved Humira	Humira and EU-Approved Humira	Humira and ABP 501		
	Protein A	3	10:3:3	< 1 ng/mg	< 1 ng/mg	< 1 ng/mg	Pass/Pass/Pass	
	Residual DNA	3	10:3:3	< 1 pg/mg	< 1 pg/mg	< 1 pg/mg	Pass/Pass/Pass	
Biological Activity	Apoptosis inhibition bioassay	1	10:21:18	95%-114%	98-110%	91-122%	Pass/Pass/Pass (Equivalency Testing)	
	Soluble TNF α binding	1	10:10:10	99%-128%	96%-121%	103-122%	Pass/Pass/Pass (Equivalency Testing)	
	Fc γ RIIIa (158V) binding	2	10:17:15	76%-114%	67%-113%	87-104%	Pass/Pass/Pass	
	Induction of ADCC	2	10:17:15	41%-127%	53%-103%	61-114%	Pass/Pass/Pass	
	Induction of CDC	2	10:17:15	84%-106%	94%-105%	82-104%	Pass/Pass/Pass	
	C1q binding	3	3:3:3	68-75%	67-92%	63-78%	Pass/Pass/Pass	
	FcRn binding	2	10:16:12	92-114%	86%-101%	81-116%	Pass/Pass/Pass	
	Reverse Signaling	2	10:10:12	93-105%	94-107%	92-103%	Pass/Pass/Pass	
	Additional Characterization							
		Binding kinetics to soluble TNF α	3	3:3:3	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass
		Binding to transmembrane TNF α (tmTNF α)	3	3:3:3	100-111%	100%-106%	101-109%	Pass/Pass/Pass
		Inhibition of soluble TNF α -induced IL-8 in HUVEC	3	3:3:3	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass
	Inhibition of soluble TNF α -induced cell death in L929 cells	3	3:3:3	Visually Similar to ABP 501 and EU-	Visually Similar to US-Licensed	Visually Similar to US-Licensed	Pass/Pass/Pass	

				Approved Humira	Humira and EU-Approved Humira	Humira and ABP 501	
	Specificity against LT α in a HUVEC assay	3	3:3:3	No neutralization detected	No neutralization detected	No neutralization detected	Pass/Pass/Pass
	Inhibition of proliferation in an MLR	3	3:3:3	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass
	Fc γ RIa binding	3	3:3:3	92-96%	96-99%	92-94%	Pass/Pass/Pass
	Fc γ RIIa (131H) binding	3	3:3:3	101-105%	95-107%	96-100%	Pass/Pass/Pass
	Fc γ RIIIa (158F) binding	3	3:3:3	83-95%	73-93%	88-98%	Pass/Pass/Pass
	Inhibition of soluble TNF α induced chemokines ex vivo	3	3:3:3	Visually Similar to ABP 501 and EU-Approved Humira	Visually Similar to US-Licensed Humira and EU-Approved Humira	Visually Similar to US-Licensed Humira and ABP 501	Pass/Pass/Pass

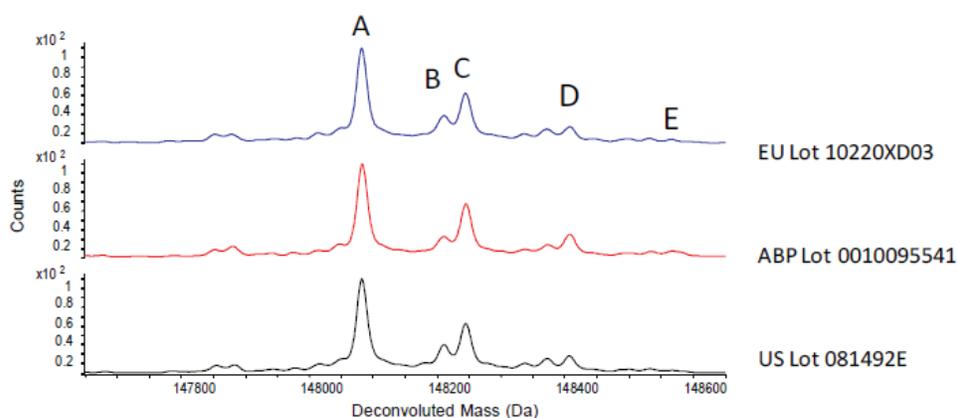
3.2.R.4.4.1 Primary Structure

Reviewer Comment: The methods used for primary structure determination (peptide map and mass spectrometry) did not include validation data as they are standard characterization methods used for a qualitative comparison. This is considered appropriate.

3.2.R.4.4.1.1 Intact molecular Mass (4:4:4)

The intact molecular mass analysis was determined for 4 lots each of ABP 501, US-licensed Humira, and EU-Approved Humira and was determined by electrospray ionization-time of flight-mass spectrometer (ESI-TOF-MS) analysis. The four lots analyzed included three developmental and one clinical lot of ABP 501. A comparison of the profile is shown below.

Figure 2. Intact Molecular Mass for Adalimumab (EU), ABP 501 (Clinical), and Adalimumab (US)



Reviewer Comment: The data provided support the conclusion of identical primary sequences between ABP 501, US-licensed Humira, and EU-Approved Humira. Peak labels reflect the identification of major glycoforms that are expected and potentially the sodium adducts (e.g., Peak B).

3.2.R.4.4.1.2 Reduced and Deglycosylated Molecular Masses of HC and LC using ESI-TOF-MS (4:4:4)

In addition to the assessment of the intact molecular mass, the reduced and deglycosylated molecular mass was assessed (data not shown) for 4 lots each of ABP 501, US-Licensed Humira and EU-Approved Humira.

Reviewer Comment: The peak profiles of the reduced/deglycosylated molecular masses of HC and LC between ABP 501, US-licensed Humira and EU-approved Humira are identical. Data support a conclusion of high similarity.

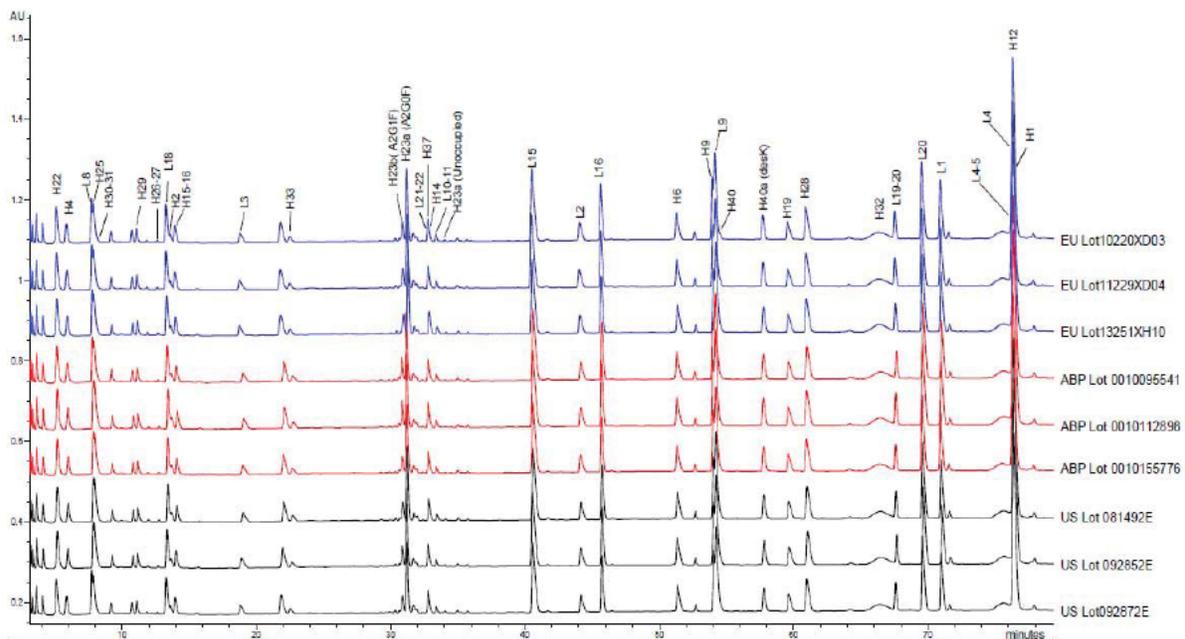
3.2.R.4.4.1.3 Reduced Peptide Map (9:7:7)

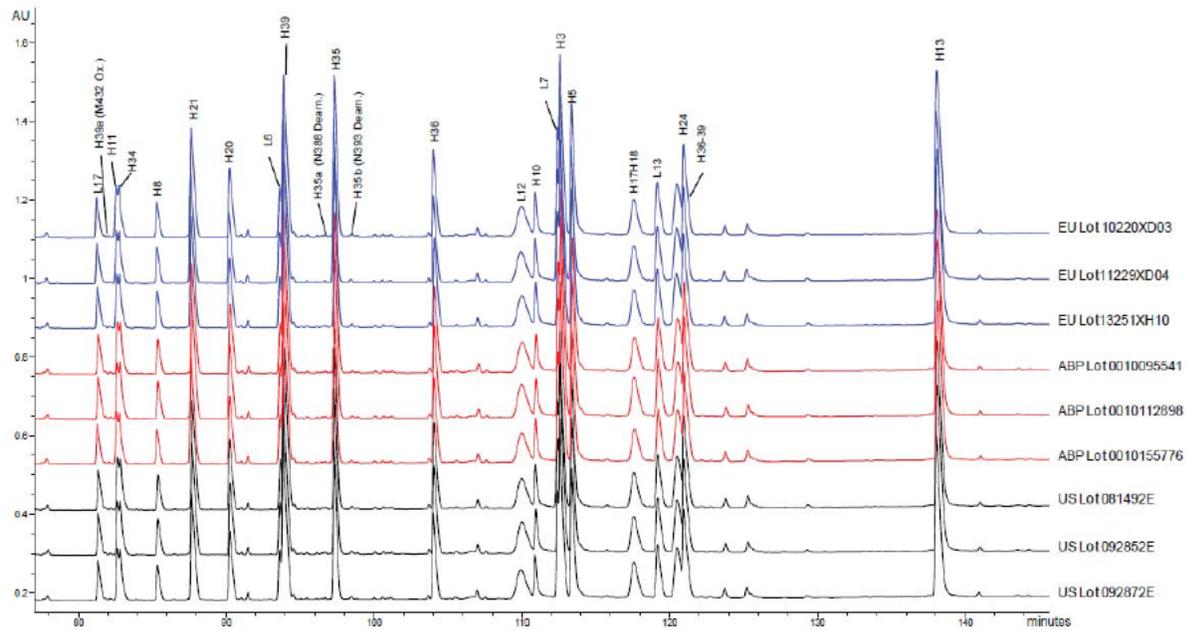
The reduced peptide map was used to compare the amino acid sequence and was performed on 9 ABP 501 lots and 7 lots each of US-licensed Humira and EU-Approved Humira. Amgen has submitted the tryptic peptide map chromatograms for the side-by-side comparison of ABP 501, US-licensed Humira, and EU-approved Humira and provided the differences between the observed and theoretical masses for the tryptic peptides in the submission. Graphic images of the peptide maps were copied directly from the submission and are shown below..

Reviewer Comment: The data support the following conclusions:

- All of the overlays showed similar peak profiles for the 3 products, with 100% coverage observed

- The differences between the observed and theoretical masses for all tryptic peptides were within 15 ppm for all 3 products.
- The same post-translational modifications (PTM) were detected between ABP 501, US-licensed Humira, and EU-approved Humira, and no new species were detected above the integrity limit (IL) of 12.6 mAU in the tryptic peptide maps for all 3 products.
- Examination of the amino acid sequence revealed a single consensus site for N-linked glycosylation located on the heavy chain at N301 in all ABP 501, US-licensed Humira, and EU-approved Humira peptide maps.
- Five low abundance peptides were identified to contain modifications and were observed in all ABP 501 and adalimumab lots. The elution positions and MS/MS spectra of these peptides were the same for all 3 products. These variants include:
 - N-linked glycan
 - unprocessed C-terminal lysine of the HC.
 - deamidation and oxidation





3.2.R.4.4.1.4 Disulfide Structure – Non-reduced Peptide Map (2:2:2)

Non-reduced peptide map was performed on 2 lots each of ABP 501, US-licensed Humira, and EU-Approved Humira to compare the disulfide structure (data not shown).

Reviewer Comment: *The expected and equivalent (for an IgG1 antibody) disulfide linkage was observed among all products.*

Taken in totality, the data support the conclusion that all three products share an identical primary sequence.

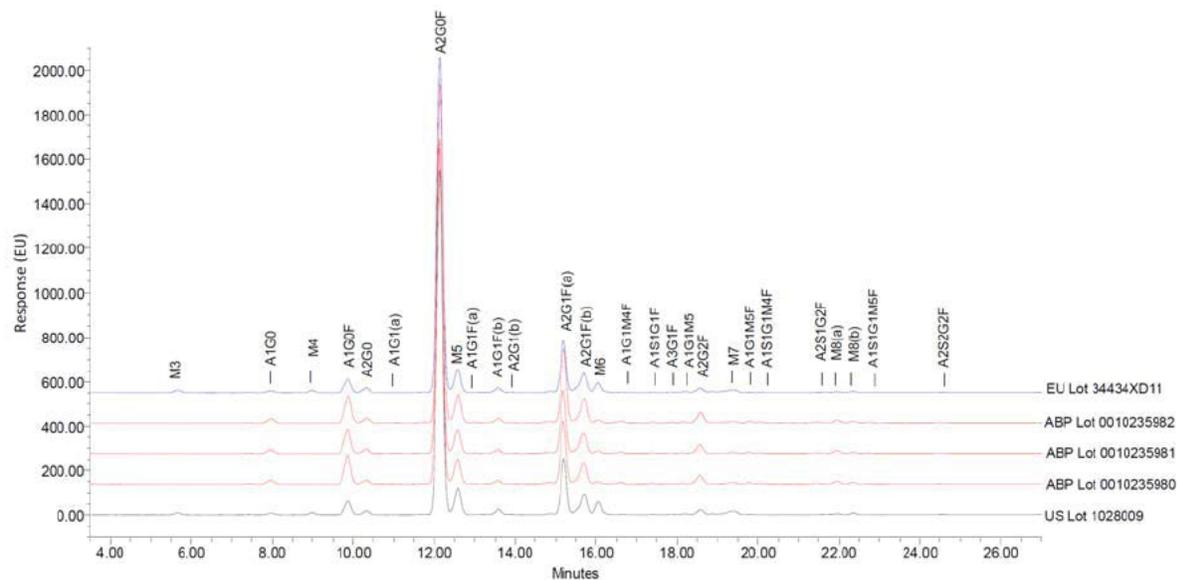
3.2.R.4.4.1.5 Glycan Map (10:24:18)

Amgen submitted a comparison of the glycan map chromatograms as depicted in the figure copied below and provided the relative amounts of the individual glycan species for ABP 501, US-licensed Humira, and EU-approved Humira in the submission.

Reviewer Comment: *This method is proposed for a specification test and the validation is described in section 3.2.S.4.3.*

The overlay shows that three products have similar profiles with the same glycans present in consistent but slightly different ratios. Glycans known to affect clinical performance based on literature reports include: 1) those that lack core fucose (denoted as afucosylated forms), which can affect binding to FcγRIIIa on NK cells, and ultimately ADCC activity; 2) high mannose forms, which also can affect the PK profile and ADCC activity; 3) sialylation, which can affect the PK profile and 4) galactosylation, which may influence CDC activity.

Figure 14. HILIC Glycan Map for Adalimumab (EU), ABP 501 (Validation), and Adalimumab (US)



Glycan Groups as Tier 2

The following glycan groups were evaluated as part of the similarity assessment as Tier 2, based on their potential to impact PK and/or effector functions:

Reviewer Comment: The grouping of the glycans into the proposed categories is considered appropriate.

- % Total afucosylation**, which includes all glycan structures lacking core fucose, that have the potential to impact ADCC

$$\% \text{ Total afucosylation} = \%A1G0 + \%A1G1(a) + \%A2G0 + \%A2G1(b) + \%A1G1M5 + \%M3 + \%M4 + \%M5 + \%M6 + \%M7 + \%M8(a) + \%M8(b)$$
- % Afucosylation**, which includes afucosylated complex and hybrid glycans

$$\% \text{ Afucosylation} = \%A1G0 + \%A1G1(a) + \%A2G0 + \%A2G1(b) + \%A1G1M5$$
- % High mannose**, which also has the potential to impact PK, and ADCC

$$\% \text{ High Mannose} = \%M5 + \%M6 + \%M7 + \%M8(a) + \%M8(b)$$
- % Galactosylation**, which has the potential to impact CDC

$$\% \text{ Galactosylation} = \%A1G1(a) + \%A1G1F(a) + \%A1G1F(b) + \%A2G1(b) + \%A2G1F(a) + \%A2G1F(b) + \%A1G1M4F + \%A3G1F + \%A1G1M5 + \%A2G2F + \%A1G1M5F + \%A2S1G2F$$
- % Sialylation**, which has the potential to impact PK and ADCC

$$\% \text{ Sialylation} = \%A1S1G1F + \%A2S1G2F + \%A2S2G2F + \%A1S1G1M4F + \%A1S1G1M5F$$

Testing results for % total afucosylation, % high mannose, % afucosylation, % galactosylation, and % sialylation are listed below.

Total Afucosylation

Figure 20. Total Afucosylation- ABP 501 Compared to Adalimumab (US) Quality Range

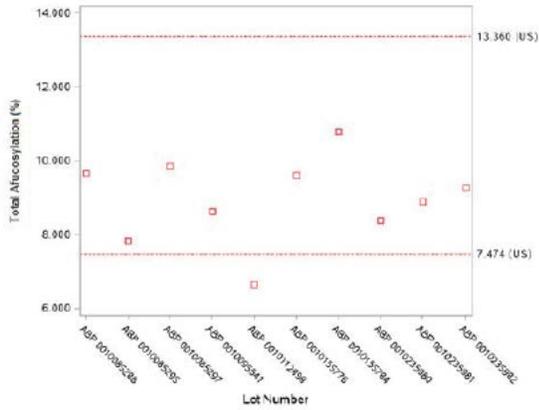


Figure 25. Total Afucosylation - ABP 501 Compared to Adalimumab (EU) Quality Range

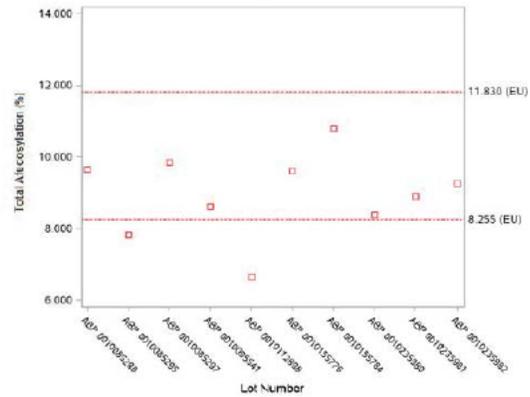
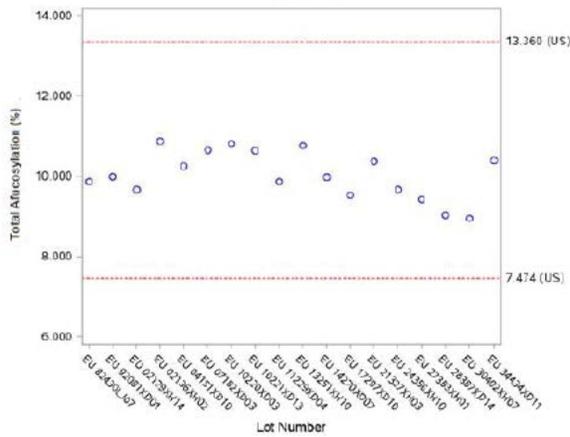


Figure 30. Total Afucosylation - Adalimumab (EU) Compared to Adalimumab (US) Quality Range



Afucosylation

Figure 22. Afucosylation - ABP 501 Compared to Adalimumab (US) Quality Range

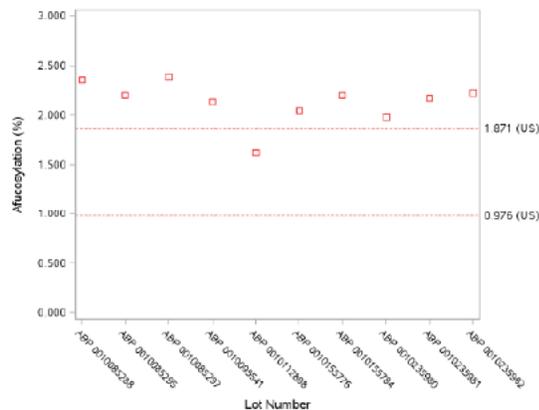


Figure 27. Afucosylation - ABP 501 Compared to Adalimumab (EU) Quality Range

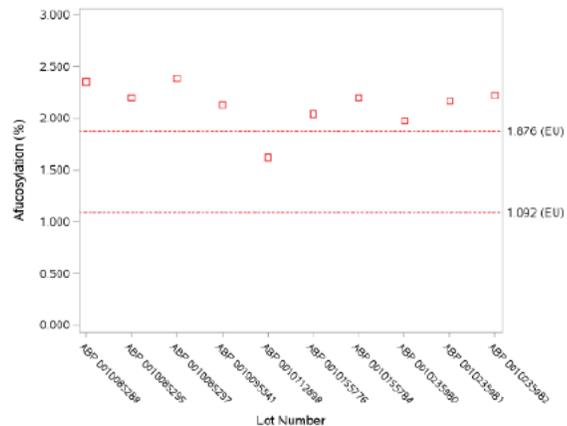
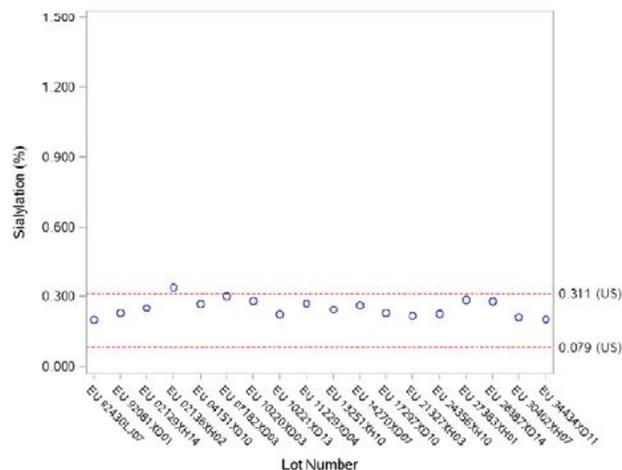


Figure 34. Sialylation - Adalimumab (EU) Compared to Adalimumab (US) Quality Range



Reviewer Comment: The following conclusions are noted for the glycosylation profile comparison among the three products:

Although the same glycans are present among all three products in the overlay, they are present in slightly different ratios

- *Regarding % total afucosylation, ninety percent (90%) of the ABP 501 lots are within the quality range of US-licensed Humira. Therefore, ABP 501 is considered similar to US-licensed Humira for % total afucosylation.*
- *Regarding afucosylation (calculated without the high mannose contribution), the results for ABP501 fall just above of the quality range for US licensed Humira proposed by the applicant. Afucosylation of ABP501 is higher than both US-licensed Humira and EU-Approved Humira.*
- *Levels of sialylation fall outside the quality range for ABP 501, though levels are quite low for all products (i.e., less than 1%).*
- *Levels of galactosylation fall above the quality range for ABP 501, relative to both US-Approved Humira and EU-Licensed Humira.*

The impact of differences in the attributes and resultant residual uncertainty is mitigated by the additional information generated by the applicant:

- *PK can be impacted by differences in glycosylation, in particular sialic acid. The results of study 2107 show that PK is similar for ABP 501, US-licensed Humira and EU-approved Humira.*
- *FcyRIIIa binding (both 158V and 158F), which may be affected by afucosylation and high mannose, is similar in ABP 501, US-licensed Humira and EU-approved Humira*
- *ADCC activity and CDC activities, which are mediated by FcyRIIIa and are indirectly linked to afucosylation/high mannose and galactosylation, respectively, are also similar in in ABP 501, US-licensed Humira and EU-approved Humira*

Additionally, Amgen has committed to establishing a specification (a real time release test at the (b) (4) step) for (b) (4) (IR response dated July 5, 2016) and (b) (4) (IR response dated June 22,

2016) to ensure no larger differences than that observed in the similarity assessment for afucosylation are observed. This is considered adequate.

Additionally, Amgen noted that for the US-licensed Humira quality range for % galactosylation, ABP 501 lots manufactured during early development demonstrated relatively higher % galactosylation levels. Improvement in ABP 501 manufacturing process controls (b) (4) led to % galactosylation levels in subsequent ABP 501 clinical and validation lots to be more similar.

(b) (4)

. Refer to section 3.2.S.2.5.

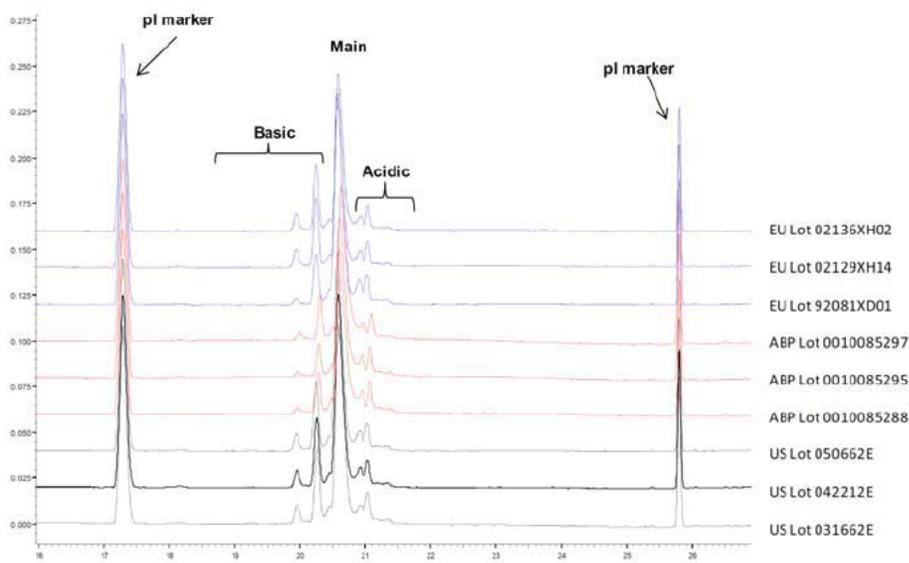
Taking together the results of the additional information (clinical and analytical) provided by the applicant, and the adjustment in the process and control strategy to ensure that ABP 501 maintains quality attributes in the range of US-licensed Humira, address the residual uncertainty raised by the differences in glycosylation between ABP501 and US licensed Humira. We conclude that the difference observed in glycosylation would not result in clinically meaningful differences and would not preclude a determination that ABP 501 is highly similar to US-licensed Humira.

3.2.R.4.4.1.6 Isoelectric Point - Capillary Isoelectric Focusing (cIEF) (3:3:3)

The determination of the isoelectric point was performed on 3 lots each of ABP 501, US-licensed Humira, and EU-approved Humira.

A comparison of the cIEF profiles for ABP 501, US-licensed Humira, and EU-approved Humira is provided in Figure 35.

Figure 35. Comparison of cIEF Profiles for Adalimumab (EU), ABP 501, and Adalimumab (US)



Reviewer Comment: The applicant did not analyze the charge variant profile by this technique within the context of related substances (charge variants) as CEX-HPLC was used. The applicant provided data

supporting the conclusion that the distribution profiles and peak intensities of the electropherograms were similar among ABP 501, US-licensed Humira and EU-approved Humira. The applicant also claims that differences in the profile measured by this method are equivalent to that noted by CEX-HPLC. -. This was assessed by Tier 3 criteria and no specific method qualification was provided given that a single experiment with pI markers for calibration was performed.

Data support the conclusion of high similarity between ABP 501 and US-licensed Humira, and the adequacy of the scientific bridge to support the use of EU-Approved Humira in Trial 20120263.

3.2.R.4.4.1.7 Extinction Coefficient (1:1:1)

Experimental determination of the extinction coefficient was performed on 1 lot each of ABP 501, US-licensed Humira, and EU-Approved Humira.

The experimental extinction coefficients of ABP 501, US-licensed Humira and EU-Approved Humira were determined by amino acid analysis (AAA). Samples were dialyzed into phosphate buffered saline (PBS) and diluted to approximately 1 mg/mL, based on the label content prior to AAA. The absorbance at 280 nm was measured for the dialyzed and diluted samples using a calibrated UV spectrophotometer referenced against PBS. Three aliquots of each dialyzed and diluted sample were subjected to vapor phase hydrolysis with boiling hydrochloric acid. The hydrolyzed samples were then reconstituted in sample dilution buffer, and the resulting amino acids were quantified by strong cation exchange chromatography and post-column derivatization with ninhydrin using an amino acid analyzer. Triplicate measurements were performed.

The experimentally-determined extinction coefficients for ABP 501, US-licensed Humira, and EU-approved Humira are provided in Table 14.

Table 14. Experimental Extinction Coefficient Determination of Adalimumab (EU), ABP 501, and Adalimumab (US)

Lot Number	Extinction coefficient ($\text{mg}^{-1} \cdot \text{cm}^{-1} \cdot \text{mL}$)
EU 10220XD03	1.45
ABP 0010085289 ^a	1.45
US 014182E	1.38

^a Extinction coefficient was tested on ABP 501 reference standard lot 0010085289, which was filled using drug substance lot 30052311. The same drug substance lot was used to fill drug product lot 0010085288, which is included in the similarity assessment.

Reviewer Comment: ABP 501 has a similar experimentally-determined extinction coefficient compared to US-licensed Humira and EU-approved Humira.

The applicant uses a value of 1.39 $\text{mg}^{-1} \text{cm}^{-1} \text{mL}$ for the experimental determination of protein concentration that was established earlier in development. Given that close agreement with the experimental value, this appears appropriate.

3.2.R.4.4.1.8 Identity by ELISA (10:3:3)

Ten ABP 501 lots were compared with 3 lots each of US-licensed Humira and EU-Approved Humira using the ID test proposed for release of DS and DP.

Reviewer Comment: The method was demonstrated to be sufficient to discriminate against other antibody products, including against Enbrel an additional TNF- α antagonist manufactured by Amgen. The data support a determination of high similarity between ABP 501 and US-licensed Humira, and the adequacy of the scientific bridge to support the use of EU-Approved Humira in Trial 20120263. This method is proposed for identification at release, and the validation is presented in section 3.2.S.4.3.

3.2.R.4.4.2 Higher Order Structure

The higher order structures of ABP 501, US-licensed Humira, and EU-Approved Humira US-licensed Humira, and EU-approved Humira were characterized as follows:

- The secondary structure was analyzed by Fourier-transformed infrared (FTIR) spectroscopy.
- Similarity of the tertiary structure was assessed by near ultraviolet (UV) circular dichroism (CD) spectroscopy.
- The thermal stability and the overall conformation of the proteins were analyzed by differential scanning calorimetry (DSC).

Reviewer Comment: Higher order structure assays are considered Tier 3 and appropriately qualified in the absence of matrix interference. Thus, no additional qualification of these methods was provided.

3.2.R.4.4.2.1 FTIR (6:6:6)

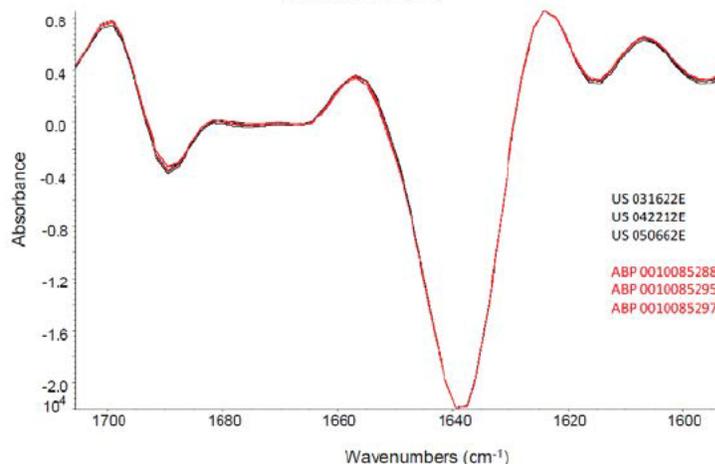
The FTIR method was performed on 6 lots each of ABP 501, US-licensed Humira, and EU-Approved Humira.

A representative second derivative FTIR spectrum of ABP 501 is provided below.

The second derivative spectrum was calculated using a 9 point smoothing of the original spectra and results are listed in the submission.

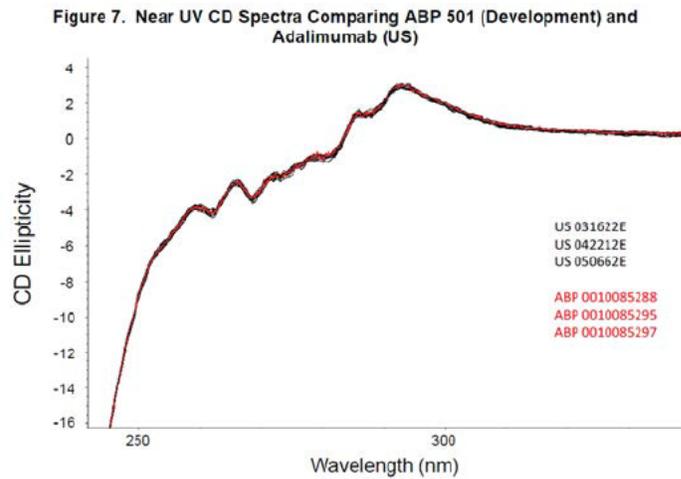
Reviewer Comment: Amgen submitted spectral similarity calculations of ABP 501, US-licensed Humira, and EU-approved Humira. Though the applicant performed a FTIR spectral similarity reference comparison that was evaluated by “tier 2” criteria, our review considered only a visual Tier 3 criteria. The data sets provide by the applicant, both the reference comparison and the spectral overlays, support a determination of high similarity between ABP 501 and US-licensed Humira, as well as the adequacy of the scientific bridge to support the use of EU-Approved Humira in Trial 20120263.

Figure 1. Second Derivative FTIR Spectra Comparing ABP 501 (Development) and Adalimumab (US)



3.2.R.4.4.2.2 Near Ultraviolet Circular Dichroism (6:6:6)

An assessment of near UV CD was performed on 6 lots each of ABP 501, US-licensed Humira, and EU-Approved Humira.



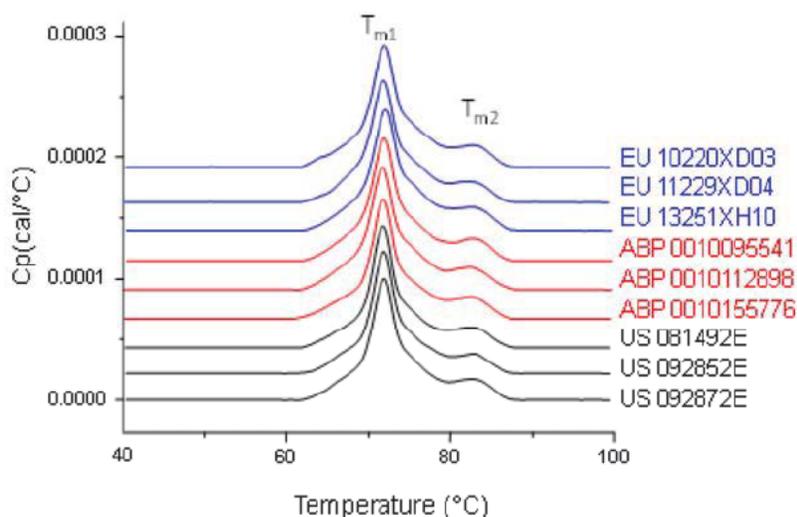
Reviewer Comment: *As with FTIR spectra, the applicant proposed a similarity reference comparison that was evaluated by “tier 2” criteria. However, our review considered only a visual Tier 3 criterion. The data sets provide by the applicant, both the reference comparison and the spectral overlays, support the conclusion that ABP 501 and US-licensed Humira are similar, as well as the adequacy of the scientific bridge to support the use of EU-Approved Humira in Trial 20120263..*

3.2.R.4.4.2.3 Differential Scanning Calorimetry (DSC) (6:6:6)

The DSC method was performed on 6 lots each of ABP 501, US-licensed Humira, and EU-Approved Humira.

An Overlay of the DSC scans for ABP 501, US-licensed Humira, and EU-Approved Humira are shown below. There are 2 thermal transitions at approximately 73.5°C and 84.6°C.

Figure 14. DSC Scans of Adalimumab (EU), ABP 501 (Clinical), and Adalimumab (US)



Reviewer Comment:

As with FTIR and CD, the applicant proposed a similarity reference comparison that was evaluated by “tier 2” criteria. However, our review considered only a visual Tier 3 criterion. The data sets provide by the applicant, both the reference comparison and the spectral overlay, support a determination of high similarity between ABP 501 and US-licensed Humira, as well as the adequacy of the scientific bridge to support the use of EU-Approved Humira in Trial 20120263.

3.2.R.4.4.3 Product-Related Substances and Impurities

Product-related substances and impurities of ABP 501, US-licensed Humira and EU-Approved Humira were assessed, as follows:

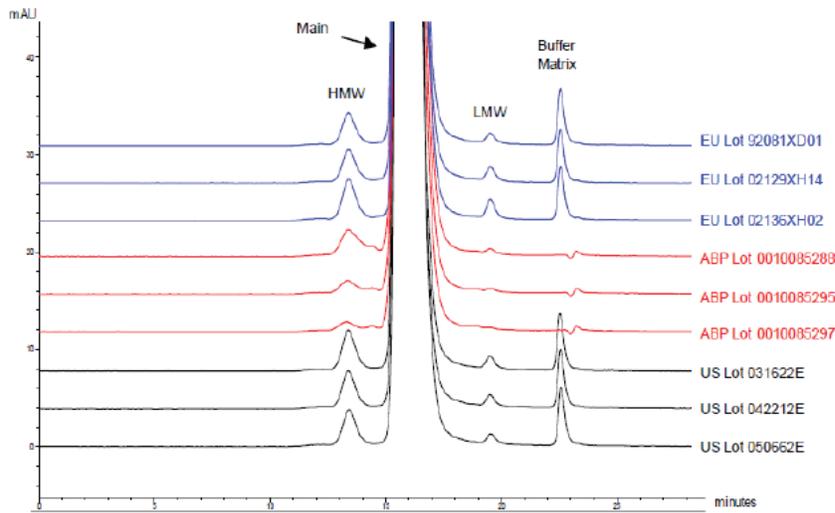
- Size variants were assessed by size exclusion high performance liquid chromatography (SE-HPLC), reduced capillary electrophoresis-sodium dodecyl sulfate (rCE-SDS), and non-reduced capillary electrophoresis-sodium dodecyl sulfate (nrCE-SDS)
- Charge variants were assessed by cation exchange high performance liquid chromatography (CEX-HPLC).

3.2.R.4.4.3.1 Size Exclusion – High Performance Liquid Chromatography (10:23:18)

SE-HPLC was performed on 10 ABP 501 lots, 23 US-licensed Humira lots, and 18 EU-Approved Humira lots. The similarity assessment was performed on (1) SE-HPLC profile comparison, which was analyzed using a Tier 3 statistical method; and (2) % HMW, which was analyzed using a Tier 2 statistical method. This Tier 2 method applied the quality range, defined as the Mean \pm 3SD of 23 US-licensed Humira lots. The similarity acceptance criteria provided that 90% of the ABP 501 lots fall within the quality range.

Reviewer Comment: This test is proposed as a specification test, and validation is presented in section 3.2.S.4.3.

A comparison of the SE-HPLC profiles for ABP 501, US-licensed Humira, and EU-approved Humira lots is provided below. Orthogonal measures of particle size are described in the particles and aggregates section (3.2.R.4.4.4).



The quality range against US-licensed Humira and EU-approved Humira, respectively, for SE-HPLC % HMW is provided in Figures 6 and 7.

Reviewer Comment:

The numerical comparison initially proposed by the applicant for the evaluation of similarity reflects an “age adjustment” performed by the applicant so that both ABP 501 and US-licensed Humira are compared at their proposed/presumed relative shelf life. A comparison using only the release values demonstrates that ABP 501 has a lower level of aggregates relative to US-licensed Humira. This comparison was provided in the March 21 2016 IR response.

Both the age-adjusted SE-HPLC HMW and the initial results are presented below

Figure 6. SE-HPLC HMW - ABP 501 Compared to Adalimumab (US) Quality Range

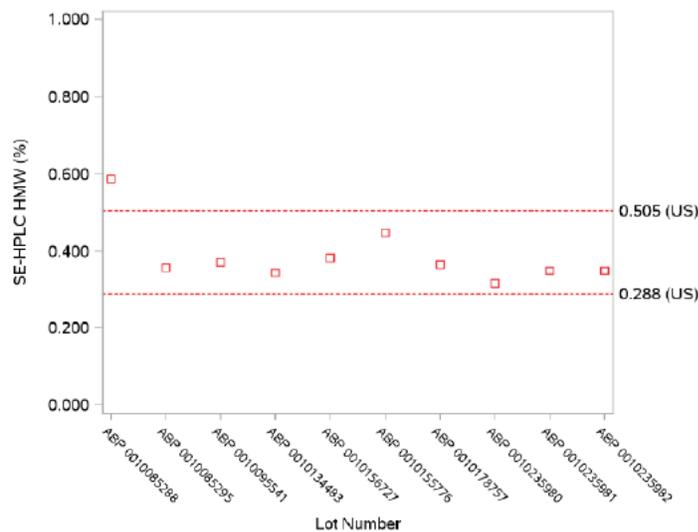
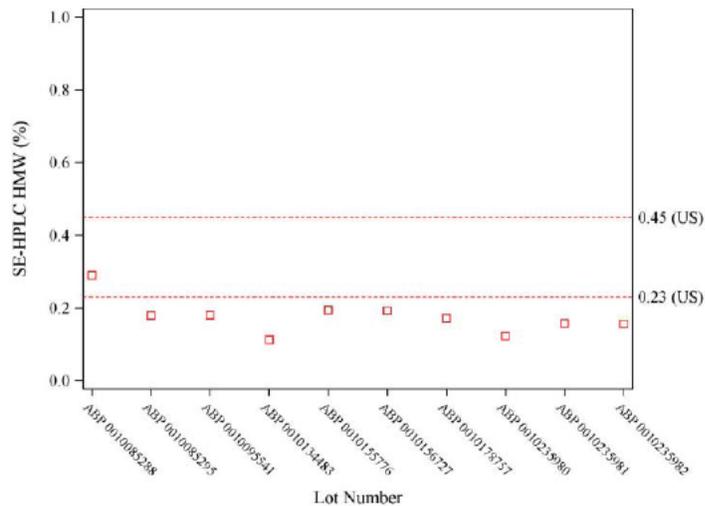


Figure 11. SE-HPLC HMW - ABP 501 Compared to Adalimumab (US) Quality Range (Initial Results)



In summary:

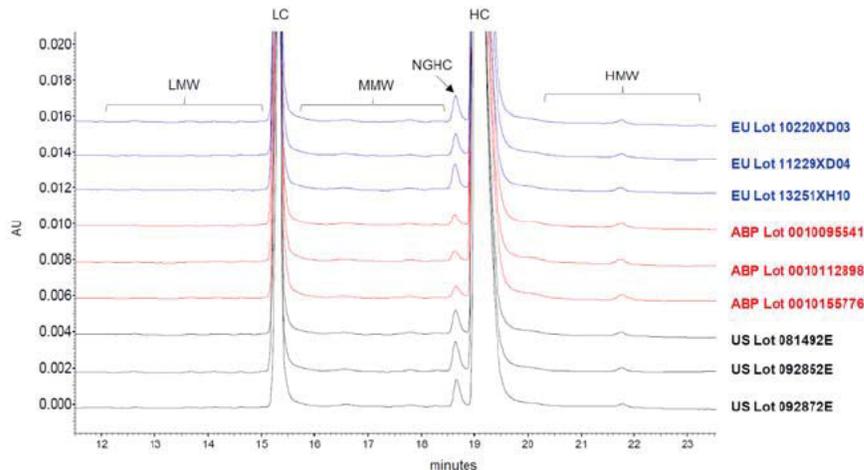
- When using the age-adjusted data, 90 percent of ABP 501 lots are within the quality range. The results demonstrate that the level of % HMW estimated for ABP 501 at (b) (4) months is similar US-Approved Humira at 24 months, although the levels in ABP 501 are lower initially.
- The chromatogram overlay led to two distinct observations: the LMW species are lower for ABP 501, and a slight “foot” or “hump” is observed in ABP 501 between the main aggregate peak and the monomer peak. As the entire aggregate peak is only 0.2% at release, this small peak is likely < 0.1% and far too small to quantitate. Thus, the contribution of this specie is considered negligible.
- Orthogonal evaluation of the aggregate peak by other detectors is presented in the Particulates and Aggregates section
- The totality of the data presented on size variants, both age-adjusted values as well as release data values, supports a determination of high similarity between ABP 501 and US-licensed Humira. Furthermore, data provided support the adequacy of the scientific bridge to support the use of EU-Approved Humira in Trial 20120263.

3.2.R.4.4.3.2 Reduced Capillary Electrophoresis – Sodium Dodecyl Sulfate (rCE-SDS) (10:24:18)

rCE-SDS was performed on 10 ABP 501 lots, 24 US-licensed Humira lots, and 18 EU-Approved Humira lots. The similarity assessment was performed on

- rCE-SDS profile comparison, which was evaluated using a **Tier 3** statistical method
- rCE-SDS size variants, which was evaluated using a **Tier 2** statistical method. Similarity assessment criteria for rCE-SDS were established on 3 groups: (1) % HC + LC; (2) % NGHC; and (3) % LMW + MMW), where:
 - HC: Heavy Chain
 - LC: Light Chain

- NGHC: Non-Glycosylated Heavy Chain
- LMW: Low Molecular Weight
- MMW: Mid Molecular Weight Species

Expanded View

The quality range of US-licensed Humira for rCE-SDS % HC+LC, NGHC, and LMW+MMW were established using the mean \pm 3SD of 24 US-licensed Humira lots. The similarity acceptance criteria provided that 90% of the ABP 501 lots fall within the quality range.

Reviewer Comment: This method is proposed as a specification test, and is presented in section 3.2.S.4.3.

The categorization of the individual peaks ((1) % HC + LC; (2) % NGHC; and (3) % LMW + MMW is considered appropriate.

The numerical comparison below that was used for initial evaluation of similarity reflects an “age adjustment” performed by the applicant so that both ABP 501 and US-licensed Humira are compared at the end of their relative shelf life ($\frac{(b)}{(4)}$ months and 24 months respectively). Of note, a comparison without age-adjustment was provided upon FDA request in the March 21, 2016 IR response. However, the conclusions do not change based on that data, and thus the original graphical comparison is provided below.

The following conclusions were drawn

- The rCE-SDS profiles for ABP 501, US-licensed Humira, and EU-approved Humira were visually similar, and no new species were observed for ABP 501 when compared with US-licensed Humira
- A lower level of % NGHC and higher level of % HC + LC was observed for ABP 501 compared to US-licensed Humira and EU-approved Humira
- For rCE-SDS % HC + LC, approximately 50% of the ABP 501 lots are within the quality range. ABP 501 had slightly higher levels of % HC + LC at $\frac{(b)}{(4)}$ months compared to US-licensed Humira at 24 months. This minor quantitative difference is primarily due to lower level of % NGHC in ABP 501. Though measured by a different test than glycan profile, the same fundamental argument that demonstrate the adequacy of functional assays to show that glycan profile differences are not considered clinically meaningful, applies here as well.

- For *rCE-SDS %LMW + MMW*, all ABP 501 lots are within the quality range.
- EU-Approved Humira demonstrated slightly different levels in *NGHC* and *%HC + %LC* relative to US-Licensed Humira. As with ABP 501, the lower *%HC + %LC* is reflective of changes in *NGHC*. The level of *%LC + %HC* is just passing for the unadjusted values and just outside of the quality range for adjusted values.

The age adjustment as well as the use of initial values both supports a determination of high similarity between ABP 501 and US-licensed Humira. The conclusions drawn from testing involving the “age adjustment” do not alter the interpretation of the data, and are thus, not included. Taken together, data provided support the adequacy of the scientific bridge to support the use of EU-Approved Humira in Trial 20120263.

rCE-SDS Results with the Age-Adjustment are presented below:

Figure 19. *rCE-SDS HC + LC - ABP 501 Compared to Adalimumab (US) Quality Range*

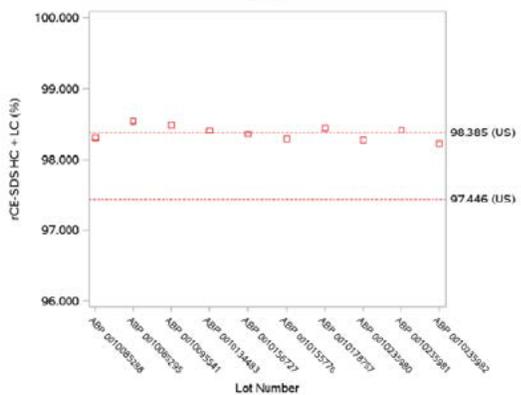


Figure 20. *rCE-SDS NGHC - ABP 501 Compared to Adalimumab (US) Quality Range*

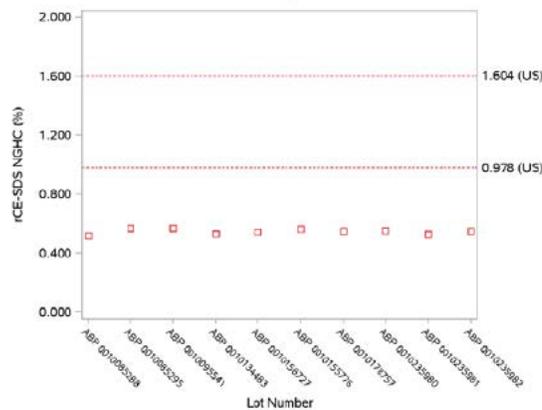
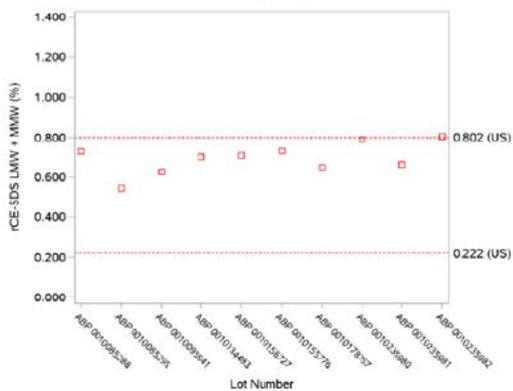


Figure 21. *rCE-SDS LMW + MMW - ABP 501 Compared to Adalimumab (US) Quality Range*



provided here on US-licensed Humira (the same comparison is applicable for ABP 501 relative to EU-Approved Humira).

Figure 33. nrCE-SDS Main Peak - ABP 501 Adalimumab (US) Quality Range of Mean

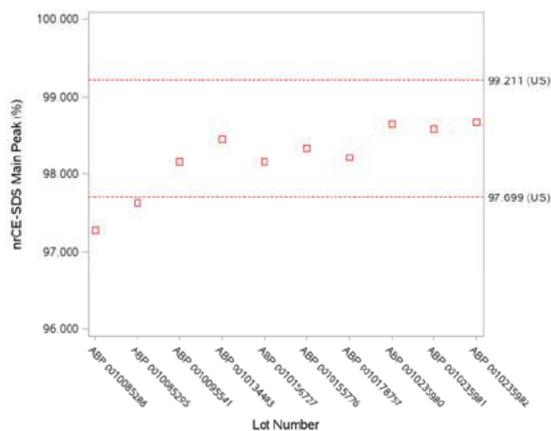
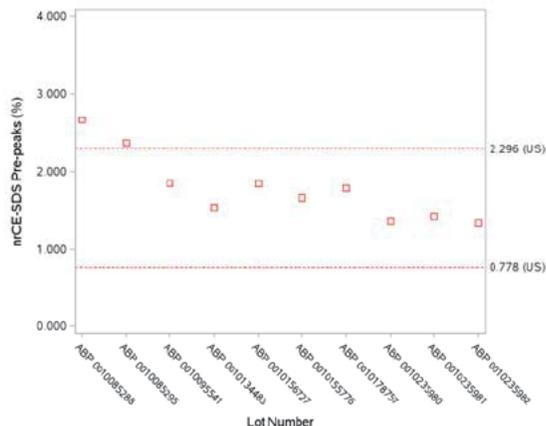


Figure 34. nrCE-SDS Pre-peaks - ABP 501 Adalimumab (US) Quality Range of Mean



Reviewer Comment: The following conclusions were drawn:

- The nrCE-SDS profiles for ABP 501 and US-licensed Humira were visually similar and no new species were observed for ABP 501 when compared to US-licensed Humira and EU-Approved Humira
- For nrCE-SDS % main peak, 80% of the ABP 501 lots are within the quality range.
- For nrCE-SDS % pre-peaks, 80% of the ABP 501 lots are within the quality range.
- The minor quantitative differences for the nrCE-SDS % main peak and % pre-peaks were observed and these do not impact the biological activity.
- The differences were limited to the early batches and given the overall very high level of purity of all products (98%-99%), the differences were considered negligible.

The slight differences observed in size variants (i.e., “fragments” or partially reduced species, more accurately that are considered pre-peaks) are not considered having clinically meaningful consequences. Though evaluated using tier 2 criteria, as the peaks themselves are considered to be fragments, Tier 3 criteria could also be acceptable. Given the high purity for all products (98-99%), and the equivalent potency results, these differences are considered to be negligible. The data in concert with review of other functional assay data support a determination of high similarity between ABP 501 and US-licensed Humira. Additionally, data provided support the adequacy of the scientific bridge to support the use of EU-Approved Humira in Trial 20120263.

3.2.R.4.4.3.4 Cation Exchange – High Performance Liquid Chromatography (CEX-HPLC) (10:23:18)

CEX-HPLC was performed on 10 ABP 501 lots, 23 US-licensed Humira lots, and 18 EU-Approved Humira lots.

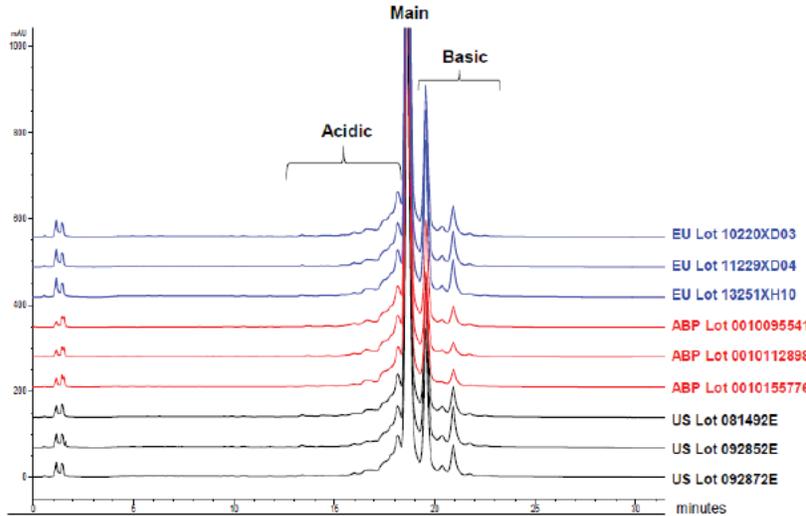
The similarity assessment was performed on

- CEX-HPLC profile comparison, which was evaluated using a Tier 3 statistical method

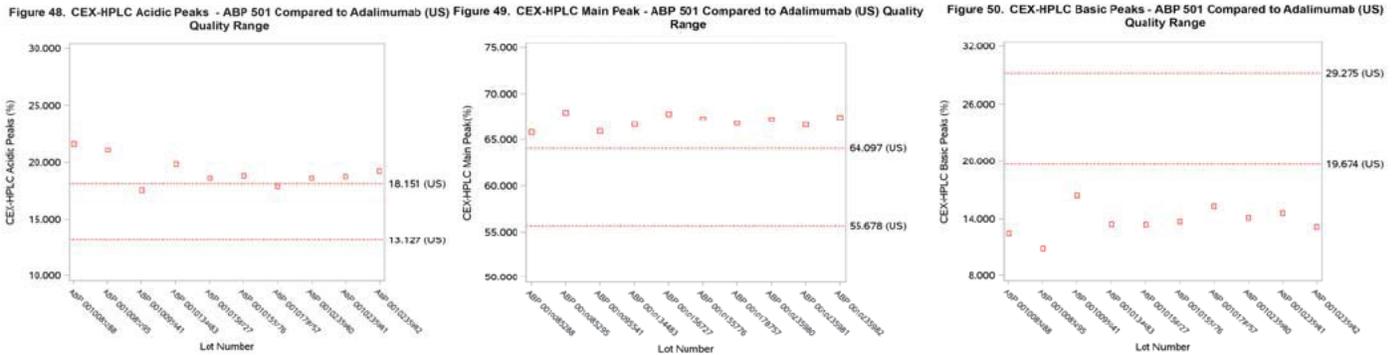
- CEX-HPLC charge groups, which was evaluated using a Tier 2 statistical method. The similarity assessment criteria for CEX-HPLC were established on 3 groups: (1) acidic peaks, (2) main peak, and (3) basic peaks

A comparison of the CEX-HPLC profiles for ABP 501, US-licensed Humira, and EU-Approved Humira lots is provided below. A comparison was made using age-adjusted values as described in the rCE-SDS section (3.2.R.4.4.3.2).

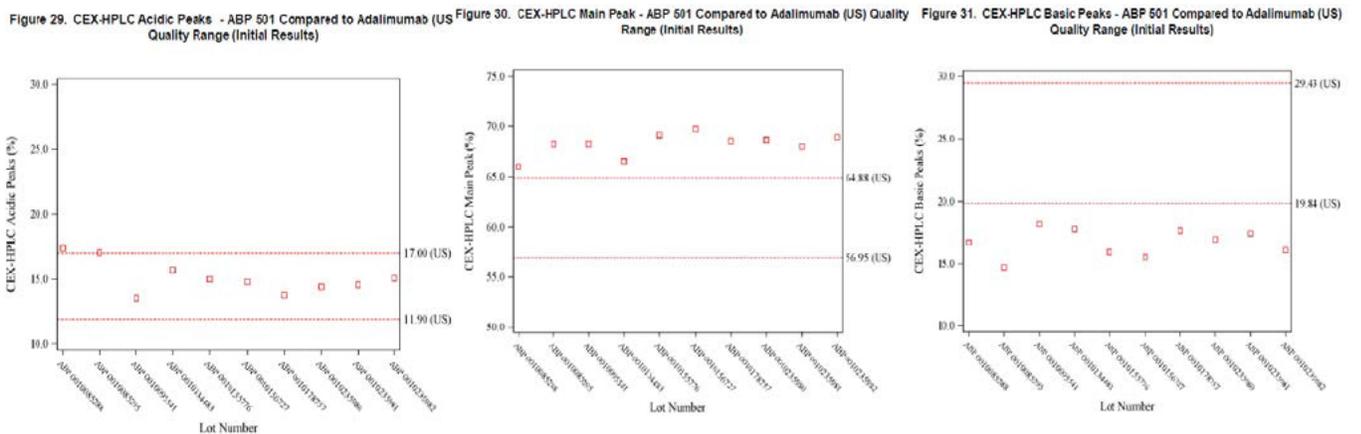
Expanded View



The CEX-HPLC results with the age-adjustment are shown below.



The CEX-HPLC results without the age-adjustment are shown below.



Reviewer Comments:

The following observations were made regarding the charge variant profile similarity assessment:

- Results from the age adjustment set result in failing values for all attributes (acidic, basic, and main peak), relative to both US-licensed Humira and EU-Approved Humira
- An unadjusted set (provided by the applicant in the March 21, 2016 IR response) of values results in the acidic variants falling just within the quality range proposed by the applicant. However, results for main peak and basic peak remain outside the quality range.
- Results for the comparison between US-Licensed Humira and EU-Approved Humira demonstrate that EU-Approved Humira falls just outside the quality range for US-licensed Humira with respect to main peak. See Figure 55 (with the age-adjustment) and Figure 36 (initial Results).

Figure 55. CEX-HPLC Main Peak - Adalimumab (EU) Compared to Adalimumab (US) Quality Range

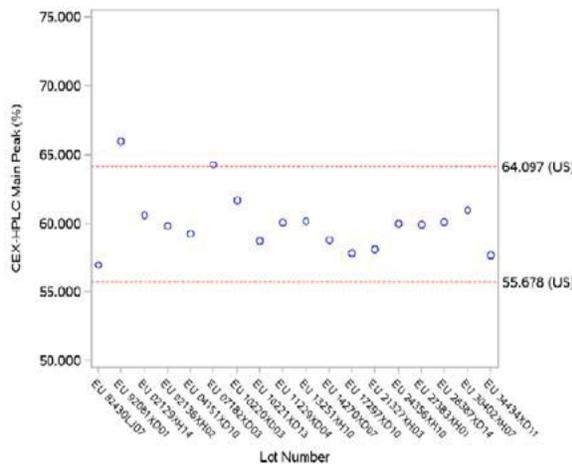
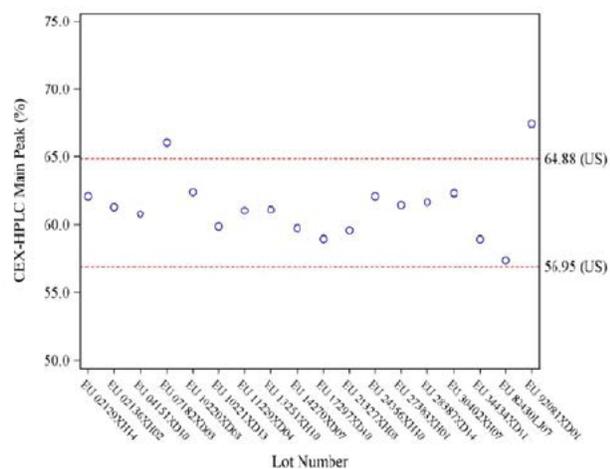


Figure 36. CEX-HPLC Main Peak - Adalimumab (EU) Compared to Adalimumab (US) Quality Range (Initial Results)



The differences observed in the charge variant profile were not considered to preclude a determination of high similarity, based on the following observations:

- As described in the characterization section, the potency of each fraction in the charge profile was collected, and assessed. Even dramatically enhanced levels of variants did not change the product performance with respect to potency.
- Additionally, the charge modifications for the acidic variant occur predominantly via deamidation of aspargines that are not located in a region expected to influence PK or potency. Other species responsible for charge modifications includes fragments and sialylation and are monitored by orthogonal techniques.
- Equivalent PK profile and FcRn binding were observed between the three products
- Equivalent binding, potency, and functional assay results demonstrate these changes are not considered significant.
- As listed in Table 5 below, treatment with carboxypeptidase A demonstrated that the differences in basic variants is the result of almost exclusively C-terminal lysine which should not affect product performance.

Table 5. CEX-HPLC Results of Carboxypeptidase B Digested Adalimumab (EU), ABP 501, and Adalimumab (US)

Lot Number	Digestion Control ^a			After Digestion		
	% Acidic Peaks	% Main Peak	% Basic Peaks	% Acidic Peaks	% Main Peak	% Basic Peaks
EU 02129XH14	13.8	62.9	23.3	16.7	79.1	4.2
ABP 0010085297	16.0	66.9	17.1	18.3	77.7	4.0
US 042212E	15.0	62.4	22.6	18.2	77.5	4.3

^a Digestion control samples were subjected to the same incubation conditions as the digested samples.

The data, in concert with review of other functional assay data, support a determination of high similarity between ABP 501 and US-licensed Humira. Additionally, the data provided support the adequacy of the scientific bridge to support the use of EU-Approved Humira in Trial 20120263.

3.2.R.4.4.4 Particles and Aggregates

Particle and aggregate profiles of ABP 501, US-licensed Humira, and EU-approved Humira were assessed using

- Subvisible particles were evaluated quantitatively by light obscuration (HIAC) and microflow imaging (MFI)
- Submicron particles were evaluated qualitatively by field flow fractionation (FFF) and dynamic light scattering (DLS)
- Solution-state aggregates were assessed by analytical ultracentrifugation sedimentation velocity (AUC-SV)
- Characterization of the oligomers separated by size-exclusion HPLC was performed by light scattering detection (SE-HPLC-LS) to provide the approximate molar mass

Subvisible Particles

The levels of subvisible particles were determined using

- The HIAC method measures $\geq 2 \mu\text{m}$, $\geq 5 \mu\text{m}$, $\geq 10 \mu\text{m}$, and $\geq 25 \mu\text{m}$
- The MFI method was used to differentiate between spherical and non-spherical particles

Reviewer Comment: *Of note, particle data from lots manufactured using [REDACTED] ^{(b) (4)} were excluded from the similarity assessment due to the subvisible particle counts from those lots not being representative of the proposed commercial process. The review of the particle size methods was performed as a portion of the pre-license inspection at ATO. These methods are considered Tier 3 and appropriate for their intended use in the similarity assessment.*

Batches used in the similarity assessment are presented below.

Table 1. Filling Technology Used to Manufacture ABP 501 Drug Product Lots

Drug Product Lot	Filling Technology Used	Drug Product Intended Use
ABP 0010085288	(b) (4)	Development, toxicology, stability
ABP 0010085295	(b) (4)	Development
ABP 0010085297	(b) (4)	Development
ABP 0010095541	(b) (4)	Clinical, stability
ABP 0010112898	(b) (4)	Clinical
ABP 0010139036	(b) (4)	Development ^a
ABP 0010139039	(b) (4)	Development ^a
ABP 0010134483	(b) (4)	Development, stability
ABP 0010156727	(b) (4)	Clinical, stability
ABP 0010155776	(b) (4)	Clinical, stability
ABP 0010155784	(b) (4)	Clinical
ABP 0010178757	(b) (4)	Clinical, stability
ABP 0010237900	(b) (4)	Process validation, stability
ABP 0010237902	(b) (4)	Process validation, stability
ABP 0010237901	(b) (4)	Process validation, stability

^a Lots manufactured during the (b) (4) investigation and were tested only for subvisible particles (Section 1.1 and Section 1.2) and for deliverable volume (Regional, General Properties).

3.2.R.4.4.4.1 HIAC Method (15:7:7)

The HIAC method, which was evaluated using a Tier 3 statistical method, and was performed on all 15 lots of ABP 501 and 7 lots each of US-licensed Humira and EU-Approved Humira.

The figures below provide comparison of the $\geq 2 \mu\text{m}$, $\geq 5 \mu\text{m}$, $\geq 10 \mu\text{m}$, and $\geq 25 \mu\text{m}$ subvisible particles.

Figure 1. HIAC $\geq 2 \mu\text{m}$ Subvisible Particles Results for Adalimumab (EU), ABP 501, and Adalimumab (US)

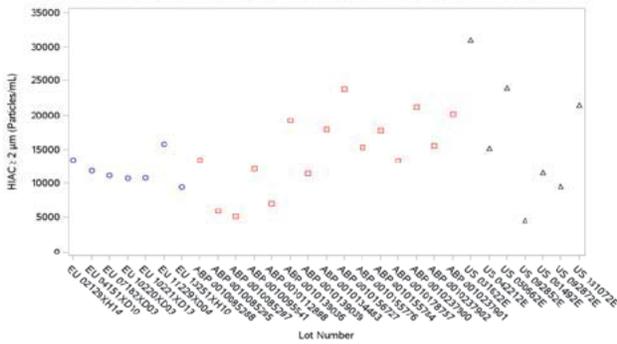


Figure 2. HIAC $\geq 5 \mu\text{m}$ Subvisible Particles Results for Adalimumab (EU), ABP 501, and Adalimumab (US)

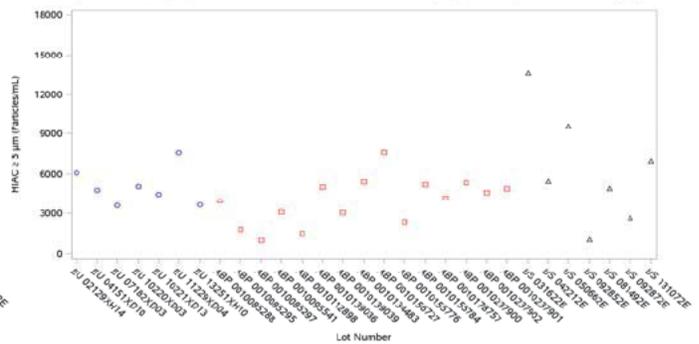


Figure 3. HIAC $\geq 10 \mu\text{m}$ Subvisible Particles Results for Adalimumab (EU), ABP 501, and Adalimumab (US)

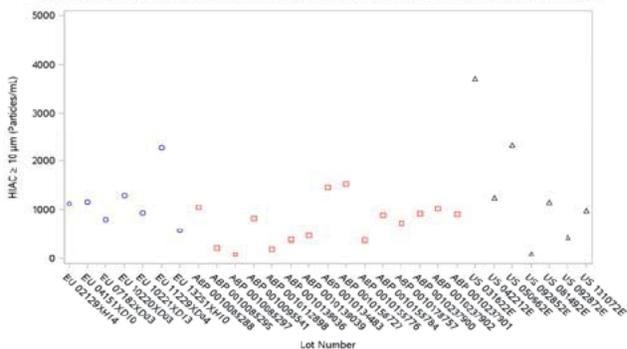
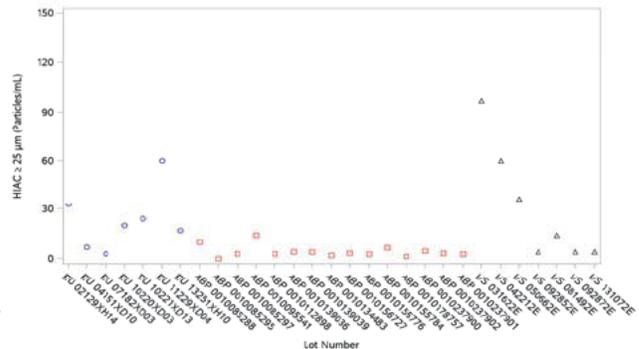


Figure 4. HIAC $\geq 25 \mu\text{m}$ Subvisible Particles Results for Adalimumab (EU), ABP 501, and Adalimumab (US)



Reviewer Comment: Data support the conclusion that the three products have similar levels of sub-visible particles across all size ranges.

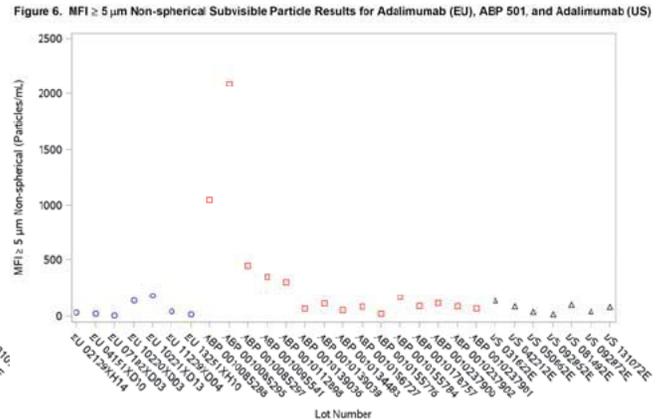
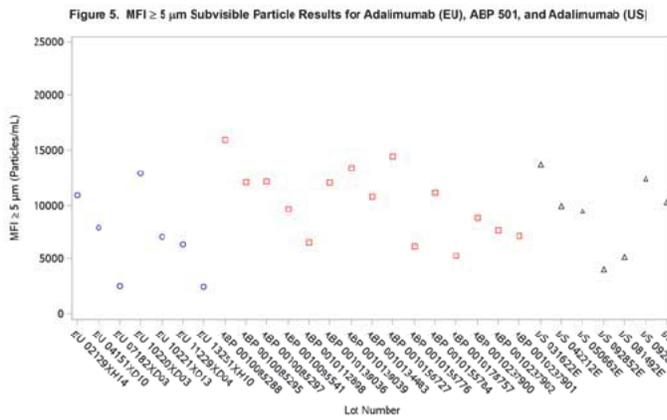
3.2.R.4.4.4.2 MFI Method (15:7:7)

The MFI method was performed on all 15 lots of ABP 501 and 7 lots each of US-licensed Humira and EU-Approved Humira.

The MFI method was used to differentiate between spherical and non-spherical particles in the $\geq 5 \mu\text{m}$ range. Similarity assessment was performed on

- $\geq 5 \mu\text{m}$ non-spherical particles, which are considered **Tier 2** assays/attributes, as these are considered to have a higher biological relevance

The figures below provide the $\geq 5 \mu\text{m}$ particles and $\geq 5 \mu\text{m}$ non-spherical subvisible particle results for ABP 501, US-licensed Humira, and EU-Approved Humira.



For the similarity assessment, each ABP 501 lot was compared against the 2 independent Tier 2 quality ranges established based on US-licensed Humira and EU-approved Humira as shown below.

Figure 7. MFI $\geq 5 \mu\text{m}$ Non-spherical Subvisible Particles - ABP 501 Compared to Adalimumab (US) Quality Range

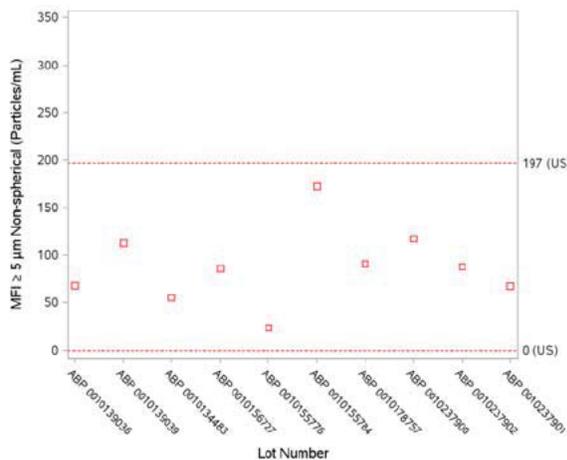
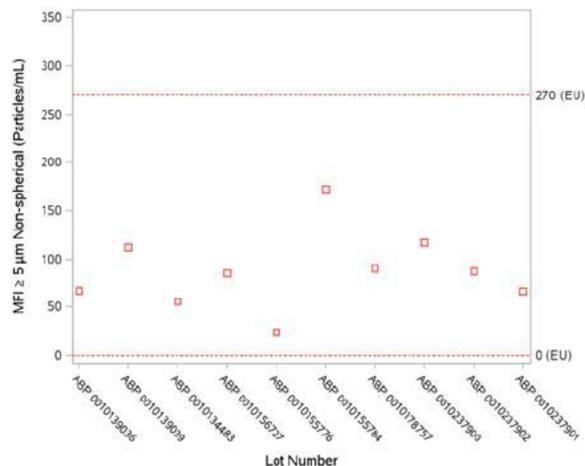


Figure 8. MFI $\geq 5 \mu\text{m}$ Non-spherical Subvisible Particles - ABP 501 Compared to Adalimumab (EU) Quality Range



Reviewer Comment:

The distinction for “non-spherical” particles serves to discriminate between (b) (4) (spherical) and protein (non-spherical). However, even without this stratification of the particle types, similar levels were observed. Evaluation of the HLAC method was performed as a portion of the inspection at the DS site. The use of the aspect ratio which establishes the criterion difference between spherical and non-spherical particles was evaluated and considered sufficient.

The following conclusions were drawn.

- The $\geq 5 \mu\text{m}$ particles and $\geq 5 \mu\text{m}$ non-spherical subvisible particle results for ABP 501, US-licensed Humira, and EU-approved Humira were visually similar
- All ABP 501 lots for the $\geq 5 \mu\text{m}$ non-spherical particles of ABP 501 are within the quality ranges of both the US-licensed Humira and EU-approved Humira. Subvisible particles data obtained the lots (0010085288, 0010085295, 0010085297, 0010095541, and 0010112898) manufactured using (b) (4) were excluded from the similarity assessment due to the subvisible particle counts from those lots not being representative of the proposed commercial process. Refer to Table 1 above.

The data support a determination of high similarity between ABP 501 and US-licensed Humira. Additionally, the data provided support the adequacy of the scientific bridge to support the use of EU-Approved Humira in Trial 20120263.

3.2.R.4.4.4.3 Field Flow Fractionation (FFF) and Dynamic Light Scattering (DLS) (6:6:6)

Six (6) lots each of ABP 501, US-licensed Humira, and EU-Approved Humira were used for both the FFF and DLS methods.

Submicron particles characterized by both FFF and DLS were evaluated using a Tier 3 statistical method, and those FFF and DLS profiles are qualitatively compared. Testing results from the FFF and DLS are listed below.

Figure 11. FFF Profiles of Adalimumab (EU), ABP 501 (Clinical) Adalimumab (US)

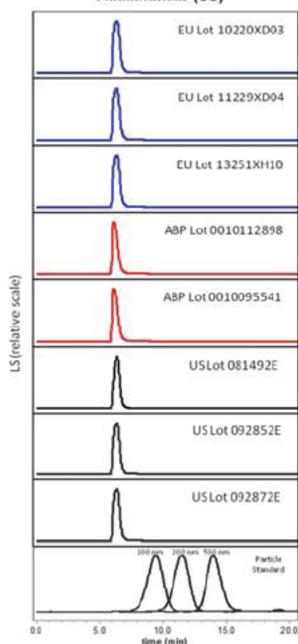
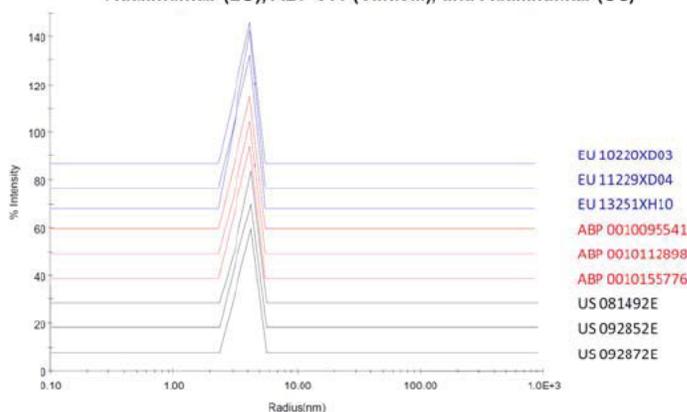


Figure 13. Dynamic Light Scattering Size Distribution Profiles for Adalimumab (EU), ABP 501 (Clinical), and Adalimumab (US)



Reviewer Comment: The FFF and DLS results indicate that ABP 501 has a similar submicron particle profile compared to US-licensed Humira and EU-approved Humira, respectively, and support a determination of highly similar for the three products. Additionally, data provided support the adequacy of the scientific bridge to support the use of EU-Approved Humira in Trial 20120263.

I agree.

3.2.R.4.4.4 Analytical Ultracentrifugation Sedimentation Velocity (AUC-SV) (3:3:3)

The AUC-SV method measures the size distribution of the product in solution, including the presence of any higher molecular weight species. The AUC-SV method is considered orthogonal to the SE-HPLC method.

AUC-SV was performed on 6 lots each of ABP 501, US-licensed Humira, and EU-Approved Humira. The similarity assessment was performed on:

- AUC-SV profile comparison, which was evaluated using a Tier 3 statistical method
- AUC-SV monomer, which was evaluated using a Tier 2 statistical method by the applicant, but was reviewed using a Tier 3 statistical evaluation by FDA

The high-resolution sedimentation coefficient distribution [c(s)] of ABP 501 compared to US-licensed Humira and EU-Approved Humira, as a function of the sedimentation coefficient, is shown in Figure 15.

The US-licensed Humira quality range for AUC-SV monomer is provided in Figure 17.

Figure 15. AUC-SV Profiles for Adalimumab (EU), ABP 501 (Clinical), and Adalimumab (US)

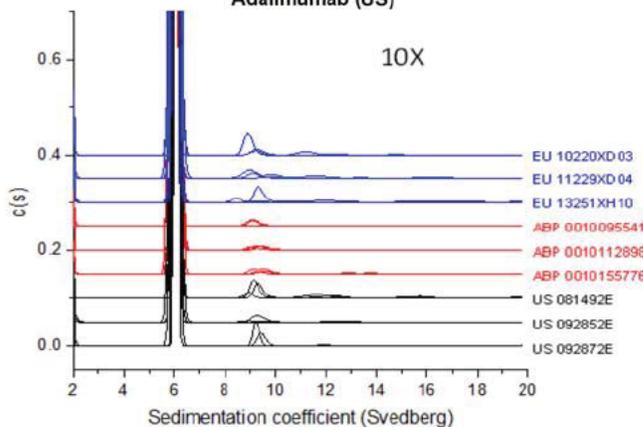
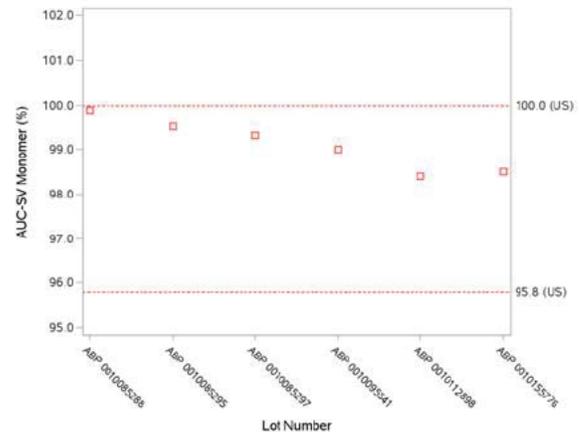


Figure 17. AUC-SV Monomer - ABP 501 Compared to Adalimumab (US) Quality Range



Reviewer Comment: The following conclusions were drawn:

- The AUC-SV results demonstrate that ABP 501 has a similar size distribution compared to US-licensed Humira and EU-approved Humira
- All ABP 501 lots are within the quality range of US-licensed Humira. Similar results are obtained for similarity between ABP 501 and EU-approved Humira, and EU-approved Humira and US-licensed Humira

Additionally, data provided support the adequacy of the scientific bridge to support the use of EU-Approved Humira in Trial 20120263.

3.2.R.4.4.4.5 Size Exclusion High Performance Liquid Chromatography with Light Scattering Detection (SE-HPLC-LS) (3:3:3)

Three ABP 501 development lots were compared side-by-side against 3 US-licensed Humira lots and 3 EU-Approved Humira lots.

Similarity assessment was performed on:

- Molar mass of the main peak and pre-peak which were evaluated using a Tier 2 statistical method.
- Light scattering profile comparison which were evaluated using a Tier 3 statistical method.

The chromatograms comparing ABP 501 with US-licensed Humira are presented in Figure 20. The molar masses of the main peak and HMW species for each sample are provided in Table 5

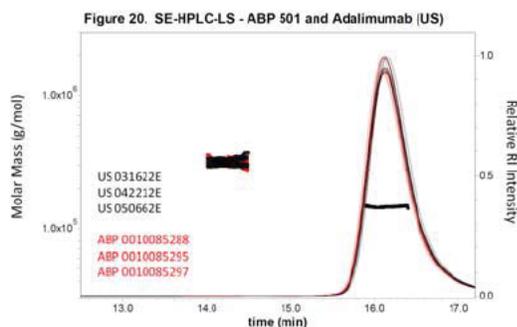


Table 5. SE-HPLC-LS Results for Adalimumab (EU), ABP 501, and Adalimumab (US)

	Main Peak (16.1 Minutes) (kDa)		Pre-peak (14.2 Minutes) (kDa)	
	Mean ^a	STD ^a	Mean ^a	STD ^a
EU 92081XD01	146	1	310	18
EU 02129XH14	145	1	310	9
EU 02136XH02	145	1	318	7
ABP 0010085288	145	1	318	7
ABP 0010085295	145	0	320	7
ABP 0010085297	145	0	322	8
US 031622E	145	0	307	11
US 042212E	145	1	318	19
US Lot 050662E	146	1	320	21

kDa = kilo Daltons; STD = standard deviation.
^a Mean and standard deviation of 3 replicate tests per sample.

Reviewer Comment:

The data demonstrate that ABP 501 has similar SE-HPLC-LS profiles and molar masses for monomer and HMW species compared to those of the US-licensed Humira and EU-approved Humira. Data also support the conclusion that the majority of HMW species observed are dimeric. Additionally, data provided support the adequacy of the scientific bridge to support the use of EU-Approved Humira in Trial 20120263.

3.2.R.4.4.5 Thermal Stability and Forced Degradation

As part of the analytical similarity assessment, thermal stability and degradation studies were performed at 50°C, 25°C, and 40°C, to aid in the comparison of ABP 501 to US-licensed Humira and EU-Approved Humira. These thermal studies evaluate potential differences in structure and in the formation of impurities and serve as the primary mode for comparison of stress stability profiles of ABP 501 to US-licensed Humira and EU-Approved Humira.

Reviewer Comment: Given that the formulations between ABP 501 and US-licensed Humira are not identical, the degradation rates are not necessarily expected to be identical.

The applicant also clarified in the March 21, 2016 IR response that the nrCE-SDS method can assess ABP 501 size variants including fragments HMW, but that the rCE-SDS and SE-HPLC are better methods suitable for that purpose. Additionally, characterization of CEX-HPLC acidic peaks demonstrated the presence of fragments monitored within the purified acidic fractions used for characterization. Finally, data were submitted showing that minimal change is observed during 18 months of storage at the intended long-term storage condition. This rationale is considered sufficient for the exclusion of this test from the forced degradation study.

3.2.R.4.4.5.1 ABP 501 Stability in the US-licensed Humira Buffer

To evaluate the stability of ABP 501, it was formulated into a buffer equivalent to the formulation of US-licensed Humira. The formulation of ABP 501 is different from US-Licensed Humira

- The ABP 501 formulation buffer is composed of 10 mM sodium acetate, 9.0 % w/v sucrose, 0.10% w/v polysorbate 80, at pH 5.2
- The adalimumab DP buffer is composed of 105 mM sodium chloride; 5.53 mM monobasic sodium phosphate dihydrate; 8.57 mM dibasic sodium phosphate dihydrate; 1.16 mM sodium citrate; 6.19 mM citric acid monohydrate; 1.2% w/v mannitol; 0.10% w/v polysorbate 80; at pH 5.2

Reviewer Comment: When formulated in the adalimumab DP buffer, ABP 501 exhibited an increased rate of high molecular weight (HMW) species formation at 50 °C as compared to ABP 501 in the ABP 501 formulation (Figure 1). However, the rate of low molecular weight (LMW) species formation in ABP 501 was not significantly impacted by the difference in buffers. . These data further corroborate that the improved stability at 50 °C for ABP 501 derives from formulation differences and not intrinsic differences in the molecule.

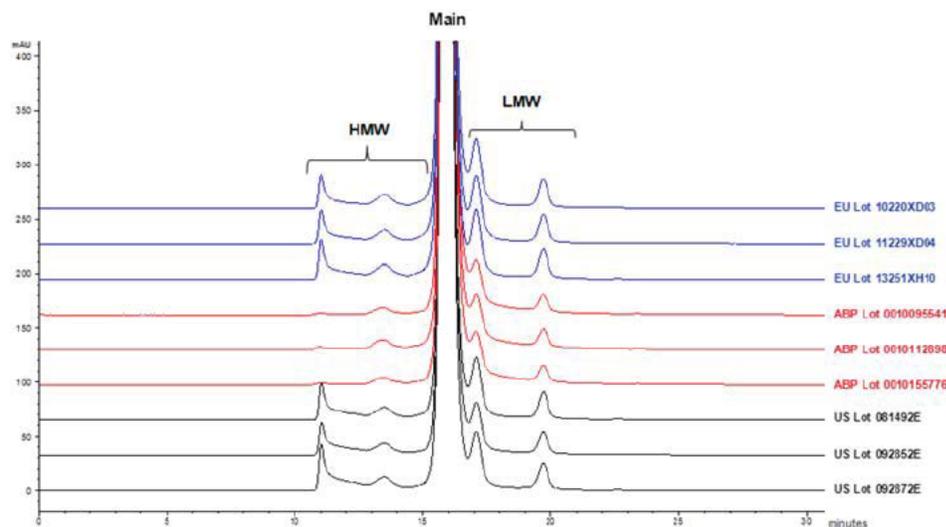
3.2.R.4.4.5.2 50°C Forced Degradation Study (3:3:3)

A study was performed to evaluate the similarity of ABP 501 to US-licensed Humira and EU-Approved Humira under the thermal forced degradation condition of 50°C for 14 days. Drug product pre-filled syringes (PFS) were subjected to thermal degradation and analyzed by SE-HPLC, rCE-SDS, CEX-HPLC, and apoptosis inhibition bioassay.

Size Exclusion High Performance Liquid Chromatography

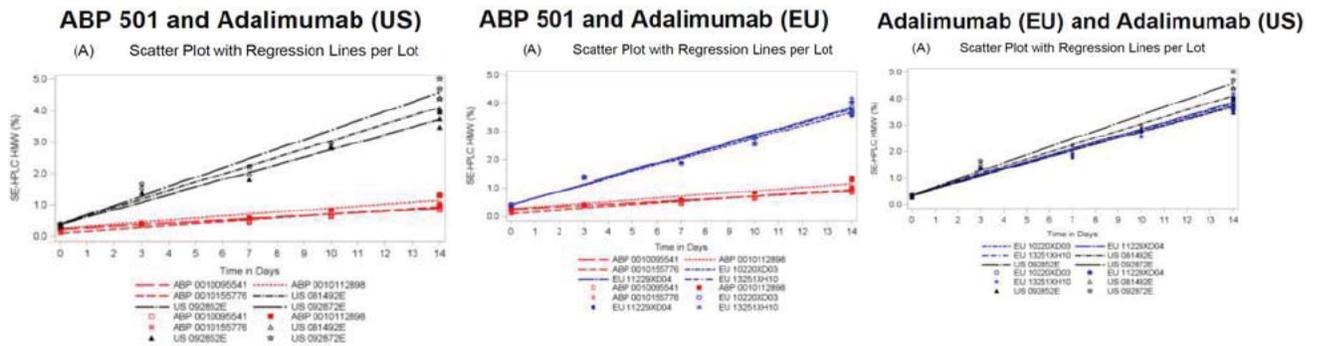
The SE-HPLC profiles of 3 ABP 501 clinical lots, 3 US-licensed Humira lots, and 3 EU-Approved Humira lots after incubation at 50°C for 14 days are overlaid in the figure below.

Figure 2. SE-HPLC Profiles of Thermal Degradation Results at 14 Days for Adalimumab (EU), ABP 501, and Adalimumab (US)



The degradation rate plots comparing % HMW species are provided in the figure below.

Figure 5. Degradation Rate Plot of SE-HPLC HMW at 50°C

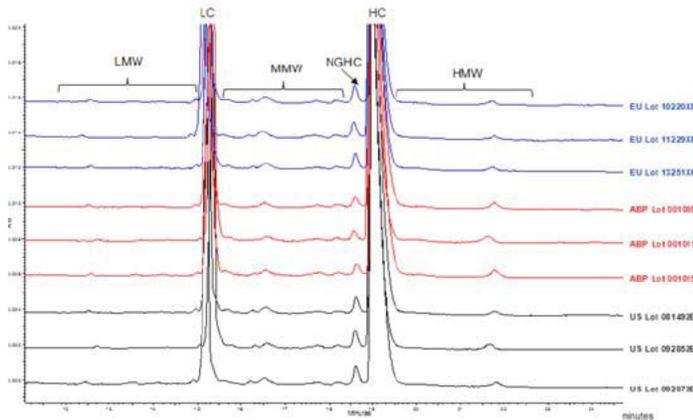


Reviewer Comment: Data demonstrate that ABP 501 is substantially more stable than US-licensed Humira and EU-Approved Humira with respect to aggregation. Additionally, no new peaks are observed in ABP 501 that are not observed in US-licensed Humira samples.

Reduced Capillary Electrophoresis – Sodium Dodecyl Sulfate (rCE-SDS)

The rCE-SDS profiles of 3 ABP 501 clinical lots, 3 US-licensed Humira, and 3 EU-Approved Humira lots after incubation at 50°C for 14 days are overlaid in the figure below.

Figure 6. Expanded rCE-SDS Profiles of Thermal Degradation Results at 14 Days for Adalimumab (EU), ABP 501, and Adalimumab (US)



The degradation rate plots comparing % HC + LC and % LMW + MMW are provided in Figure 7 and Figure 8, respectively.

Figure 7. Degradation Rate Plot of rCE-SDS % HC + LC at 50°C

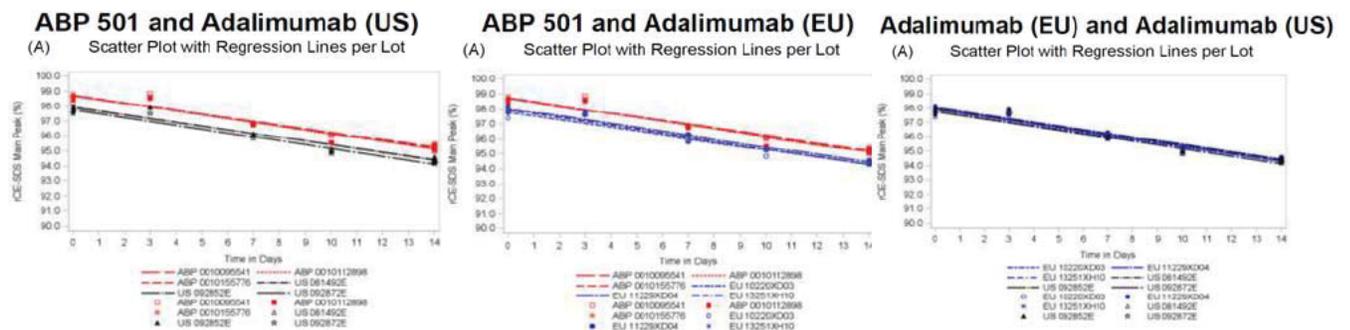
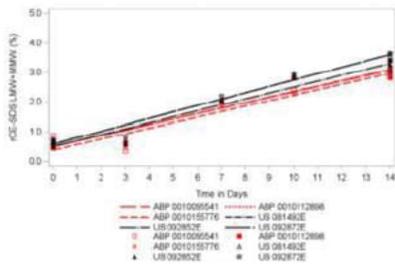


Figure 8. Degradation Rate Plot of rCE-SDS % LMW + MMW at 50°C

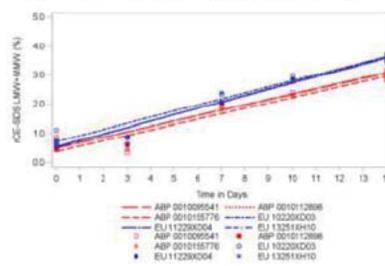
ABP 501 and Adalimumab (US)

(A) Scatter Plot with Regression Lines per Lot



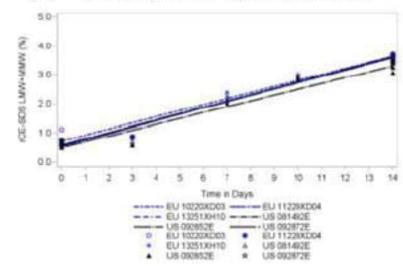
ABP 501 and Adalimumab (EU)

(A) Scatter Plot with Regression Lines per Lot



Adalimumab (EU) and Adalimumab (US)

(A) Scatter Plot with Regression Lines per Lot



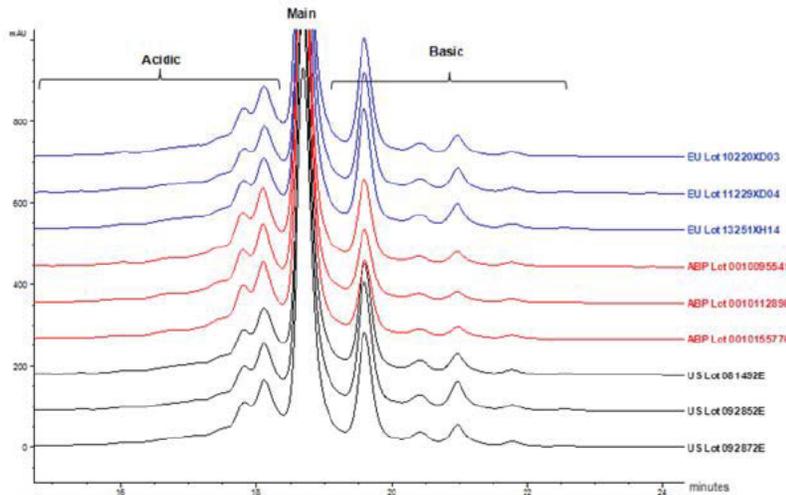
Reviewer Comment: The following observations were made:

- The 3 ABP 501 lots tested were similar to the 3 lots each of US-licensed Humira and EU-approved Humira with respect to both the levels of % HC+LC and % LMW+MMW.
- The profile of thermally degraded ABP 501 was similar to US-licensed Humira and EU-approved Humira with respect to the presence of the same peaks. Differences observed by SE-HPLC are driven by aggregates which are not quantified by this method.

Cation Exchange High Performance Liquid Chromatography (CEX-HPLC)

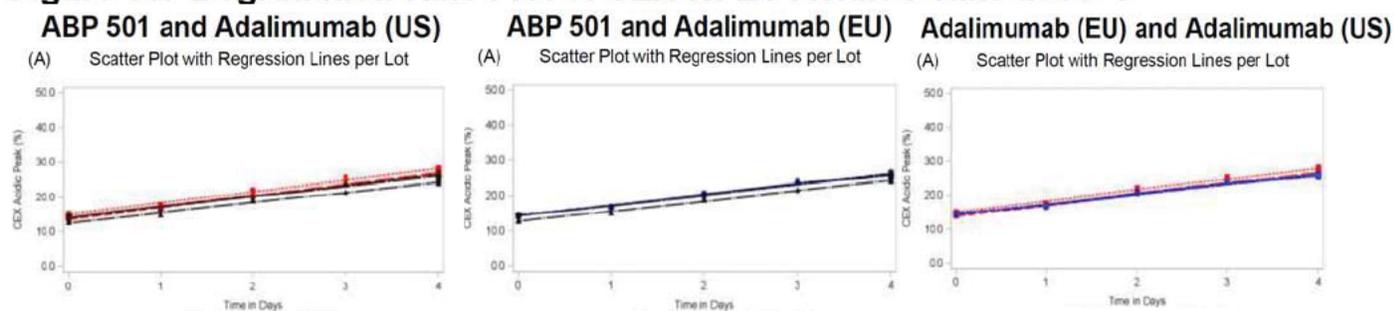
The CEX-HPLC profiles of 3 ABP 501 clinical lots, 3 US-licensed Humira, and 3 EU-Approved Humira lots incubated at 50°C for 4 days are overlaid in Figure 13.

Figure 13. Expanded CEX-HPLC Profiles of Thermal Degradation Results at 4 Days for Adalimumab (EU), ABP 501, and Adalimumab (US)



The degradation rate plots comparing main peak, acidic peaks, and basic peaks are provided in Figure 14, Figure 15, and Figure 16, respectively.

Figure 15. Degradation Rate Plot of CEX-HPLC Acidic Peaks at 50°C

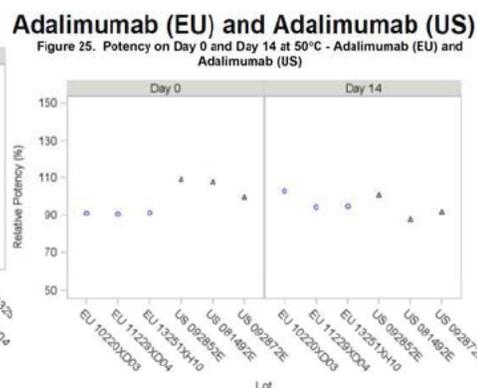
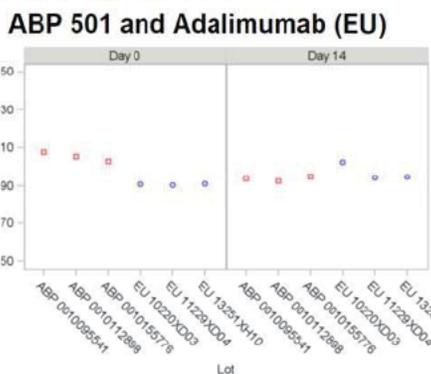
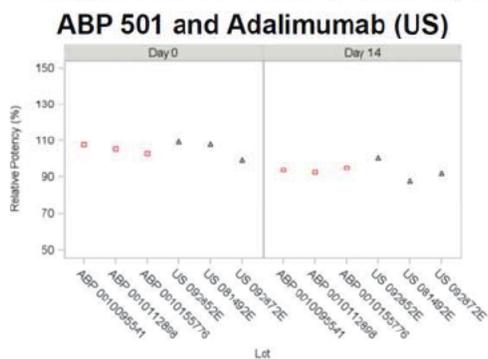


Reviewer Comment: The profile of thermally degraded ABP 501 was similar to US-licensed Humira and EU-approved Humira with respect to the presence of the same peaks.

Apoptosis Inhibition Bioassay (Potency)

The potency results between ABP 501, US-licensed Humira and EU-approved Humira are presented in Figure 23.

Figure 23. Potency on Day 0 and Day 14 at 50°C



Reviewer Comment: Of note, no significant loss in potency was observed for either of the 3 products from Day 0 to Day 14.

Reviewer Comment for the Conclusion of the 50°C Forced Degradation Study:

In conclusion, the degradation profiles for SE-HPLC, rCE-SDS, CEX-HPLC, and apoptosis inhibition bioassay are similar for ABP 501, US-licensed Humira and EU-approved Humira, and support a determination of highly similar for the three products. Of note, ABP 501 is more stable to the formation of aggregates under these conditions, likely because of the different formulation buffer. Additionally, the data support the analytical component of the scientific bridge to support the use of EU-Approved Humira in study 20120263.

3.2.R.4.4.5.3 Accelerated (25°C) AND Stressed (40°C) (2:1:1)

In addition to the 50°C forced degradation study, an accelerated stability study at 25°C and a stressed stability study at 40°C were performed on ABP 501, US-licensed Humira, and EU-Approved Humira to evaluate the similarity of the degradation profiles.

Due to the possibility that forced degradation at 50°C could inhibit certain degradation mechanisms, the accelerated and stressed stability studies were conducted to compare alternate degradation pathways. For instance, the potential of trace amounts of proteases to degrade the product could be detected at 40°C and not at 50°C due to inactivation of the proteases.

To obtain discernible changes in product quality, drug product syringes were incubated at 25°C for 6 months and 40°C for 3 months. Thermal stability was monitored by testing the samples at pre-determined time points using stability indicating methods. Since the lots were not tested side-by-side, it is expected that the inherent variability from the assays may contribute to variability in degradation rates. The samples at each time point were evaluated with SE-HPLC, rCE-SDS, CEX-HPLC, and apoptosis inhibition bioassay.

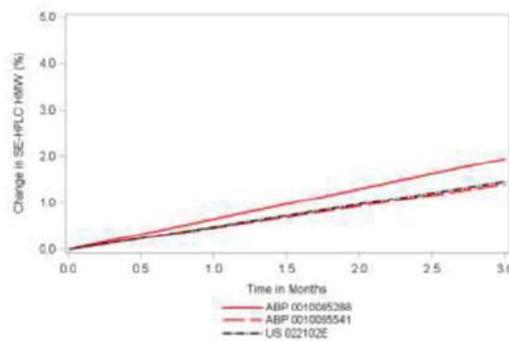
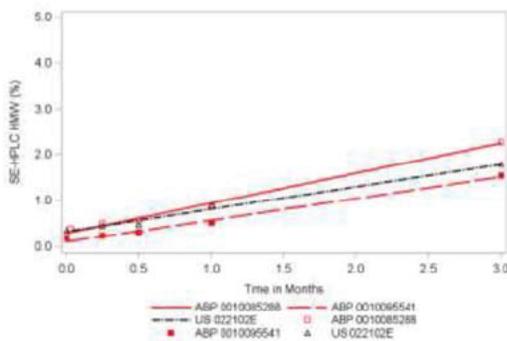
Reviewer Note: In this section, only degradation rates comparison between ABP 501 and US-licensed Humira at 40°C are presented.

Size Exclusion High Performance Liquid Chromatography

Figure 27. Degradation Rate Plot of SE-HPLC HMW at 40°C - ABP 501 and Adalimumab (US)

(A) Scatter Plot with Regression Lines per Lot

(B) Regression Lines with Common Intercept at Zero



Reduced Capillary Electrophoresis – Sodium Dodecyl Sulfate (rCE-SDS)

Figure 34. Degradation Rate Plot of rCE-SDS % HC + LC at 40°C - ABP 501 and Adalimumab (US)

(A) Scatter Plot with Regression Lines per Lot

(B) Regression Lines with Common Intercept at Zero

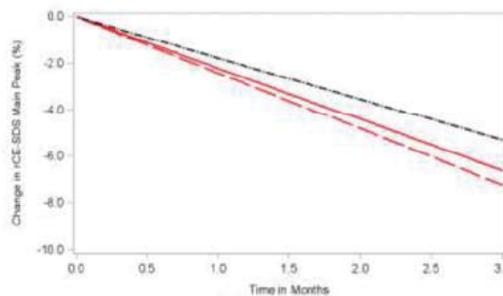
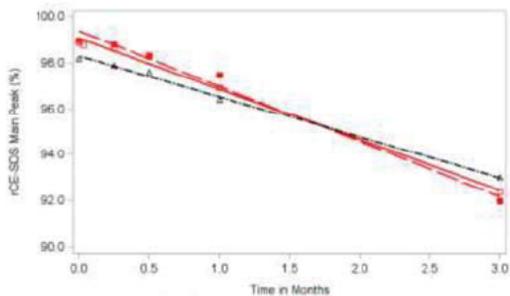
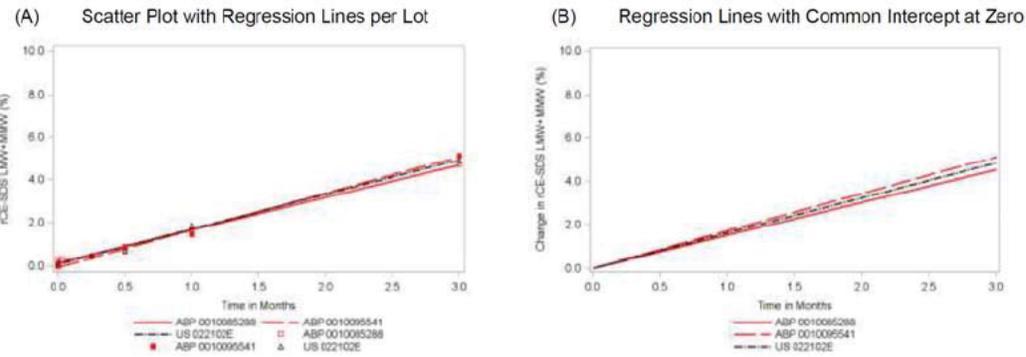


Figure 35. Degradation Rate Plot of rCE-SDS % LMW + MMW at 40°C - ABP 501 and Adalimumab (US)



Cation Exchange High Performance Liquid Chromatography (CEX-HPLC)

Figure 47. Degradation Rate Plot of CEX-HPLC Main Peak at 40°C - ABP 501 and Adalimumab (US)

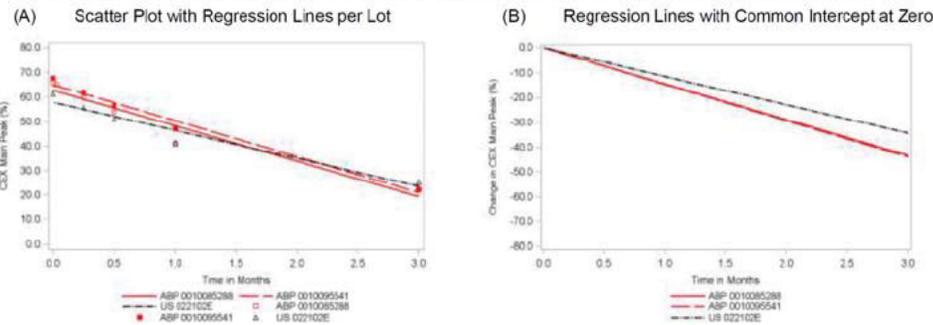


Figure 48. Degradation Rate Plot of CEX-HPLC Acidic Peaks at 40°C - ABP 501 and Adalimumab (US)

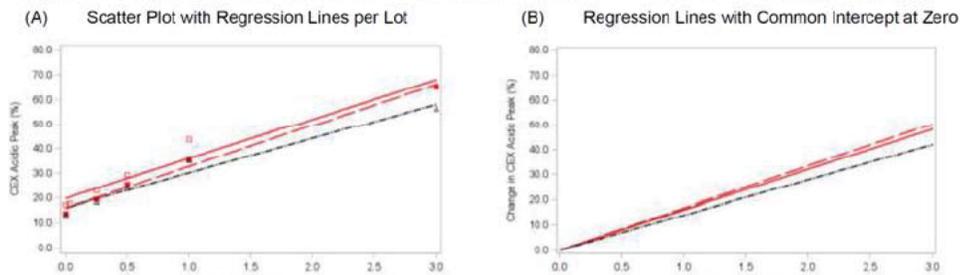
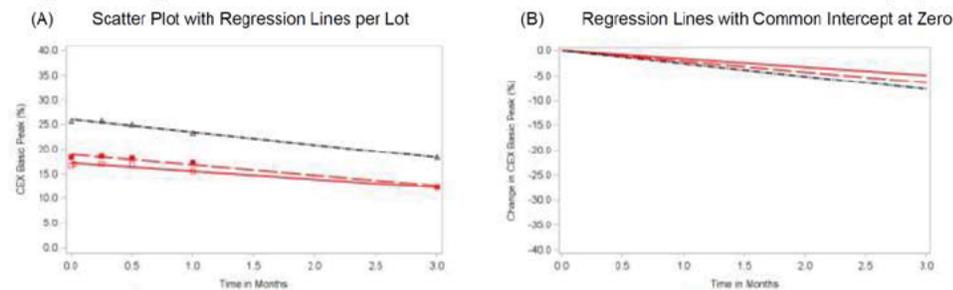


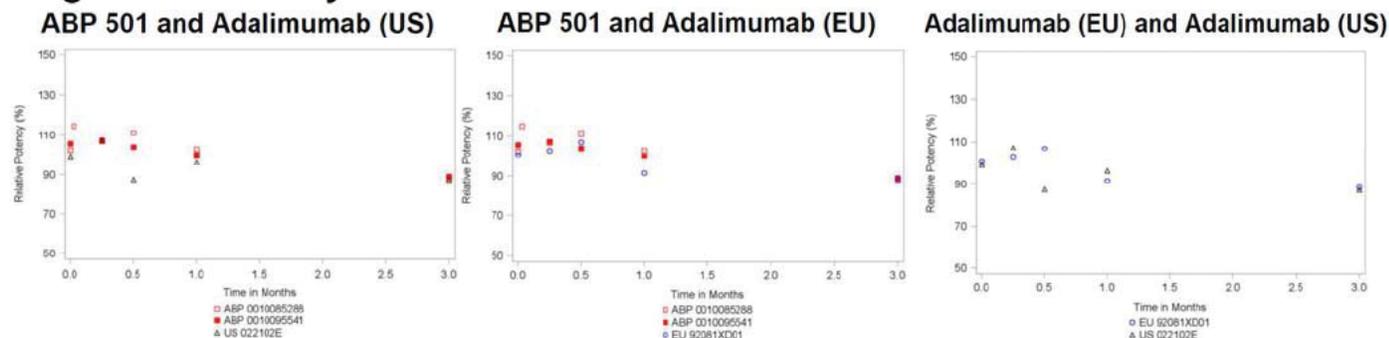
Figure 49. Degradation Rate Plot of CEX-HPLC Basic Peaks at 40°C - ABP 501 and Adalimumab (US)



Apoptosis Bioassay (Potency)

Similarity was assessed by plotting the potency results for 1 ABP 501 development lot, 1 ABP 501 clinical lot, and 1 US-licensed Humira lot incubated at 25°C and 40°C (Figure 63).

Figure 63. Potency Results at 40°C



Reviewer Comment: As with the degradation profiles at 50°C, the profiles for SE-HPLC, rCE-SDS, CEX-HPLC, and apoptosis inhibition bioassay (potency) for ABP 501, US-licensed Humira and EU-approved Humira are similar at both accelerated and stressed conditions. Data support a determination of high similarity between ABP 501 and US-licensed Humira, and the adequacy of the scientific bridge to support the use of EU-Approved Humira in the clinical study 20120263.

3.2.R.4.4.6 General Properties

This section describes the similarity assessment of ABP 501, US-licensed Humira, and EU-Approved Humira for product strength evaluated by measuring protein concentration and deliverable volume. Additional comparative characterization of other general properties is presented for the 3 products, which includes osmolality, pH, appearance, color, clarity, and polysorbate 80 concentration.

Reviewer Comment: Osmolality, pH, and appearance are compendial methods, and validation data are not required. The polysorbate 80 and protein concentration methods are validated in section 3.2.S.4.3. Only protein concentration was evaluated with a tier 2 statistical method. The remaining attributes were assessed by Tier 3 criteria.

3.2.R.4.4.6.1 Protein Concentration (10:23:18)

A determination of protein concentration testing was performed on 10 ABP 501, 23 US-licensed Humira, and 18 EU-Approved Humira lots. The extinction coefficient used for measure the protein concentration was experimentally determined to be (b) (4) (mg/mL) earlier in development. Passing results were obtained for each of the stepwise comparisons based on analysis using a tier 2 method. A comparison of ABP 501 relative US-licensed Humira is presented below. The test is proposed as a rejection limit for DP manufacture.

Figure 2. Protein Concentration - ABP 501 Compared to Adalimumab (US) Quality Range

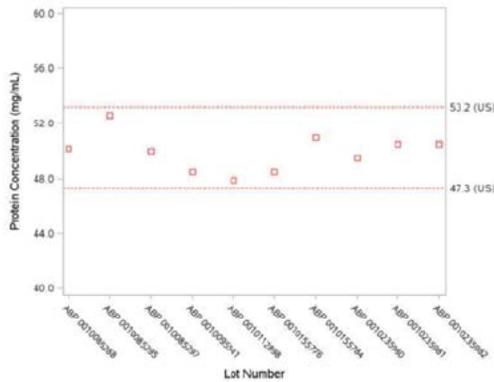
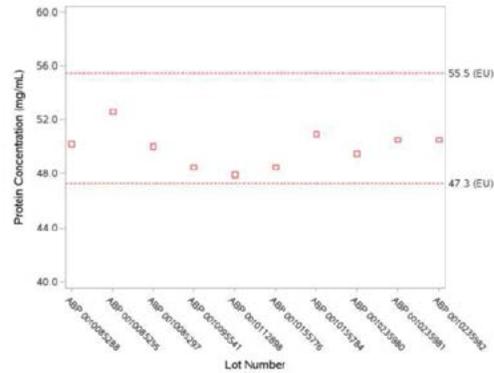


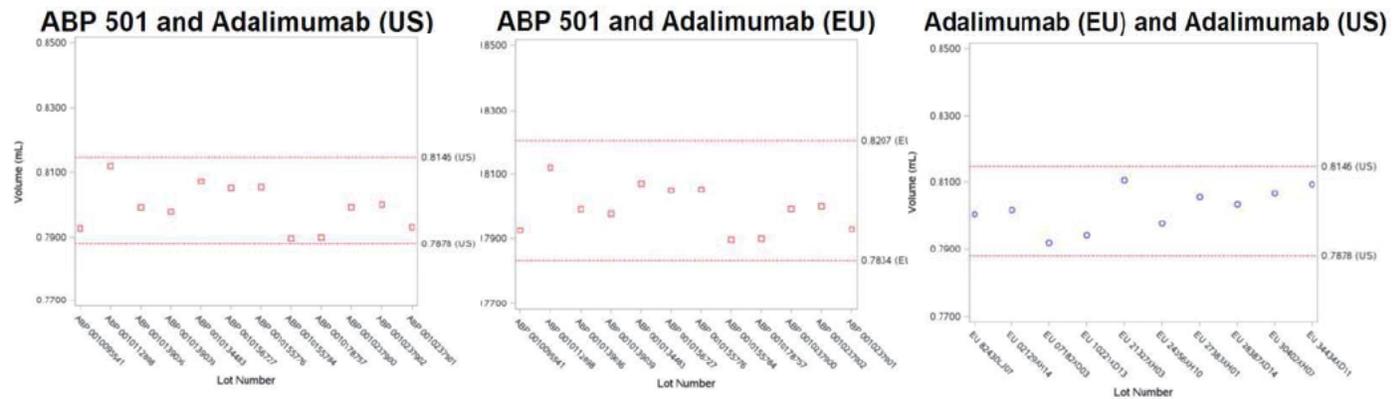
Figure 3. Protein Concentration - ABP 501 Compared to Adalimumab (EU) Quality Range



Reviewer Comment: Only a comparison of ABP 501 to US-licensed is presented in this review. Data support a determination of high similarity between ABP 501 and US-licensed Humira, and the adequacy of the scientific bridge to support the use of EU-Approved Humira in Trial 20120263.

3.2.R.4.4.6.2 Deliverable Volume (15:14:10)

Deliverable volume testing was performed on 15 ABP 501, 14 US-licensed Humira lots, and 10 EU-Approved Humira lots. The deliverable volume in the prefilled syringes also informs product strength and is evaluated using a Tier 2 method.



Reviewer Comment: Data support a determination of high similarity and the adequacy of the analytical component of the scientific bridge to support the use of EU-Approved Humira in clinical study 20120263.

3.2.R.4.4.6.3 Osmolality(10:3:3)

For the similarity assessment for osmolality, 10 ABP 501 lots were compared with 3 lots each of US-licensed Humira and EU-Approved Humira for osmolality.

Table 3. Osmolality Results for ABP 501, Adalimumab (US), and Adalimumab (EU)

Lot Number	Osmolality (mOsm/kg)
EU 92081XD01	298
EU 02129XH14	303
EU 04151XD10	299
ABP 0010085288	318
ABP 0010085295	313
ABP 0010085297	320
ABP 0010095541	311
ABP 0010112898	311
ABP 0010155776	315
ABP 0010155784	317
ABP 0010235980	313
ABP 0010235981	319
ABP 0010235982	311
US 031622E	313
US 042212E	312
US 050662E	312

Reviewer Comment: Osmolality results are not expected to be identical given the difference in formulation, but should be within the same overall range. Data support a determination of high similarity between ABP 501 and US-licensed Humira and the use of EU-Approved Humira in clinical trial 20120263.

3.2.R.4.4.6.4 pH (10:3:3)

For the similarity assessment of pH, 10 ABP 501 lots were compared with 3 lots each of US-licensed Humira and EU-Approved Humira, using Tier 3 criteria. All results were within the predicted range for each of the products.

Reviewer Comment: pH results are not expected to be identical given the difference in formulation, but should be within the same intended range. Data support a determination of high similarity and the use of EU-Approved Humira in clinical trials. (b) (4)

3.2.R.4.4.6.5 Polysorbate 80 (10:1:1)

For the similarity assessment of polysorbate, 10 ABP 501 lots were compared with 1 lot each of US-licensed Humira and EU-Approved Humira, using Tier 3 criteria.

Reviewer Comment: Results (below) are not expected to be identical given the difference in formulation, but should be within the same overall range. Data support a determination of high similarity between ABP 501 and US-licensed Humira and the use of EU-Approved Humira in clinical trial 20120263.

Table 8. Polysorbate 80 Results for Adalimumab (EU), ABP 501, and Adalimumab (US)

Lot Number	Polysorbate 80 (% w/v)
EU 02129XH14	0.09
ABP 0010085288	0.09
ABP 0010085295	0.09
ABP 0010085297	0.09
ABP 0010095541	0.09
ABP 0010112898	0.10
ABP 0010155776	0.09
ABP 0010155784	0.10
ABP 0010235980	0.10
ABP 0010235981	0.10
ABP 0010235982	0.10
US 042212E	0.09

3.2.R.4.4.6.6 Appearance/Color/Clarity (10:3:3)

For the similarity assessment of appearance as well as color and clarity, 10 ABP 501 lots were compared with 3 lots each of US-licensed Humira and EU-Approved Humira. Results for appearance were assessed relative to the Tier 3 criteria of the expectation of a “liquid solution essentially free of visible particles”. Clarity was assessed relative to compendial tests of “Reference IV”, which reflects a clear to slightly opalescent solution. Color was assessed relative to the expectation of a colorless to slightly yellow solution. Values of “passing” were obtained for all samples.

***Reviewer Comment:** Results are not expected to be identical given the difference in formulation, but should be largely similar. Data support a determination of high similarity of ABP 501 relative to US-licensed Humira and the use of EU-Approved Humira in clinical trials.*

3.2.R.4.4.7 Process-Related Impurities

Process-related impurities such as host cell protein (HCP), host cell DNA, and leached protein A, were characterized in ABP 501, US-licensed Humira, and EU-Approved Humira. Due to the anticipated differences in the cell line and manufacturing process, the process-related impurities in ABP 501 are not expected to match US-licensed Humira. The analysis of process-related impurities was intended to characterize any significant differences in ABP 501 that may have an adverse impact upon safety.

3.2.R.4.4.7.1 Host Cell protein (HCP) (10:3:3)

The residual HCP in ABP 501, US-licensed Humira, and EU-Approved Humira were characterized and compared using

- an HCP ELISA method that provides quantitative measurement of total HCP detected through the use of anti-HCP antibodies
- a 2-dimensional differential in-gel electrophoresis (2D-DIGE) method

Reviewer Comment: Given that a different cell is used, Tier 3 criteria are the most appropriate assessment for comparison. Qualification data describing the appropriate coverage of the assay are presented below.

Host Cell Protein – ELISA

The HCP ELISA method was performed on 10 ABP 501 drug substance lots and 3 lots each of US-licensed Humira, and EU-Approved Humira and results are listed in Table 1.

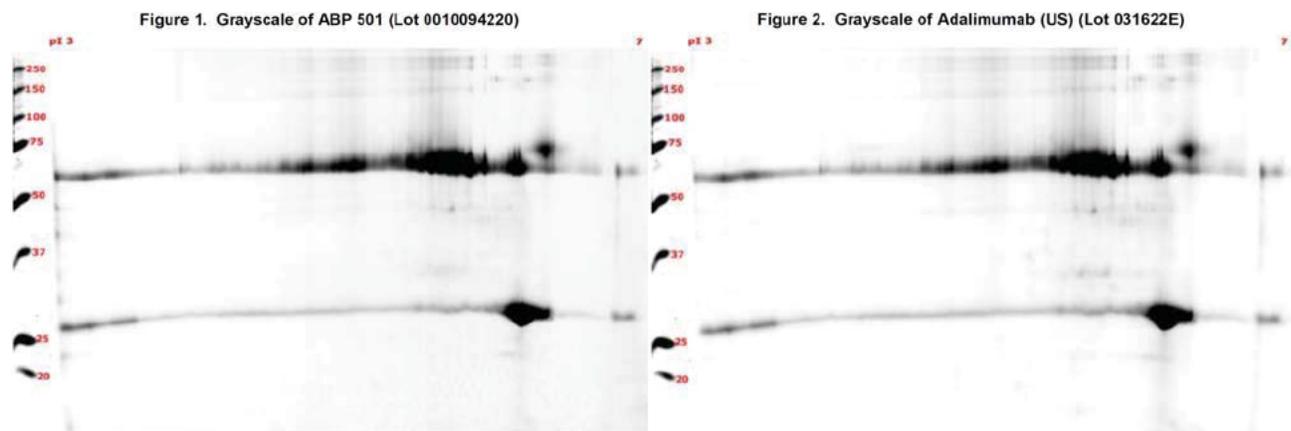
Table 1. HCP ELISA Levels for Adalimumab (EU), ABP 501, and Adalimumab (US)

Lot Number	HCP (ng/mg) ^a
EU 92081XD01	171
EU 02129XH14	111
EU 02136XH02	87
ABP 30052311	44
ABP 30071211	46
ABP 30080811	25
ABP 0010094219	< 5
ABP 0010094220	5
ABP 0010140760	8
ABP 0010140761	8
ABP 0010235980	13
ABP 0010235981	13
ABP 0010235982	14
US Lot 031622E	129
US Lot 042212E	166
US Lot 050662E	168

^a LOQ is 12 ng/mL (0.2 ng/mg).
The units of ng/mg are converted using the sample protein concentrations (50 mg/mL).

Analysis by the 2D-DIGE method

The grayscale images of ABP 501 and US-licensed Humira are provided in Figure 1 and Figure 2, respectively.



Reviewer Comment: *The following observations were made:*

- *All spots of the 2D-DIGE images, including both product and residual HCP spots, were digitally analyzed. ABP 501 and US-licensed Humira were determined to be 98.9% similar*
- *The results of HCP measured by the ELISA were qualitatively compared between ABP 501 and US-licensed Humira (Table 1 above)*

Data support the conclusion that the levels of HCP are similar and appropriate for ABP 501. These data support a determination of high similarity and the appropriateness of the use of EU-Approved Humira in clinical trial 2012063.

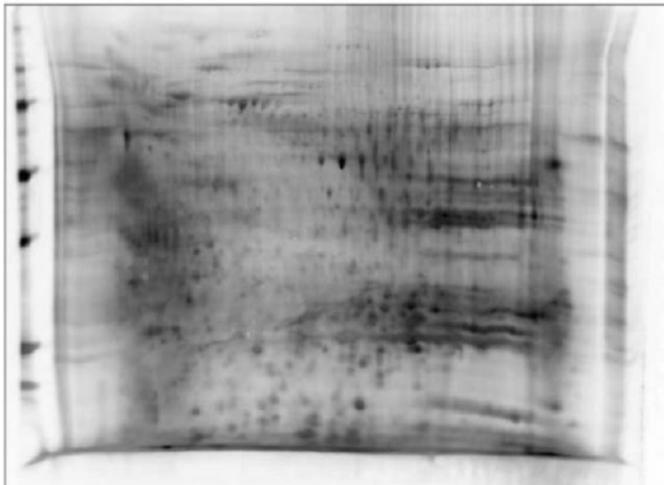
Coverage of anti-HCP antibodies

Additional information was provided regarding the coverage and sensitivity of the HCP assay in the July 5, 2016 response to IR. The following information was presented by the sponsor:

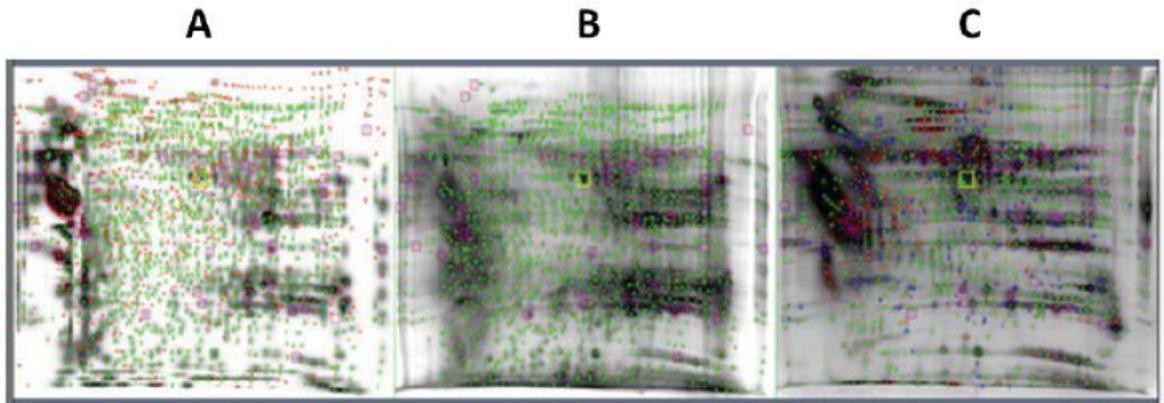
The polyclonal antibody coverage to individual CHO HCP protein species present in the HCP standard was determined using a 2D western blot method, where the HCPs were separated first by isoelectric point and subsequently by molecular weight.

The figure below shows the total CHO HCP image antigen pool which contains proteins that range in size from below 15 kD to approximately 250 kD and range in pI from (b) (4).

Figure 4. 2D SDS-PAGE Epicocconone Base Fluorescent Total Protein Stained Image of the HCP Pool



In Figure 6, image A was designated as the master gel containing all detected spots from total protein stain and western blot. Image B was designated as the image containing all detected spots from total protein stain. Image C was designated as the image containing all detected spots from the western blot.

Figure 6. Total Protein Stain and Western Images

Green spots indicate a match between B and C. Red spots indicate no match between B and C. A purple spot indicates a landmark and a confirmation of match between B and C.

The total protein stain image contained a total spot count of 1,259 spots and the western image contained a total spot count of 1,044 spots when processed by PDQuest 2D image analysis software. The percentage coverage was calculated using with the total spot counts of 2D total protein stain and 2D western blot as 82.9%. This level of coverage is considered appropriate.

3.2.R.4.4.7.2 Protein A – ELISA (10:3:3)

The protein A - ELISA method was performed on 10 ABP 501 drug substance lots and 3 lots each of EU-Approved Humira and US-licensed Humira.

***Reviewer Comment:** A summary of the validation characteristics are presented in the submission section 3.2.S.4.3 as this method was used throughout development.*

Levels of Protein A were undetectable for all products. Data support a determination of high similarity between ABP 501 and US-licensed Humira

Data also support the use of EU-Approved Humira in clinical trial 2012063.

3.2.R.4.4.7.3 Residual DNA – Quantitative Polymerase Chain Reaction

The residual DNA analysis by quantitative polymerase chain reaction (qPCR) was performed on 10 ABP 501 drug substance lots, and 3 lots each of EU-Approved Humira and US-licensed Humira. ***Reviewer Comment:** A summary of the validation characteristics are presented in the submission section 3.2.S.4.3, as this method was used throughout development.*

***Reviewer Comment:** Levels of DNA were undetectable for all products. Data support a determination of high similarity.*

3.2.R.4.4.8 BIOLOGICAL ACTIVITY

Reviewer Comment: Assays used for analytical similarity assessment of the biological activities pertaining to the primary and secondary mechanisms of action for ABP 501, US-licensed Humira, and EU-approved Humira, are summarized in the below table. Method Qualification was considered for each method provided below except for those denoted as “Additional characterization” and C1q binding, as they are considered exploratory pharmacology assays. C1q data were requested in the March 21, 2016 IR response and qualification data for binding to sTNF α , Binding to Fc γ RIIIa (158V), Binding to FcRn, ADCC, and CDC were provided on March 21 as well. Additional data in support of the sensitivity of ADCC, CDC, and Fc γ RIIIa (158V) were provided in the July 5, 2016 IR.

Analytical methods used for analytical similarity assessment of the biological activities

Method	Relevant Activity	Tier
Apoptosis inhibition bioassay (potency)	sTNF α	1
Binding to sTNF α	sTNF α	1
Binding to Fc γ RIIIa(158V)	FcR	2
Binding to C1q	C1q	3
ADCC	mbTNF α and FcR	2
CDC	mbTNF α and FcR	2
Binding to FcRn	FcR	2
Reverse Signaling	mbTNF α	2
Additional Characterization		
Binding kinetics to sTNF α	sTNF α	3
Binding to NHP sTNF α	NHP sTNF α	3
Binding to mbTNF α	mbTNF α	3
Comparative Neutralization of Human TNF α -induced Signaling in HUVEC : Inhibition of sTNF α -induced IL-8 Inhibition of LT α -induced IL-8	sTNF α LT	3
Neutralization of Human and Cynomolgus Monkey TNF α -induced Cell Death in L929 Cell	sTNF α NHP sTNF α	3
Inhibition of Proliferation in a Mixed Lymphocyte Reaction (MLR)	mbTNF α and FcR	3
Binding to Fc γ RIa	FcR	3
Binding to Fc γ RIIa(131H)	FcR	3
Binding to Fc γ RIIIa(158F)	FcR	3
Comparative Neutralization of TNF α -induced Chemokine Production in Whole Blood	sTNF α NHP sTNF α	3

HUVEC: human umbilical vein endothelial cells

LT α = lymphotoxin alpha

MLR = mixed lymphocyte reaction

NHP = nonhuman primate

3.2.R.4.4.8.1 Apoptosis Inhibition Bioassay (Potency) (10:21:18)

The apoptosis inhibition bioassay was performed on 10 ABP 501, 21 US-licensed Humira, and 18 EU-Approved Humira lots. Figure 1 shows the % relative potency of ABP 501, US-licensed Humira, and EU-approved Humira relative to ABP 501 reference standard.

Reviewer Comment: This method is proposed as a specification test, thus the review of its validation is presented in section 3.2.S.4.1.

The apoptosis inhibition bioassay (potency) assesses the primary mechanism of action and is considered a Tier 1 assay/attribute. The results of the similarity assessment were evaluated using an equivalence test.

Results of the equivalence test performed by Amgen on the lots of ABP 501 vs. US-licensed Humira, ABP 501 vs. EU-approved Humira, and US-licensed Humira vs. EU-approved Humira for the potency are presented below.

Table 2. Equivalence Test Results for Relative Potency - ABP 501 to Adalimumab (US)

Assay/Attribute	Adalimumab (US) Mean	ABP 501 Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative Potency	105.50	103.77	-1.73	-5.17	1.72	± 8.64	Statistically Equivalent

Table 3. Equivalence Test Results for Relative Potency - ABP 501 to Adalimumab (EU)

Assay/Attribute	Adalimumab (EU) Mean	ABP 501 Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative Potency	102.83	103.77	0.94	-4.42	6.29	± 14.04	Statistically Equivalent

Table 4. Equivalence Test Results for Relative Potency – Adalimumab (EU) to Adalimumab (US)

Assay/Attribute	Adalimumab (US) Mean	Adalimumab (EU) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative Potency	105.50	102.83	-2.66	-6.84	1.51	± 8.64	Statistically Equivalent

Reviewer Comment: The claim for the statistical evaluation of equivalency for the potency was confirmed by Dr. Meiyu Shen (CMC statistical reviewer). Data support a determination of highly similar for ABP 501 to US-licensed Humira, and are appropriate to justify the relevance of comparative data generated from clinical the clinical trial 20120263.

3.2.R.4.4.8.2 sTNF α binding (10:10:10)

The sTNF α binding assay was performed on 10 ABP 501, 10 US-licensed Humira, and 10 EU-Approved Humira lots. The sTNF α binding method is a solid phase enzyme-linked immunosorbent assay (ELISA).

The sTNF α binding assay assesses the primary mechanism of action and was evaluated by equivalence test (Tier 1).

Results of the equivalence test performed by Amgen on the lots of ABP 501 vs. US-licensed Humira, ABP 501 vs. EU-approved Humira, and US-licensed Humira vs. EU-approved Humira for the sTNF α assay are presented below.

Table 6. Equivalence Test Results for Relative Binding to sTNF α - ABP 501 and Adalimumab (US)

Assay/Attribute	Adalimumab (US) Mean	ABP 501 Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative Binding to sTNF α	111.83	108.10	-3.74	-11.03	3.55	± 15.02	Statistically Equivalent

Table 7. Equivalence Test Results for Relative Binding to sTNF α - ABP 501 and Adalimumab (EU)

Assay/Attribute	Adalimumab (EU) Mean	ABP 501 Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative Binding to sTNF α	111.33	108.10	-3.23	-9.39	2.93	± 10.58	Statistically Equivalent

Table 8. Equivalence Test Results for Relative Binding to sTNF α - Adalimumab (EU) and Adalimumab (US)

Assay/Attribute	Adalimumab (US) Mean	Adalimumab (EU) Mean	Estimated Difference Across Means	Lower Bound of 90% Confidence Interval on Difference in Means	Upper Bound of 90% Confidence Interval on Difference in Means	EAC	Conclusion
Relative Binding to sTNF α	111.83	111.33	-0.51	-7.22	6.21	± 15.02	Statistically Equivalent

Reviewer Comment: The claim for the statistical evaluation of equivalency for the sTNF α binding assay was confirmed by Dr. Meiyu Shen (CMC statistical reviewer). Data support a determination of highly similar for ABP 501 to US-licensed Humira, and are appropriate to justify the relevance of comparative data generated from clinical studies that used EU-approved Humira.

Additionally, in their March 21, 2016 IR response, the applicant provided MDR-001472 that summarized qualification activities for this method. The method was adapted from method TP-001302 “Etanercept (Enbrel) Receptor Binding Assay”. Little additional optimization was required. The parameters of accuracy (concentrations 85%-115% in three replicates), linearity, repeatability, and intermediate precision were evaluated. Robustness was not considered.

3.2.R.4.4.8.3 Fc γ RIIIa (158V) Binding (10:17:15)

The Fc γ RIIIa (158V) binding assay assesses comparative binding of the Fc region to Fc γ R (158V), and is orthogonal to the ADCC assay in assessing the biological property of Fc-mediated function. Fc γ RIIIa (158V) binding was evaluated using a Tier 2 statistical method, defining the quality range as the mean \pm 3SD of 17 US-licensed Humira lots. The figure below depicts the Fc γ RIIIa (158V) binding results.

Figure 24. Relative Binding to Fc γ RIIIa - ABP 501 Compared to Adalimumab (US) Quality Range

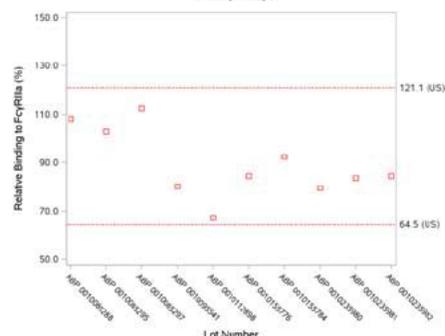


Figure 25. Relative Binding to Fc γ RIIIa - ABP 501 Compared to Adalimumab (EU) Quality Range

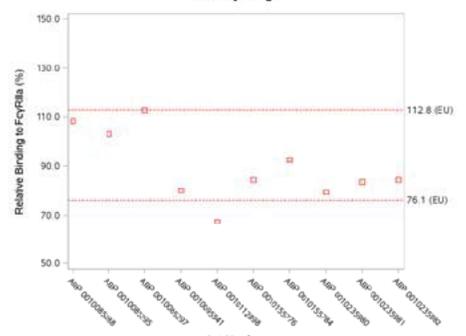
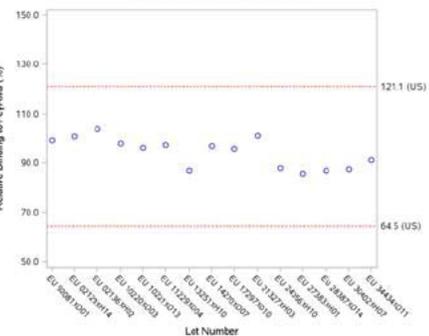
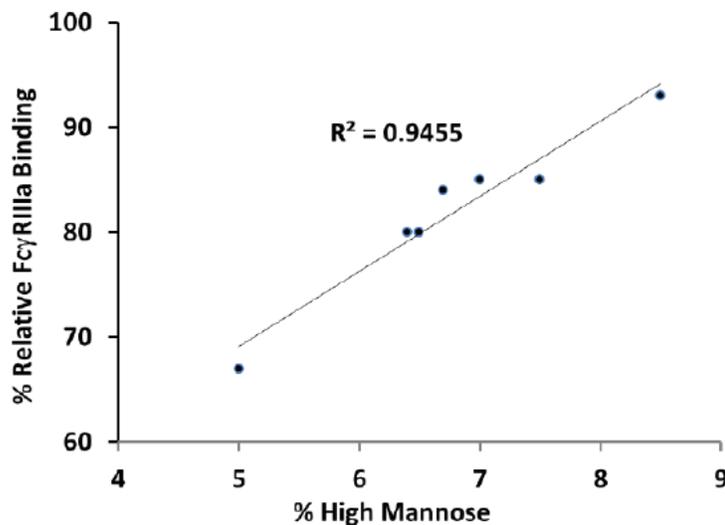


Figure 26. Relative Binding to Fc γ RIIIa - Adalimumab (EU) Compared to Adalimumab (US) Quality Range



Reviewer Comment: Results demonstrated ABP 501 has similar FcγRIIIa (158V) binding compared to US-licensed Humira and EU-approved Humira, respectively. Additionally, FcγRIIIa (158F) binding affinity was also evaluated using a Tier 3 statistical method, which also supported the conclusion of similarity. Amgen also provided data on March 21, 2016 to demonstrate that the FcγRIIIa assay is appropriately qualified. The method was evaluated and demonstrated to possess adequate linearity and precision. Additionally, the applicant provided a graphical evaluation comparing levels of high mannose and binding affinity for FcγRIIIa (158V) in a response to IR provided on July 5, 2016. As expected, a strong correlation was observed. Data support a determination of high similarity for ABP 501 to US-licensed Humira, and are appropriate to justify the relevance of comparative data generated from clinical and nonclinical studies that used EU-approved Humira.

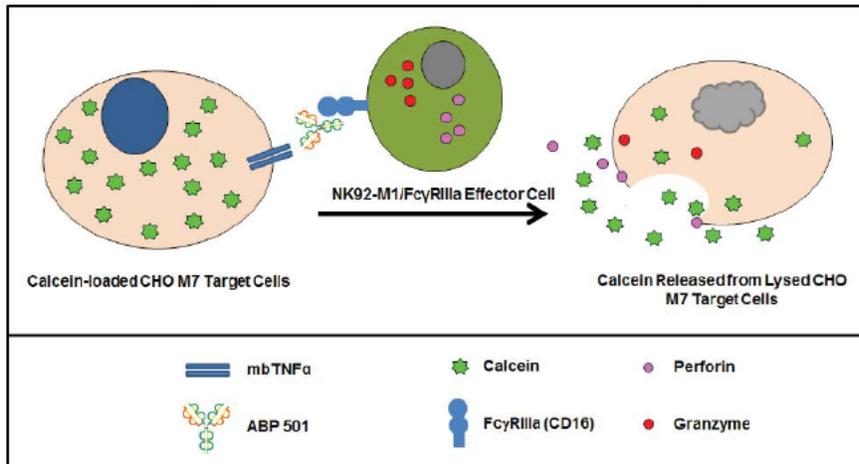
Figure 1. FcγRIIIa Binding Assay Responsiveness to High Mannose



3.2.R.4.4.8.4 Antibody-dependent Cell-mediated Cytotoxicity (ADCC) (10:17:15)

For the ADCC assay, CHO M7 cells, that stably express a TNFα converting enzyme (TACE)-resistant form of mbTNFα on their cell surfaces, are used as target cells. NK92-M1 cells, stably transfected with human FcγRIIIa (also known as CD16), are used as effector cells. Briefly, target cells are loaded with calcein-AM, which readily enters the cells where it is cleaved by intracellular esterases to the polar fluorochrome, calcein and is retained within cells with intact plasma membranes. These calcein-labeled target cells are opsonized with increasing concentrations of ABP 501 prior to co-incubation with NK-92M1/CD16 effector cells. Upon target cell lysis, calcein is released into the media. After removing the culture supernatant from any remaining intact cells, the amount of calcein released can be measured using a microplate reader and is directly proportional to the target cell lysis. A schematic of the ADCC assay is shown in Figure 51.

Figure 51. Schematic of the ABP 501 ADCC Assay



The quality range was established using the mean \pm 3SD derived from 17 US-licensed Humira lots.. Results are shown in the figures below.

Figure 12. Relative ADCC Activity - ABP 501 Compared to Adalimumab (US) Quality Range

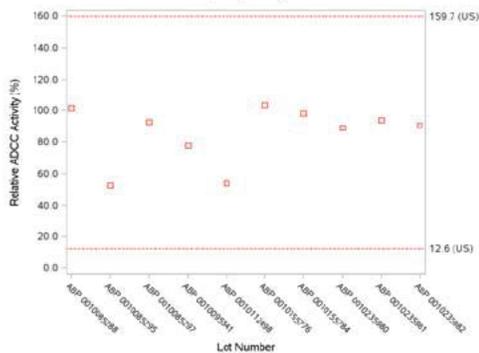


Figure 13. Relative ADCC Activity - ABP 501 Compared to Adalimumab (EU) Quality Range

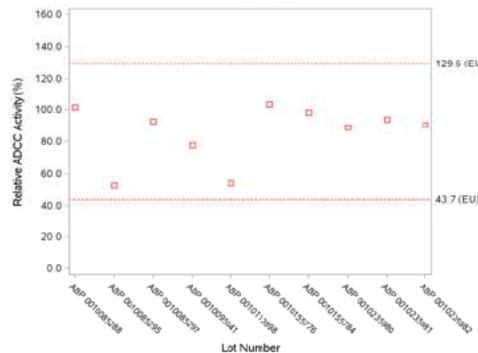
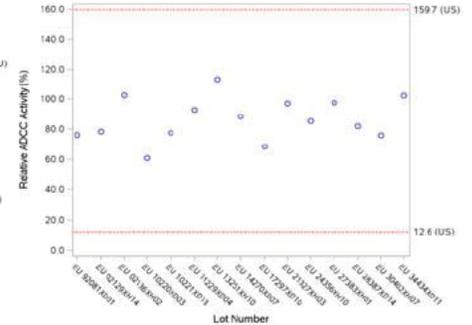


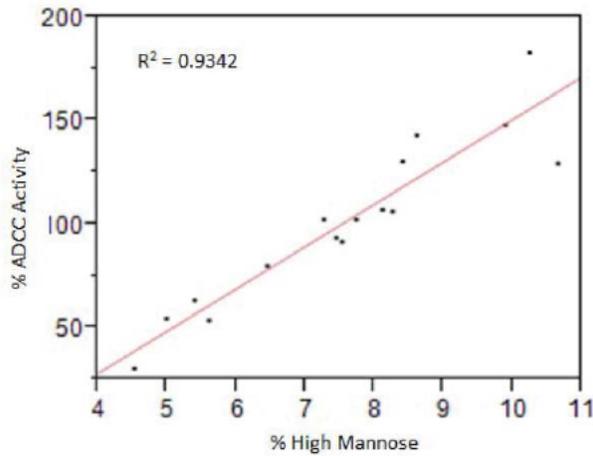
Figure 14. Relative ADCC Activity - Adalimumab (EU) Compared to Adalimumab (US) Quality Range



Reviewer Comment: The results demonstrated ABP 501 has similar ADCC activity compared to US-licensed Humira and EU-approved Humira, respectively.

Amgen also provided qualification data in their March 21, 2016 that supports the qualification of this method. The qualification report (TRPT-026575) demonstrates that specificity (no binding to untransfected cells), linearity (60-160%), precision (across the five linearity concentration ranges), and accuracy were considered. In addition, in response to the IR provided on July 5, 2016, the applicant demonstrated that the high mannose levels correlate with FcγRIIIa (presented in the previous section) and ADCC activity (figure below). Additionally, data were evaluated on inspection that demonstrated the equivalent response of the transfected NK cells to PMBCs. Taken collectively, these data demonstrate the ADCC activity to be sufficiently responsive to changes in product quality. These data also support the contention that slight changes in levels of high mannose and afucosylation are not expected to have clinically significant consequences. Data support a determination of high similarity and the adequacy of the analytical component of the scientific bridge to support the use of EU-Approved Humira in the clinical trial 20120263.

Figure 2. ADCC Assay Responsiveness to High Mannose



3.2.R.4.4.8.5 C1q Binding (3:3:3)

In their March 21, 2016 IR response, Amgen provided C1q assay data. Additionally, they noted that binding to C1q is also assessed as part of the CDC assay given that binding to C1q reflects one step in that mechanism of action. Binding to C1q was assessed using a direct binding ELISA, where bound C1q is detected using an anti-C1q horseradish peroxidase conjugated antibody. The data provided are summarized below, in a table directly copied from the submission.

Table 1. C1q Binding Results for Adalimumab (EU), ABP 501 and Adalimumab (US)

Lot Number	C1q Binding (%)	Estimated Material Age (Months) ^a
EU 49051XD01	77	11
EU 50062XD11	63	10
EU 53083XH12	78	7
ABP 0010155776	80	31
ABP 0010178757	67	25
ABP 0010257725	92	4
US 1024658	75	19
US 1028009	68	17
US 1039181	73	10

^a Reflects estimated material age at the time of testing

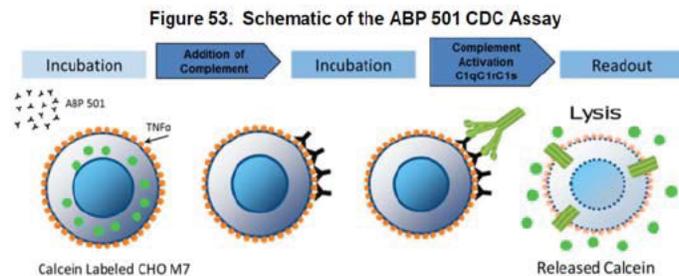
Reviewer Comment: The original IR item from FDA stated that a Quality Range analysis should be used to evaluate C1q binding. As only 3 lots of data were provided, a quality range analysis is not appropriate. As noted elsewhere in the review, equivalent CDC activity and the absence of structural differences between ABP 501 and US-licensed Humira suggest that no difference in C1q binding is expected. Thus, these data are considered suitable to confirm a conclusion of no difference in C1q affinity. Additionally, the three individual replicates were performed independently and demonstrate the method to possess adequate precision.

The data support a determination of high similarity between ABP 501 and US-licensed Humira. Furthermore, they support the adequacy of the scientific bridge for the use of EU-Approved Humira in clinical trial 20120263.

3.2.R.4.4.8.6 Complement-dependent Cytotoxicity (CDC) (10:17:15)

The CDC assay assesses the biological activity of an Fc-mediated effector function, and it is performed in vitro using engineered cell lines expressing a non-cleavable membrane expressed TNF α and rabbit complement. The CDC method was performed on 10 ABP 501, 17 US-licensed Humira, and 15 EU-Approved Humira lots. Figure 15 shows the sTNF α binding results.

For the CDC assay, CHO M7 cells have been transfected to stably express a TACE-resistant form of transmembrane TNF α on their cell surface. The CHO M7 cells are loaded with calcein-AM. This reagent readily enters cells where it is cleaved by nonspecific esterases to become fluorescent and trapped within the cell membrane. The calcein loaded target cells are first incubated with different dose concentrations of antibody, then complement is added and a second incubation is performed. After the complement incubation, the supernatant is removed and the fluorescence is measured using a microplate reader. The fluorescence intensity is directly proportional to the amount of cellular lysis, as shown in Figure 53.



The CDC method was performed on 10 ABP 501, 17 US-licensed Humira, and 15 EU-Approved Humira lots. CDC is evaluated using a Tier 2 statistical method. The quality range was established using the mean \pm 3SD derived from 17 US-licensed Humira lots. The results are listed below.

Figure 16. Relative CDC Activity - ABP 501 Compared to Adalimumab (US) Quality Range

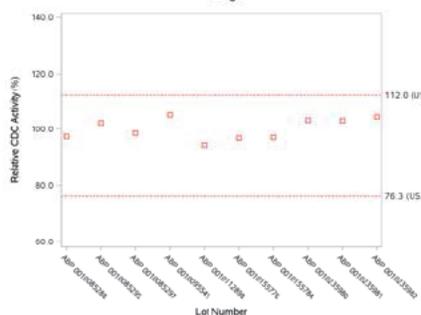


Figure 17. Relative CDC Activity - ABP 501 Compared to Adalimumab (EU) Quality Range

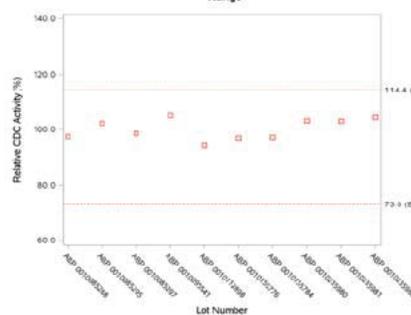
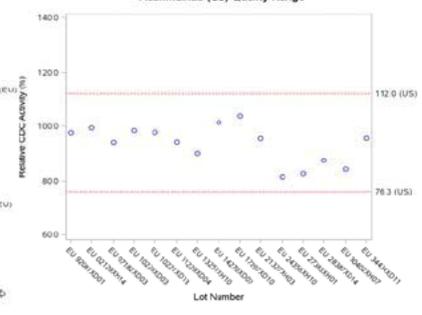


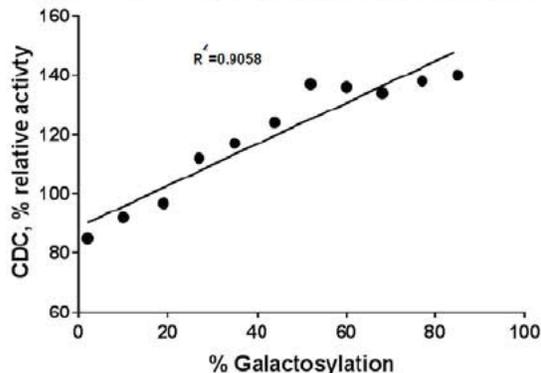
Figure 18. Relative CDC Activity - Adalimumab (EU) Compared to Adalimumab (US) Quality Range



Reviewer Comment: Amgen also provided data on March 21, 2016 that support the qualification of this method. As with other functional assays, qualification data that evaluated specificity, linearity/range, precision and accuracy were considered. Additionally, the adequacy of the CDC method was reviewed during the course of the PAI inspection from May 31 to June 6, 2016. Finally, in their IR response dated July 5, 2016, the applicant provided data that demonstrate that the assay is sensitive to changes in levels

of galactosylation, as shown below. These data are considered sufficient to demonstrate that differences in levels of galactosylation are not considered to have clinically significant consequences. The data support a determination of high similarity and the adequacy of the analytical component of the scientific bridge to support the use of EU-Approved Humira in the clinical trial 20120263.

Figure 3. CDC Assay Responsiveness to Galactosylation

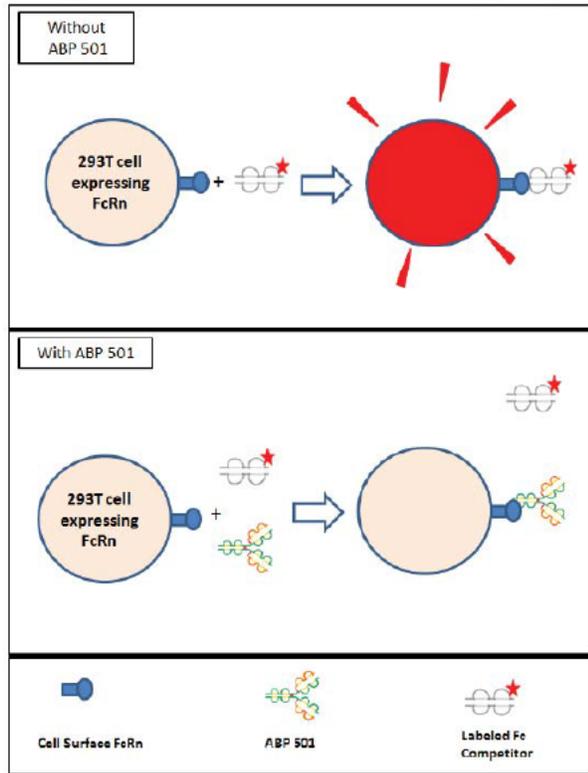


3.2.R.4.4.8.7 FcRn Binding (10:16:12)

The FcRn binding assay assesses comparative binding of the Fc region to FcRn, which contributes to the PK of the molecule. A cell-based FcRn binding assay that uses the human embryonic kidney cell 293 (HEK-293) was used. In the method, ABP 501 was incubated with fluorescently labeled IgG1-Fc. The labeled Fc sample serves as a competitor in the assay. The FcRn binding method was performed on 10 ABP 501, 16 US-licensed Humira, and 12 EU-Approved Humira lots.

A cell-based FcRn binding assay using a variant of the human embryonic kidney cell line 293 (293T) was developed to test the binding of the ABP 501 Fc moiety to FcRn. A clonal 293T cell population, with cells expressing FcRn on their surface, was used in the assay. Briefly, the competitive binding assay is based on the ability of ABP 501 to compete with fluorescently labeled recombinant IgG1-Fc for binding to cell surface-expressed FcRn. In the assay, ABP 501 is incubated with FcRn-expressing cells and a fixed concentration of fluorescently labeled IgG1-Fc at room temperature. After the incubation, the assay plate is read on a fluorescence-enabled reader for measuring the cell-bound fluorescence. Fluorescence data from each well are recorded and analyzed. A schematic of the cell-based FcRn binding assay is shown in Figure 47

Figure 47. Schematic of the ABP 501 FcRn Binding Assay



FcRn binding is evaluated using a Tier 2 statistical method. The quality range was established using the mean \pm 3SD derived from 16 US-licensed Humira lots. The results are presented below.

Figure 20. Relative Binding to FcRn - ABP 501 Compared to Adalimumab (US) Quality Range

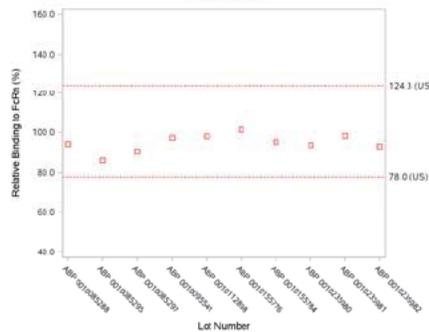


Figure 21. Relative Binding to FcRn - ABP 501 Compared to Adalimumab (EU) Quality Range

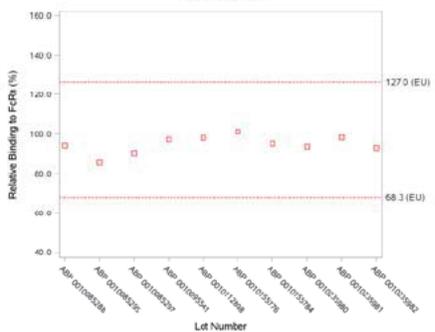
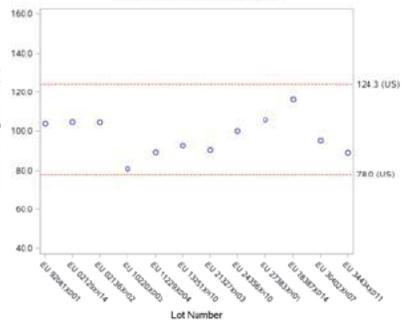


Figure 22. Relative Binding to FcRn - Adalimumab (EU) Compared to Adalimumab (US) Quality Range



Reviewer Comment:

Data support a determination of high similarity and the adequacy of the analytical component of the scientific bridge to support the use of EU-Approved Humira in the clinical trial 20120263.

3.2.R.4.4.8.8 Reverse Signaling (10: 10:12)

Reviewer Comment: The Agency requested reverse signaling data to support the justification for the extrapolation to Inflammatory Bowel Disease (IBD) indications in its IR dated May 19, 2016.

The applicant subsequently developed an assay and provided results in the August 11, 2016 IR response (as well as provided a status update on August 2, 2016). The assay selected is a reproduction of literature results, and the reproducible dose response curve, coupled with the description is sufficient to consider the method appropriate for evaluation of reverse signaling. Further discussion on the importance of reverse signaling is presented in section 3.2.S.1.3.

The reverse signaling assay assesses the Fab and Fc-mediated functions of adalimumab and ABP 501 through engagement of mbTNF α on the target Jurkat:mbTNF α cells and transmission of a signal into the cells which causes apoptosis. Reverse signaling is considered a **Tier 2** assay/attribute.

The reverse signaling assay utilizes an engineered Jurkat cell line constitutively expressing a non-cleavable version of mbTNF α (Mitoma H, Horiuchi T, Tsukamoto H, et al. *Arthritis Rheum.* 2008; 58:1248-1257). The reverse signaling method utilizes fluorescence activated cell sorting (FACS) and both Annexin V dye for the detection of phosphatidyl serine (PS) as a measure of apoptosis as well as propidium iodide (PI) for the detection of general cytotoxicity. The method schematic is shown in Figure 1.

Jurkat:mbTNF α cells are incubated with dilutions of control and test samples for 18 to 20 hours at 37°C in a CO₂ incubator. The plate is spun to pellet the cells, and the excess media is removed and replaced with a staining cocktail containing Annexin V and PI dyes. The cells are stained for 15 minutes in a dark room at room temperature. Binding buffer is added, and the samples are run in a FACS machine within 1 hour of staining. The results are analyzed by performing gating analysis to identify the different populations of interest (Annexin V positive, Annexin V positive and PI positive, Annexin V negative and PI negative). The percentage of cells in the Annexin V positive gate is used for the generation of dose response curves and the determination of the EC₅₀ for each sample. Software is used to perform a 4-parameter data analysis and a constrained model curve fit to the data. Relative reverse signaling activities are calculated based on the ratio of EC₅₀ values of the reference standard curve relative to the test sample.

Figure 1. Representation of Reverse Signaling Assay

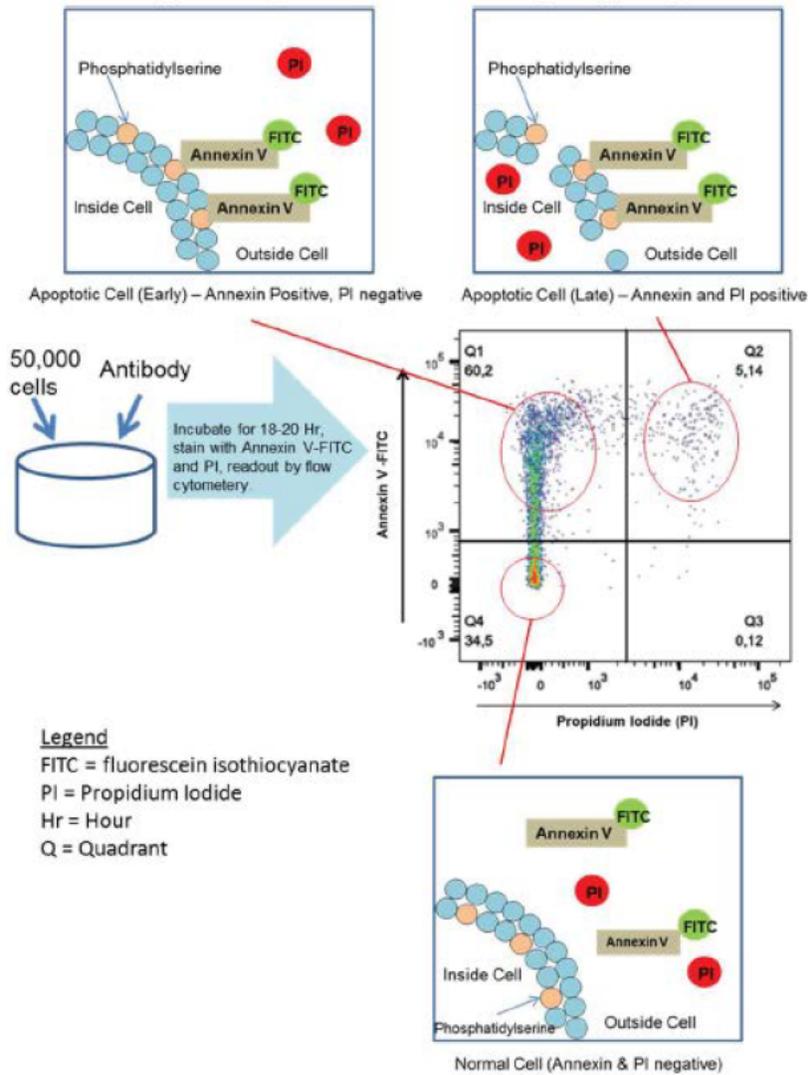
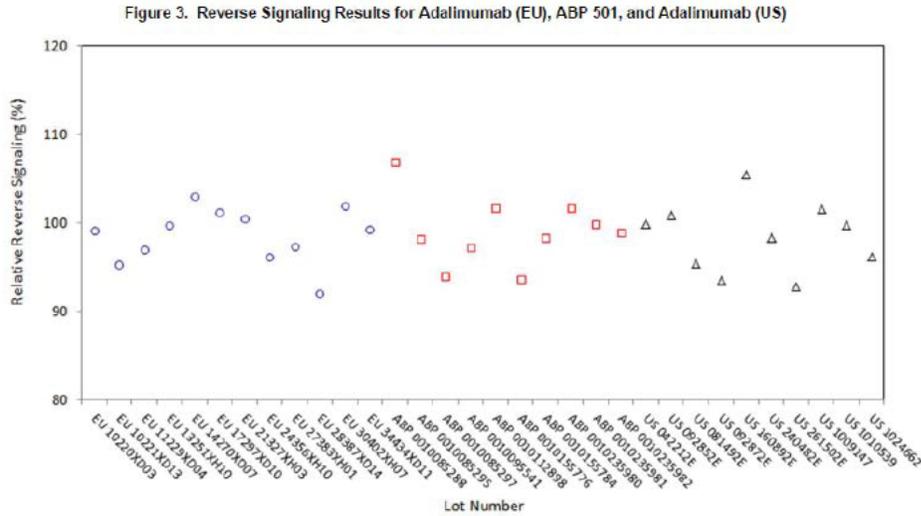


Figure 3 provides the results that compare reverse signaling results are similar across the 3 products.



The quality range for the reverse signaling was established using the mean \pm 3SD derived from 10 US-licensed Humira lots. The results are listed below.

Figure 4. Relative Reverse Signaling Activity - ABP 501 Compared to Adalimumab (US) Quality Range

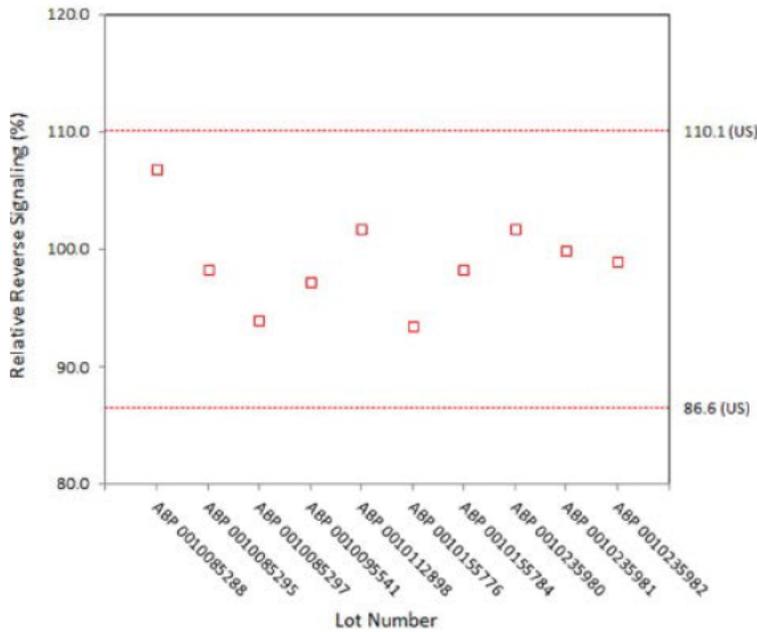


Figure 5. Reverse Signaling Activity - ABP 501 Compared to Adalimumab (EU) Quality Range

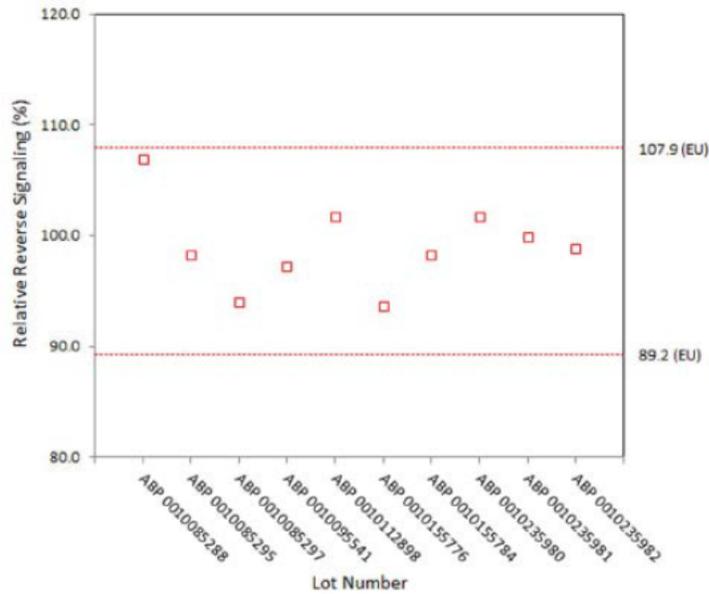
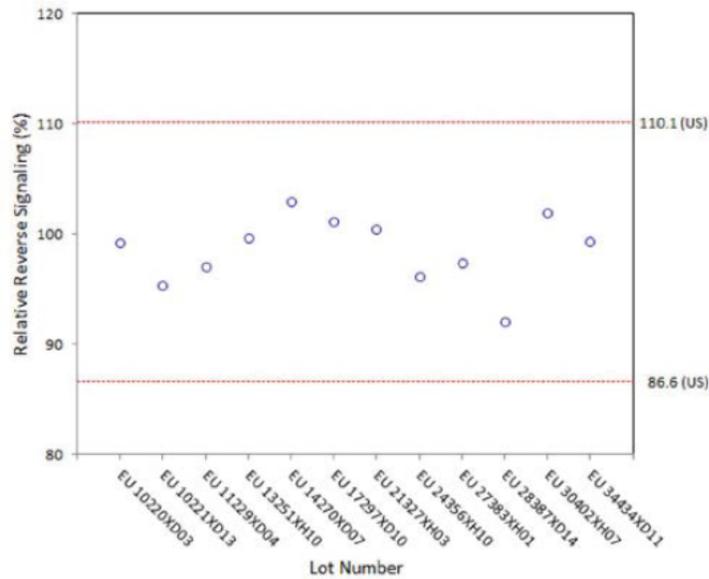


Figure 6. Relative Reverse Signaling Activity - Adalimumab (EU) Compared to Adalimumab (US) Quality Range



Reviewer Comment:

Data support a determination of high similarity and the adequacy of the analytical component of the scientific bridge to support the use of EU-Approved Humira in the clinical trial 20120263.

BIOLOGICAL ACTIVITY – ADDITIONAL CHARACTERIZATION**3.2.R.4.4.8.9 Binding Kinetics to TNF α (3:3:3)**

A total of three lots of each of the products were tested side by side in the SPR binding assays, in three independent experiments. Results are provided in the table 2 below. Data were also presented to evaluate the binding kinetics of the three products to cynomolgus sTNF α (though not presented).

Table 2. Comparative Binding Affinity of ABP 501, Adalimumab (US), and Adalimumab (EU) to Human TNF α by Biacore Single Cycle Kinetics

Experiment	Sample	On Rate k_a (1/Ms)	Off Rate k_d (1/s)	Equilibrium K_d (pM)
1	ABP 501 Lot 0010085289	7.62 E + 5	3.94 E - 5	52
	Adalimumab (US) Lot 042212E	7.45 E + 5	3.94 E - 5	53
	Adalimumab (EU) Lot 92081XD01	8.08 E + 5	4.38 E - 5	54
2	ABP 501 Lot 0010085295	7.69 E + 5	3.73 E - 5	48
	Adalimumab (US) Lot 031622E	8.34 E + 5	3.98 E - 5	48
	Adalimumab (EU) Lot 02129XH14	8.58 E + 5	3.90 E - 5	46
3	ABP 501 Lot 0010085297	8.35 E + 5	4.28 E - 5	51
	Adalimumab (US) Lot 050662E	8.12 E + 5	4.27 E - 5	53
	Adalimumab (EU) Lot 07182XD03	8.65 E + 5	4.44 E - 5	51

Reviewer Comment:

Data support a determination of high similarity between ABP 501 and US-licensed Humira and the appropriateness of the use of EU-Approved Humira in clinical trial 20120263.

3.2.R.4.4.8.10 Binding to Membrane-associated TNF α (3:3:3)

Adalimumab is known to bind mbTNF α as well as sTNF α , ultimately blocking signaling induced by mbTNF α or perhaps mediating cellular effects directly by engaging mbTNF α . Modulation of cellular activities subsequent to binding mbTNF is thought to be especially relevant to efficacy in inflammatory bowel disease (IBD). Binding to mbTNF α was tested in a cell-based binding competition assay using CHO cells overexpressing non-cleavable TNF α (CHO-M7) and Alexa 488 (A488)-labeled ABP 501.

For the analytical similarity assessment, the percent relative binding data were generated by testing 3 ABP 501 lots along with 3 US lots and 3 EU lots of innovator material (3:3:3 testing) in 3 independent determinations each. The results provided in Table 4.

Table 4. Comparison of ABP 501, Adalimumab (US), and Adalimumab (EU) in Cell-based Membrane Bound TNF α Binding Assay

Sample	Assay 1	Assay 2	Assay 3	Mean	SD	CV
ABP 501 Lot 0010112898	109.0%	106.0%	102.0%	106%	3.5	3%
ABP 501 Lot 0010155776	99.2%	98.4%	109.0%	102%	5.9	6%
ABP 501 Lot 0010155784	101.0%	97.4%	103.0%	100%	2.8	3%
Adalimumab (US) Lot 240482E	115.0%	95.8%	88.3%	100%	13.8	14%
Adalimumab (US) Lot 251412E	110.0%	114.0%	109.0%	111%	2.6	2%
Adalimumab (US) Lot 261512E	116.0%	94.9%	101.0%	104%	10.9	10%
Adalimumab (EU) Lot 21327XH03	118.0%	98.3%	112.0%	109%	10.1	9%
Adalimumab (EU) Lot 24356XH10	114.0%	99.7%	111.0%	108%	7.5	7%
Adalimumab (EU) Lot 27383XH01	114.0%	90.6%	98.0%	101%	12.0	12%

Reviewer Comment: *The results of mbTNF α binding assay were assessed using a Tier 3 statistical evaluation. Data are supportive of high similarity between ABP 501 and US-Licensed Humira and support the appropriateness of the use of EU-Approved Humira in clinical trials.*

3.2.R.4.4.8.11 Comparative Neutralization of Human TNF α -induced Signaling in HUVEC (3:3:3)

TNF α and the related cytokine lymphotoxin alpha (LT α) can both induce inflammatory signaling in human umbilical vein endothelial cells (HUVEC) in vitro. Due to its binding specificity for TNF α , adalimumab can neutralize the ability of TNF α , but not LT α , to induce interleukin-8 (IL-8) secretion in HUVEC.

Assays to monitor induced IL-8 secretion in HUVEC were developed as an orthogonal characterization assay (following TNF α stimulation) and confirmation of specificity (following LT α stimulation). In these studies, HUVEC were stimulated with 3 ng/mL human TNF α or 10 ng/mL human LT α in the presence of increasing concentrations of ABP 501, US-licensed Humira, or EU-approved Humira; the resulting IL-8 secretion was assessed after 4 hours.

A total of three lots of each of the products were tested side by side in the. Results are listed in Figure 2 and Table 5 below.

Figure 2. Representative Inhibition of IL-8 Production in HUVEC by ABP 501, Adalimumab (US), and Adalimumab (EU)

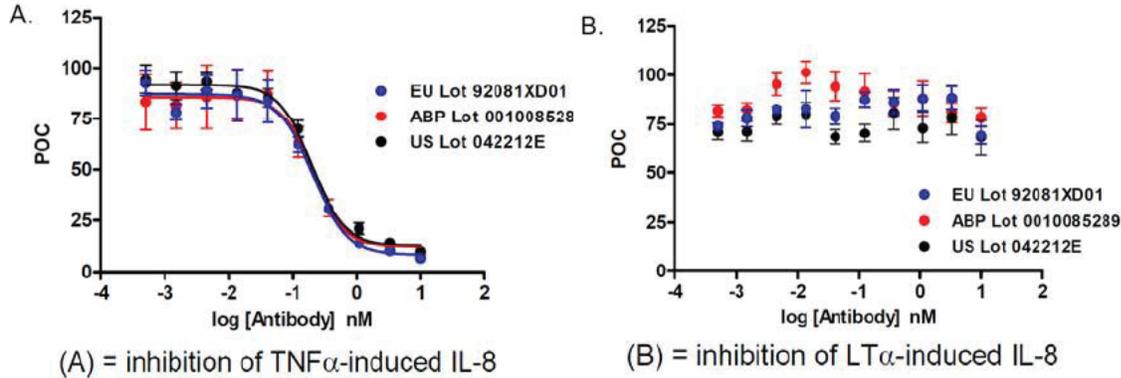


Table 5. Potency of Inhibition of TNF α -induced IL-8 in HUVEC

Sample	Assay 1 EC ₅₀ (pM)	Assay 2 EC ₅₀ (pM)	Assay 3 EC ₅₀ (pM)	Assay 4 EC ₅₀ (pM)
ABP 501 Lot 0010085289	192	253	211	204
Adalimumab (US) Lot 042212E	253	131	200	171
Adalimumab (EU) Lot 92081XD01	225	181	208	177
ABP 501 Lot 0010085295	—	—	—	294
Adalimumab (US) Lot 031622E	—	—	—	156
Adalimumab (EU) Lot 02129XH14	—	—	—	168
ABP 501 Lot 0010085297	—	—	—	200
Adalimumab (US) Lot 050662E	—	—	—	166
Adalimumab (EU) Lot 07182XD03	—	—	—	222

— = not determined

Reviewer Comment: The results support the following conclusions:

- Dose-response curves from a representative experiment using a single lot of each product were similar for ABP 501, US-licensed Humira, and EU-approved Humira (Figure 2A)
- As expected ABP 501, ABP 501, US-licensed Humira, and EU-Approved Humira did not affect LT α -induced IL-8 production in HUVEC (Figure 2B)
- Similar potencies for the 3 products were observed as listed in Table 5

Reviewer Comment: Data support the conclusion of high similarity between ABP 501 and US-licensed Humira and the adequacy of the analytical component of the scientific bridge to use EU-Approved Humira in clinical trial 20120263.

3.2.R.4.4.8.12 Neutralization of Human and Cynomolgus Monkey TNF α -induced Cell Death in L929 Cell

TNF α can induce necrotic cell death under specific conditions *in vitro*, and adalimumab can neutralize this activity. In these studies, murine L929 cells were sensitized with actinomycin D (2 μ g/mL for 2 hours) and then stimulated with human or cynomolgus monkey TNF α in the presence of increasing concentrations of ABP 501, US-licensed Humira, or EU-Approved Humira.

The potency of inhibition of human and NHP TNF α -induced cell death has also been assessed across 3 lots of each product and results of representative experiments are shown in Figure 3A and Figure 3B, respectively. Potencies for neutralizing human TNF α -induced cell death are shown in Table 6.

Figure 3. Representative Inhibition of TNF α -induced Cell Death by ABP 501, Adalimumab (US), and Adalimumab (EU)

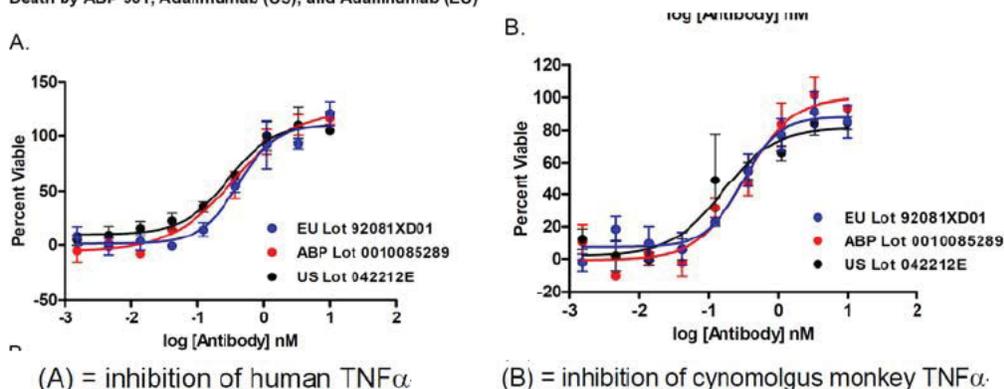


Table 6. Potency of Inhibition of Human TNF α -induced Cell Death in L929 Cells Across Multiple Lots of ABP 501, Adalimumab (US), and Adalimumab (EU)

Sample	Assay 1 EC ₅₀ (pM)	Assay 2 EC ₅₀ (pM)	Assay 3 EC ₅₀ (pM)	Assay 4 EC ₅₀ (pM)
ABP 501 Lot 0010085289	390	240	343	511
Adalimumab (US) Lot 042212E	1355	284	291	379
Adalimumab (EU) Lot 92081XD01	2018	294	407	356
ABP 501 Lot 0010085295	—	—	—	457
Adalimumab (US) Lot 031622E	—	—	—	391
Adalimumab (EU) Lot 02129XH14	—	—	—	306
ABP 501 Lot 0010085297	—	—	—	454
Adalimumab (US) Lot 050662E	—	—	—	544
Adalimumab (EU) Lot 07182XD03	—	—	—	338

— = not determined

Reviewer Comment: Data demonstrate that the potencies of ABP 501, US-licensed Humira, and EU-approved Humira, as determined by the ability to inhibit both human and NHP TNF α -induced cell death are generally similar. However, potencies of the US-licensed Humira and EU-approved Humira appeared to be reduced in assay 1 compared with assays 2, 3, and 4, though this likely due to inherent assay variability.

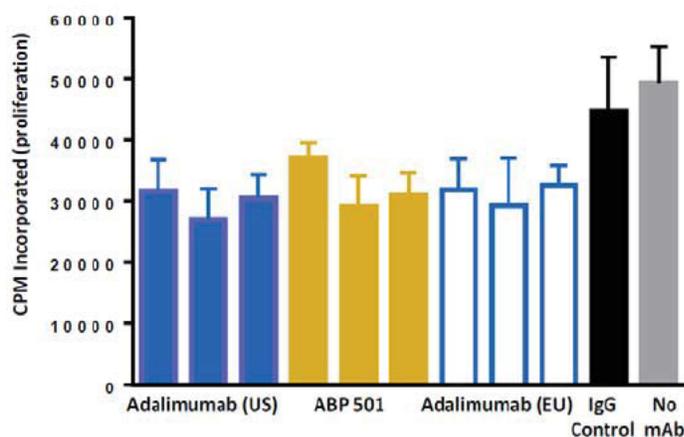
Though highly variable, data support that the potency of ABP 501, US-licensed Humira, and EU-approved Humira to inhibit both human and NHP TNF α -induced cell death are generally similar.

3.2.R.4.4.8.13 Inhibition of Proliferation in a Mixed Lymphocyte Reaction (MLR) (3:3:3)

It has been reported that adalimumab is able to induce regulatory macrophages *in vitro*, and infliximab, another TNF antibody, also has the same effect *in vivo* which is correlated with clinical efficacy¹. These investigators demonstrated that regulatory macrophages are responsible for the inhibition of T cell proliferation in a mixed lymphocyte reaction (MLR), and that activity is dependent upon binding to mbTNF α and to Fc gamma (Fc γ) receptors. Since this activity appears to be important for the efficacy observed in IBD, an MLR was developed using primary cells from 2 different donors chosen to produce an optimal proliferation response.

Results are shown in Figure 4. Each point is an individual test, with n = 5 replicates per mAb sample and n = 10 replicates in the no antibody sample. Each column of data points represents a unique lot of test mAb. The induction component of regulatory macrophages, though not assessed individually is evaluated by staining for CD206. Data representing proliferation are presented below.

Figure 1. Inhibition of proliferation in an MLR: comparison of ABP 501 to adalimumab



adalimumab (EU) = Humira®, which is approved and marketed in the European Union; adalimumab (US) = Humira®, which is approved and marketed in the United States; CPM = counts per minute; IgG= immunoglobulin G; mAb = monoclonal antibody; MLR = mixed lymphocyte reaction. Each bar represents a unique lot tested at 5 μ g/mL, with n = 5 replicates per mAb sample and n = 10 replicates in the no antibody sample, with some outlier values excluded (Report R20140036).

Source: Graph format modified from results reported in Report R20140036. Module 4.2.1.1

Reviewer Comment: Amgen noted that a robust and reproducible dose response for this assay was difficult to demonstrate for adalimumab due to the small signal window and variability attributed to the use of primary cells. Therefore, the assay was run with 2 concentrations of test mAbs and used to qualitatively assess the ability of the mAb to inhibit cellular proliferation. ABP 501, US-licensed Humira, and EU-approved Humira are similarly able to inhibit cellular proliferation in an MLR at 5 μ g/mL.

Additionally, Amgen also thermally degraded samples of ABP 501 (60°C for 14 days) prior to a second evaluation in this MLR study and demonstrated the MLR assay to be sufficiently sensitive to observe diminished activity for degraded samples. Data support a determination of high similarity between ABP 501 and US-licensed Humira and the adequacy of the scientific bridge for use of EU-Approved Humira in trial 20120263.

1 | Vos, A. C. W., et al, [Inflamm Bowel Dis](#). 2012 Mar;18(3):401-8.

3.2.R.4.4.8.14 FcγRIa Binding Analysis (3:3:3)

Binding to the activating, high affinity FcγRIa expressed on macrophages, dendritic cells (DCs), and neutrophils was assessed in a competitive AlphaLISA™ binding assay. Results are listed in Table 9.

Table 9. Summary of FcγRIa AlphaLISA™ Results for ABP 501, Adalimumab (US), and Adalimumab (EU) Lots

Sample	% Relative Binding to FcγRIa					
	Assay 1	Assay 2	Assay 3	Mean	SD	% CV
ABP 501 Lot 0010112898	97.6	98.2	102.0	99	2.4	2
ABP 501 Lot 0010155776	98.1	95.1	99.3	98	2.2	2
ABP 501 Lot 0010155784	100.8	90.7	97.2	96	5.1	5
Adalimumab (US) Lot 240482E	93.6	89.5	93.8	92	2.4	3
Adalimumab (US) Lot 251412E	97.3	92.0	98.0	96	3.3	3
Adalimumab (US) Lot 261512E	94.8	91.9	98.8	95	3.5	4
Adalimumab (EU) Lot 21327XH03	92.0	91.6	93.1	92	0.8	1
Adalimumab (EU) Lot 24356XH10	97.1	90.8	93.3	94	3.2	3
Adalimumab (EU) Lot 27383XH01	99.1	88.3	93.8	94	5.4	6

Reviewer Comment: Results demonstrate the 3 ABP 501 lots tested were similar to the 3 lots each of US-licensed Humira and EU-approved Humira with respect to their level of FcγRIa binding affinity. Data support a determination of high similarity between ABP 501 and US-licensed Humira and the adequacy of the scientific bridge for use of EU-Approved Humira in trial 20120263.

3.2.R.4.4.8.15 FcγRIIa (131H) Binding Analysis (3:3:3)

Fc gamma receptor Type IIa is an activating receptor expressed on macrophages, DC, and neutrophils. In this study, a competitive AlphaLISA™ binding assay was used to assess the binding of ABP 501, US-licensed Humira, and EU-Approved Humira to FcγRIIa (131H). Results are listed in below.

Table 10. Summary of FcγRIIa(131H) AlphaLISA™ Results for ABP 501, Adalimumab (US), and Adalimumab (EU) Lots

Sample	% Relative Binding to FcγRIIa					
	Assay 1	Assay 2	Assay 3	Mean	SD	% CV
ABP 501 Lot 0010112898	109.4	99.0	111.6	107	6.7	6
ABP 501 Lot 0010155776	105.4	98.6	107.6	104	4.7	5
ABP 501 Lot 0010155784	98.4	87.1	100.0	95	7.0	7
Adalimumab (US) Lot 240482E	108.0	93.8	101.3	101	7.1	7
Adalimumab (US) Lot 251412E	111.9	95.3	106.7	105	8.5	8
Adalimumab (US) Lot 261512E	108.2	93.5	101.1	101	7.4	7
Adalimumab (EU) Lot 21327XH03	108.1	87.7	93.3	96	10.5	11
Adalimumab (EU) Lot 24356XH10	106.3	92.2	99.1	99	7.1	7
Adalimumab (EU) Lot 27383XH01	106.2	93.7	99.9	100	6.3	6

Reviewer Comment: Data demonstrate that the 3 ABP 501 lots tested were similar to the 3 lots each of US-licensed Humira and EU-approved Humira with respect to their level of FcγRIIIa binding. Data support a determination of high similarity between ABP 501 and US-licensed Humira and the adequacy of the scientific bridge for use of EU-Approved Humira in trial 20120263.

3.2.R.4.4.8.16 FcγRIIIa (158F) Binding Analysis (3:3:3)

The FcγRIIIa has 2 allelic variants. FcγRIIIa (158V) is the high affinity allotype, and occurs most frequently, whereas FcγRIIIa (158F) occurs less frequently and has a lower binding affinity to Fc than does FcγRIIIa (158V). A competitive AlphaLISA™ binding assay was developed to assess the binding of 3 lots each of ABP 501, US-licensed Humira, and EU-Approved Humira to FcγRIIIa (158F).

Results are presented below.

Table 11. Summary of FcγRIIIa(158F) AlphaLISA™ Results for ABP 501, Adalimumab (US), and Adalimumab (EU) Lots

Sample	% Relative Binding to FcγRIIIa					
	Assay 1	Assay 2	Assay 3	Mean	SD	% CV
ABP 501 Lot 0010112898	73.8	72.0	74.1	73	1.1	2
ABP 501 Lot 0010155776	91.1	90.7	96.1	93	3.0	3
ABP 501 Lot 0010155784	86.5	79.6	93.9	87	7.2	8
Adalimumab (US) Lot 240482E	81.8	80.8	87.3	83	3.5	4
Adalimumab (US) Lot 251412E	96.8	90.1	97.4	95	4.1	4
Adalimumab (US) Lot 261512E	84.3	84.5	84.4	84	0.1	0
Adalimumab (EU) Lot 21327XH03	91.3	107.7	95.8	98	8.5	9
Adalimumab (EU) Lot 24356XH10	89.4	95.0	83.9	89	5.6	6
Adalimumab (EU) Lot 27383XH01	83.1	98.0	83.0	88	8.6	10

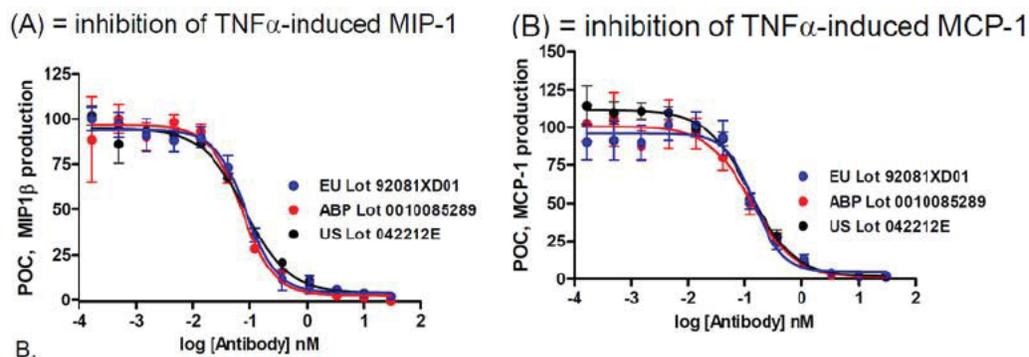
Reviewer Comment: Data from the 3 ABP 501 lots tested were similar to the 3 lots each of US-licensed Humira and EU-approved Humira with respect to their level of FcγRIIIa (158F) binding.

3.2.R.4.4.8.17 Comparative Neutralization of TNFα-induced Chemokine Production in Whole Blood

TNFα stimulation of human and NHP whole blood induces the production of the chemokine macrophage inflammatory protein-1 beta (MIP-1β) and monocyte chemoattractant protein-1 (MCP-1). Although there is variability in the response from donor to donor, inhibition of this response by anti-TNFα antibodies provides an important comparative measure of biological activity. Healthy human or cynomolgus monkey blood (50% final assay concentration) was stimulated with human TNFα (3 ng/mL) or NHP TNFα (10 ng/mL), respectively, in the presence of increasing concentrations of ABP 501, US-licensed Humira, or EU-Approved Humira.

Results are shown in the figure below.

Figure 9. Representative Inhibition of Human TNF α Activity in Human Whole Blood by ABP 501, US-licensed Humira, and EU-Approved Humira



Reviewer Comment: Data demonstrate that the 3 ABP 501 lots tested were similar to the 3 lots each of US-licensed Humira and EU-approved Humira with respect to the production of the chemokine macrophage inflammatory protein-1 beta (MIP-1 β) and monocyte chemoattractant protein-1 (MCP-1) in TNF α -stimulated human and NHP whole blood. These data support a determination of high similarity between ABP 501 and US-licensed Humira and the adequacy of the scientific bridge for use of EU-Approved Humira in trial 20120263.

5.3.1.4 Bioanalytical and Analytical Methods for Human Studies

In the ABP 501 clinical studies, the detection of anti-drug antibody (ADA) and neutralizing activity against ABP 501, US-licensed Humira, and EU-approved Humira were assessed using the following approach:

- All samples are evaluated using a two-tiered assay approach (MET-003222) that consists of a screening assay and a specificity assay
- Samples positive in any of the binding ADA assay (ABP 501, US-licensed Humira, and EU-approved Humira) were assessed for neutralizing antibodies (Nabs) activity against ABP 501 using a qualitative cell-based method (ICDCB 36) or a TNF α target-binding assay method (MET-003554)

Of note, samples positive in any of the 3 binding ADA were assessed for neutralizing activity against ABP 501.

Reviewer Comment:

Assessment of neutralizing activity is ABP 501 is appropriate and preferred. The use of a competitive binding assay in lieu of a cell-based assay for neutralization is considered appropriate given that the target (TNF- α) is the soluble form in circulation for both RA and PsO patients.

Assays and versions used in the ABP 501 clinical program are described in Table 1.

Table 1. Assays and Version Used in ABP 501 Clinical Studies

Study Phase	Immunoassay Used (Method Number and Version)	Bioassay Used (Method Number and Version)
Study 20110217 phase 1	MET-003222 version 2.0	Method ICDCB 36 version 2.0
Study 20120262 phase 3	MET-003222 version 3.0	MET-003554 versions 2.0, 3.0, and 4.0
Study 20120263 phase 3	MET-003222 versions 3.0 and 4.0	MET-003554 versions 3.0 and 4.0

The bioanalytical method and method validation reports for ADAs are summarized in Table 7

Table 7. Summary of Bioanalytical and Analytical Reports Related to Antidrug Antibody Testing

Study Reference No.	Purpose	Site of Analysis	Analyte Measured	Biomatrix	Method Type	Assay Range (Drug Tolerance)	Study Report Location
Method ICDCB 36	Cell-based bioassay method and validation for detection of binding ADAs	(b) (4)	Antidrug (ABP 501, adalimumab [US], adalimumab [EU]) neutralizing antibodies	Serum	Electrochemiluminescent	500 ng/mL of positive control antibody can tolerate 160 ng/mL of excess ABP 501	Module 5.3.1.4
MET-003222	Immunoassay method for detection of binding ADAs	Amgen Inc. Thousand Oaks, CA	Antidrug (ABP 501, adalimumab [US], adalimumab [EU]) binding antibodies	Serum	Electrochemiluminescent	45 ng/mL anti-adalimumab antibody positive control can tolerate 25 µg/mL of drug	Module 5.3.1.4
MVR-000450	Immunoassay method validation	Amgen Inc. Thousand Oaks, CA	Antidrug (ABP 501, adalimumab [US], adalimumab [EU]) binding antibodies	Serum	Electrochemiluminescent	45 ng/mL of anti-adalimumab antibody positive control can tolerate 25 µg/mL of drug	Module 5.3.1.4
MET-003554	Target-binding bioassay method for detection of neutralizing ADAs	Amgen Inc. Thousand Oaks, CA	Antidrug (ABP 501, adalimumab [US], adalimumab [EU]) neutralizing antibodies	Serum	Electrochemiluminescent	0.85 µg/mL of anti-adalimumab positive control antibody in neat serum in presence of 0.156 to 0.3125 µg/mL excess drug	Module 5.3.1.4

In study 20110217, healthy subjects were monitored for the development of ADA against all three products (ABP 501, US-licensed Humira, and EU-approved Humira). Samples were assessed at study start, days 16, 29, and 63. Rates were similar in the study (43% for ABP 501, 50% for US-licensed Humira, and 51% for EU-approved Humira). Neutralizing activity was assessed using the ABP 501 binding antibody. Rates were similar for neutralizing activity (18% for ABP 501, 22% for US-licensed Humira, and 21% for EU-approved Humira).

Two clinical studies supporting efficacy were also evaluated, Study 20120262 (arthritis), and in Study 2012063 (Plaque Psoriasis). In study 20120262, subjects were evaluated and compared at baseline, week 4, week 12, and week 26/end of study. In study 20120263, subjects were analyzed and compared at baseline, week 4, week 16, and discontinuation/end of study. This study included a subset of subjects who transitioned to ABP 501 at re-randomization after 16 weeks treatment with adalimumab and achievement of PASI 50 response or better.

In Study 20120262, rates for ADA formation were 38% for ABP 501 and 38% for US-Approved Humira. In Study 20120263 up to week 16, the rate of ADA formation was 55% for ABP 501 and 64% for EU-Approved Humira. The rate of neutralizing antibody formation for ABP 501 was 10% and 14% for EU-Approved Humira. Comparisons over the entire study were made for ABP 501, EU-Approved Humira, and EU-Approved Humira/ABP 501. The incidence of developing binding or neutralizing ADAs was similar for all 3 groups (binding: 68.4%, 74.7%, and 72.7%; neutralizing: 13.8%, 20.3%, 24.7%, respectively).

An Immunoassay to Detect Antibodies to ABP 501, US-Licensed Humira and EU-Approved adalimumab in Human Serum (Method-003222, versions 2.0 and 3.0)

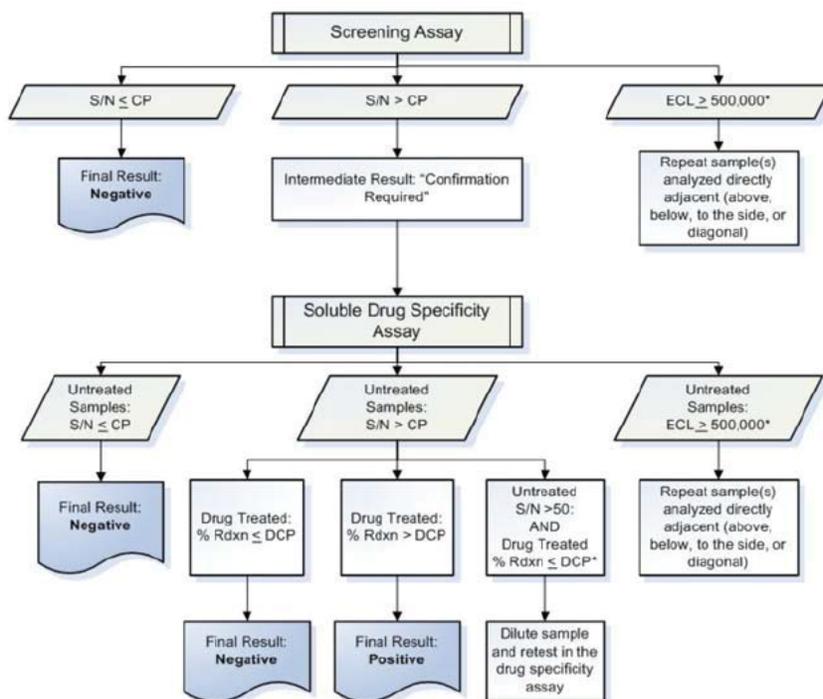
This electrochemiluminescent (ECL) bridging immunoassay used to detect anti-drug antibodies (ADA) against ABP 501, US-Licensed Humira and EU-approved Humira in human serum on the Meso Scale Discovery SECTOR Imager 6000 or MSD Quickplex.

This method is using a two-tiered assay approach that consists of a screening assay and a specificity assay as shown in Figure 3 below.

Screening Assay: Samples are screened in the method using conjugated reagents appropriate for the specific drug of interest. Samples with a signal-to-noise (S/N) value greater than the assay cut point (ACP) are then tested to confirm specificity of the response.

Specificity Assay: samples that demonstrate signal depletion greater than the depletion cut point (DCP) in the presence of an excess of ABP 501 or adalimumab corresponding to the conjugates used, are reported as positive for the presence of binding ATA to the specific drug used for analysis. Samples that are positive for binding ADA are subsequently tested for neutralizing antibodies using a different method.

Figure 3.
Result Determination Flow Diagram



S/N: signal-to-noise ratio; % Rdxn: percent S/N reduction; CP: assay cut point; DCP: depletion cut point
Note: This diagram is a result flow diagram and does not necessarily reflect the assay flow as detailed in the analytical procedure.
* Event not flagged within SL.

In brief, samples are treated with a 300 mM acetic acid to enable antibody complex dissociation prior to analysis. Samples are then incubated with a conjugate/neutralization mixture consisting of biotinylated

therapeutic (ABP 501, Humira®-US or Humira®-EU), corresponding ruthenylated therapeutic (ABP 501, Humira®-US or Humira®-EU), 1 M Tris pH 9.5, an Fc fusion protein specific for TNF- α (Etanercept, a.k.a. Enbrel®) and soluble therapeutic corresponding to the conjugates used (specificity assay only).

***Reviewer Comment:** The use of individual product biotinylated and ruthenylated therapeutics is appropriate given the equivalent sensitivities and drug tolerances for each as determined during validation.*

During this incubation the 2 antigen binding sites of the ADA are able to bind and form a bridge between the biotin and ruthenium labeled therapeutic molecules. The sample mixture is then added to a blocked MSD streptavidin high bind microtiter plate. The biotinylated-therapeutic binds to the streptavidin-coated surface of the well resulting in the immobilization of the bridged complex. The plate is washed to remove any unbound complexes. MSD read buffer T containing tripropylamine (TPA) is added to each well. Using the MSD 6000 plate reader or MSD Quickplex, a voltage is applied across the plate-associated electrodes. The result is a series of electrically induced oxidation-reduction reactions with the ruthenium (from the captured complex) and TPA. The signal is measured and reported as ECL units.

Method Validation (Report, MVR-000450)

This validation report describes the validation of a qualitative immunoassay for the detection of antibodies to ABP 501, and adalimumab in human serum. The experiments outlined in this report were performed according to Analytical Method Validation Protocols MVP-000262 v1.0 and MVP-000262 v2.0.

- MVP-000262 v1.0 is a validation protocol that was used to support method MET-003222 v1.0 and v2.0 during Phase 1
- MVP-000262 v2.0 describes additional parameters that were evaluated to support the Phase 3 clinical validation of revised (v3.0) analytical method MET-003222

Summary of Method Validation for MET-03222 v 1.0 and v2.0 (for the Phase 1 study) is listed below.

Validation Experiment	Results	
Assay Cut Point (CP)	S/N:	1.15
Depletion Cut Point (DCP)	%Depletion	37%
For ABP 501; Humira®-EU; Humira®-US	(n) donors tested:	36
	(n) samples tested:	72
ABP 501 Screening Sensitivity	Concentration:	5 ng/mL
Humira®-EU Screening Sensitivity	Concentration:	<5 ng/mL
Humira®-US Screening Sensitivity \	Concentration:	< 5 ng/mL
ABP 501 Specificity Sensitivity at DCP	Concentration:	17 ng/mL
Humira®-EU Specificity Sensitivity at DCP	Concentration:	15 ng/mL
Humira®-US Specificity Sensitivity at DCP	Concentration:	9 ng/mL
Drug Tolerance in Specificity Assay	anti-Humira® Ab detectable in presence of 25 µg/mL drug	
ABP 501 Drug Tolerance	27 ng/mL anti-Humira® Ab	
Humira®-EU Drug Tolerance	21 ng/mL anti-Humira® Ab	
Humira®-US Drug Tolerance	21 ng/mL anti-Humira® Ab	

Reviewer Comment: . Met-003222 v2.0 was used for the detection of ADAs for both ABP 501 and Humira products for the phase 1 study. Version 2.0 was fundamentally unchanged from version 1.0 with the exception that the low positive control concentration was changed.

The level of the drug tolerance for the method (MET-003222 v 2.0) is 25 µg/mL that is appropriate for the clinical uses.

5.3.1.4.1 Method Validation for the MET-03222 v 3.0 (Report MVR-000450)

The following method parameters were validated according to the Analytical Method Validation Protocol, MVP-000262v2.0, and Immunoassay Validation SOP-000376 to support the clinical validation of analytical method MET-003222 v3.0.

Validation Experiment	Results		
Assay Cut Point (CP) Depletion Cut Point (DCP) For ABP 501; Humira®-EU; Humira®-US	S/N:	1.21	
	%Depletion	30%	
	(n) healthy donors:	36 (Phase 1), 202 (Study 20110217)	
	(n) rheumatoid arthritis donors	57	
	(n) psoriasis donors	30	
	(n) total samples tested: (n) total samples tested all drugs	325 with each drug 1242	
ABP 501 Screening Sensitivity	Concentration:	<10 ng/mL	
Humira®-EU Screening Sensitivity	Concentration:	5.9ng/mL	
Humira®-US Screening Sensitivity\	Concentration:	6.0ng/mL	
ABP 501 Specificity Sensitivity at DCP	Concentration:	23.8 ng/mL	
Humira®-EU Specificity Sensitivity at DCP	Concentration:	12.3 ng/mL	
Humira®-US Specificity Sensitivity at DCP	Concentration:	23.5 ng/mL	
Drug Tolerance in Specificity Assay	anti-Humira® Ab detectable in presence of 25 µg/mL drug		
ABP 501 Drug Tolerance	39.3 ng/mL		
Humira®-EU Drug Tolerance	14.6 ng/mL		
Humira®-US Drug Tolerance	30.8 ng/mL		
Precision		S/N	ECL
ABP 501 Intra-Assay Precision CV (28 replicates)	Negative Control (NC)	N/A	19%
	LPC = 25 ng/mL	18%	12%
	HPC= 250 ng/mL	19%	9%
Humira®-EU Intra-Assay Precision CV (8 replicates)	Negative Control (NC)	N/A	9%
	LPC = 25 ng/mL	10%	8%
	HPC= 250 ng/mL	16%	13%
Humira®-US Intra-Assay Precision CV (12 replicates)	Negative Control (NC)	N/A	12%
	LPC = 25 ng/mL	4%	18%
	HPC= 250 ng/mL	14%	8%
ABP 501 Inter-Assay Precision CV (15 days)	NC	N/A	18%
	LPC = 25 ng/mL	10%	12%
	HPC= 250 ng/mL	19%	9%
Humira®-EU Inter-Assay Precision CV (3 days)	NC	N/A	8%
	LPC = 25 ng/mL	16%	11%
	HPC= 250 ng/mL	18%	13%
Humira®-US Inter-Assay Precision CV (6 days)	NC	N/A	15%
	LPC = 25 ng/mL	11%	13%
	HPC= 250 ng/mL	20%	14%
Final Reagent Concentrations: Low Positive Control (LPC) High Positive Control (HPC) [drug] in specificity reaction buffer	LPC= 25 ng/mL HPC=250 ng/mL 100 µg/mL ABP 501, Humira®-EU or Humira®-US		

Reviewer Comment: Version 3.0 included editorial changes as well as edits to the cut point given the method was revalidated for the intended treatment population. This is considered appropriate.

Critical Reagents

- Biotinylated-ABP 501 (B-ABP 501), B-Humira-US, and B-Humira-EU
- Ruthenylated-ABP 501 (R-ABP 501), R-Humira-US, and R-Humira-EU
- Affinity purified rabbit polyclonal anti-ABP 501 antibody (Amgen, Lot P138291.104).
- Affinity purified rabbit polyclonal anti-Humira antibody (Amgen, Lot 879365#89).

Reviewer's Comments: Amgen provided characterization results for the biotinylated and ruthenylated critical reagents by the SEC-HPLC and (b) (4) as,

- B- ABP 501, Humira®-EU and Humira®-US and unlabeled ABP 501, Humira®-EU and Humira®-US chromatographic profiles were comparable. Figures 1 and 2 are shown here.
- (b) (4) results for both the biotinylated and ruthenylated drugs demonstrated acceptable recovery compared to the unlabeled drug. Thus there was no impact on the binding capability of the drug after conjugation to biotin or ruthenium, respectively.

These are acceptable.

Figure 1. Conjugated ABP 501 SEC HPLC Overlay (Absorbance: 215 nm)

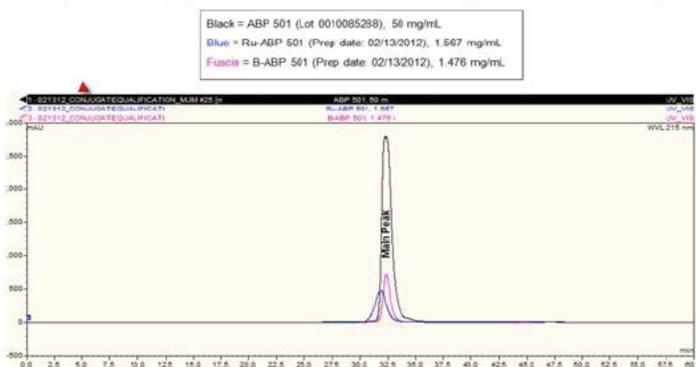
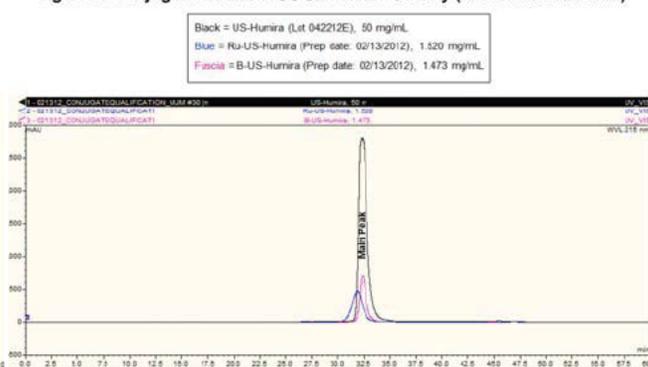


Figure 3. Conjugated Humira®-US SEC HPLC Overlay (Absorbance: 215 nm)



Assay Cut Point

Assay cut point (CP) is defined as the population-specific threshold for differentiating a potentially positive sample from a negative sample.

- Health Donors - Phase 1: 36 human serum samples from 18 males and 18 females
- Combined cut point with Rheumatoid Arthritis, Psoriasis and Healthy Donors – Phase: The CP was further evaluated in donors from rheumatoid arthritis (n=57) and psoriasis (n=30) disease populations. In total, 430 samples were analyzed on 15 plates from multiple plate lots by two analysts on different dates.

Results are listed in Figures 7 and 15.

Figure 7. Biostatistics Summary of the Assay Cut Point (ACP) Analysis (Phase 1)

	Pooled
Number of Donors	36
Number of Samples	216
Max	1.29
Min	0.87
Number of Donors Used in Analysis	36
Number of Samples	216
Max	1.29
Min	0.87
LS-mean	1.03
Standard Error of LS-mean on Transformed Scale	0.01
Standard Deviation of Future Sample on Transformed Scale	0.07
ACP	
Upper Bound on	
95% Prediction Limit	1.15
99% Prediction Limit	1.22

Figure 15. Phase 3 Summary of Statistical Results for Combined CP Estimation from Rheumatoid Arthritis, Psoriasis and Healthy Donors (Refer to RPT-048523 for footnotes)

	Results
Number of Donors	325 ^a
Number of Samples	1242
Max	1.62
Min	0.67
Number of Donors Used in Analysis	325 ^a
Number of Samples	1229 ^b
Max	1.48
Min	0.67
LS-mean	1.05
Standard Error of LS-mean on Transformed Scale	0.01
Standard Deviation of Future Sample on Transformed Scale	0.09
ACP	
Upper Bound on	
95% Prediction Limit	1.21
99% Prediction Limit	1.29

^a Two biological outliers (BRH701412 and BRH701427) were excluded.

^b Statistical outliers removed were summarized in Table 4.

Reviewer Comment: Amgen concluded as

- *Healthy Donors Phase 1: The CP was established as $S/N = 1.15$*
- *Rheumatoid Arthritis, Psoriasis and Healthy Donors – Phase3: Based on statistical analysis, the CPs for each population across each therapeutic (ABP 501, Humira®-EU and Humira®-US) were combined to derive a single CP. The CP at the 95% prediction limit was established as $S/N = 1.21$ for each therapeutic assay in each population.*

These are acceptable and consistent with guidance establishing a 5% false positive rate for screening

Depletion Cut Point (Specificity Assay)

Depletion cut point (DCP) is defined as the specific threshold for differentiating a confirmed positive sample from a negative sample.

Results are listed in Figures 8 and 16.

Figure 8. Biostatistics Summary of the Depletion Cut Point (DCP) Analysis(Phase 1)

	Pooled
Number of Donors	36
Number of Samples	216
Max (%)	34
Min (%)	-24
Number of Donors Used in Analysis	36
Number of Samples	216
Max (%)	34
Min (%)	-24
LS-mean of %Depletion	4%
Standard Error of LS-mean on Transformed Scale	0.03
Standard Deviation of Future Sample on Transformed Scale	0.12
DCP%	
95% Prediction Limit	22%
99% Prediction Limit	29%
99.9% Prediction Limit	37%

Figure 16. Phase 3 Summary of Statistical Results for Combined DCP Estimation from Rheumatoid Arthritis, Psoriasis and Healthy Donors (Refer to RPT-048523 forfootnotes)

	Results
Number of Donors	325 ^a
Number of Samples	1225
Max (%)	44%
Min (%)	-43%
Number of Donors Used in Analysis	324 ^b
Number of Samples	1206 ^b
Max (%)	36%
Min (%)	-43%
LS-mean of %Depletion	2%
Standard Error of LS-mean of T/U on Transformed Scale	0.01
Standard Deviation of T/U of a Future Sample on Transformed Scale	0.11
DCP%	
95% Prediction Limit	18%
99% Prediction Limit	24%
99.9% Prediction Limit	30%

^a Two biological outliers (BRH701412 and BRH701427) were excluded.

^b Statistical outliers removed were summarized in Table 7.

Reviewer’s Comments: *The following conclusions were drawn:*

- *Healthy Donors Phase 1: The DCP at the 99.9% prediction limit was determined as 37%*
- *Rheumatoid Arthritis, Psoriasis and Healthy Donors – Phase3: The DCP at the 99.9% prediction limit was chosen to be used and determined to be 30% for each therapeutic assay in each population.*

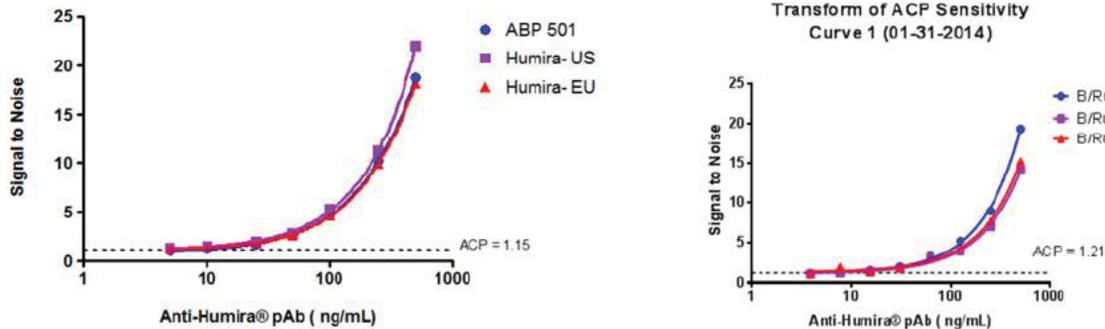
These are acceptable.

Assay Sensitivity

Screening assay sensitivities are defined as the lowest concentration of antibody detected within the assay that produces a S/N at the CP value of 1.15 for the Phase 1 or at the CP value of 1.21 for the Phase 3, respectively.

The dose-response curves are shown in Figures 9 and 17.

Figure 9. Screening Assay Dose-Response Curve-1 (5 to 500 ng/mL) (Phase 1) Figure 17. Anti-Humira® pAb Phase 3 Screening Assay Dose Response Curves

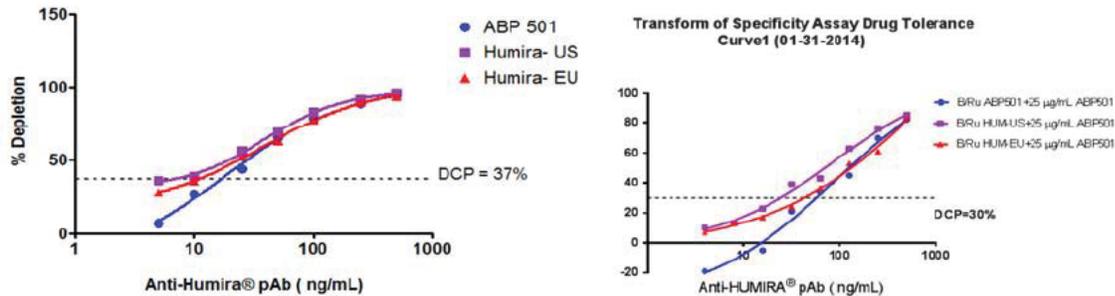


Specificity assay sensitivities are defined as the concentration of antibody detected interpolated from the dose response curve at the DCP value of 37% for the Phase 1 or at the DCP value of 30% for the Phase 3, respectively.

To determine the specificity assay sensitivity, anti-Humira® antibody was diluted in pooled normal human serum (PNHS) using concentrations ranging from 5 to 500 ng/mL. These samples were prepared in duplicate, and analyzed in the presence of 100 µg/mL of excess therapeutic for each therapeutic (ABP 501, Humira®-EU and Humira®-US).

The specificity assay dose-response curves are shown in Figures 11 and 20.

Figure 11. Specificity Assay-1 Dose-response Inhibition Results (Phase 1) Figure 20: Anti-Humira® pAb Phase 3 Specificity Assay-Drug Tolerance Results Curves 1 and 2



Reviewer Comment: The following conclusions were drawn for the screen assay sensitivities:

- *Healthy Donors Phase 1: The DCP at the 99.9% prediction limit was determined as 37%*
- *Rheumatoid Arthritis, Psoriasis and Healthy Donors – Phase3: The DCP at the 99.9% prediction limit was chosen to be used and determined to be 30% for each therapeutic assay in each population.*

This is considered adequate.

Sensitivity results for both the screening and specificity assays are listed in Tables 4 and 13.

Table 4. Average Sensitivity (ng/mL) at ACP (S/N = 1.15) and DCP=37% (Phase 1)

	Sensitivity at ACP			Sensitivity at DCP=37%		
	Prep 1 (ng/mL)	Prep 2 (ng/mL)	Mean (ng/mL)	Prep 1 (ng/mL)	Prep 2 (ng/mL)	Mean (ng/mL)
ABP 501	7.50	3.21	5.36	16.73	16.71	16.72
Humira®-EU	1.08	5.50	3.29	10.86	19.64	15.25
Humira®-US	<5	<5	<5	6.73	12.11	9.42

Table 13. Anti-Humira® pAb Average Sensitivity (ng/mL) at ACP (S/N = 1.21) and DCP=30% (Phase 3)

	Sensitivity at CP S/N=1.21			Sensitivity at DCP=30%		
	Prep 1 (ng/mL)	Prep 2 (ng/mL)	Mean (ng/mL)	Prep 1 (ng/mL)	Prep 2 (ng/mL)	Mean (ng/mL)
ABP 501	<10	2.2	<10	25.9	21.6	23.8
Humira®-EU	5.9	NA	5.9	12.3	NA	12.3
Humira®-US	3.5	8.5	6.0	9.6	37.4	23.5

Reviewer Comment: The following conclusions were drawn:

- Screening sensitivities are < 10 ng/mL for ABP 501, 6.0 ng/mL for US-licensed Humira, and 5.9 ng/mL for EU-approved Humira
- Specificity sensitivities are 23.8 ng/mL for ABP 501, 23.5 ng/mL for US-licensed Humira, and 12.3 ng/mL for EU-approved Humira

This is considered adequate.

Drug Tolerance

To validate that the screening and specificity assays could tolerate the presence of excess drug, two dose response curves containing 25 µg/mL of ABP 501 spiked into the negative control serum containing anti-Humira® pAb at concentrations from 3.9 to 500 ng/mL were tested against ABP 501, Humira®-EU and Humira®-US conjugates.

Drug tolerance results for the screening and specificity assays for the Phase 1 are shown in Figures 13 and 14 as well as Table 6.

Figure 13. Screening Assay-Drug Tolerance Results (Phase 1)

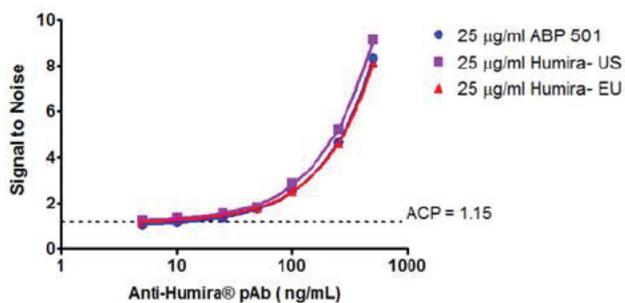


Figure 14. Specificity Assay-Drug Tolerance Results (Phase 1)

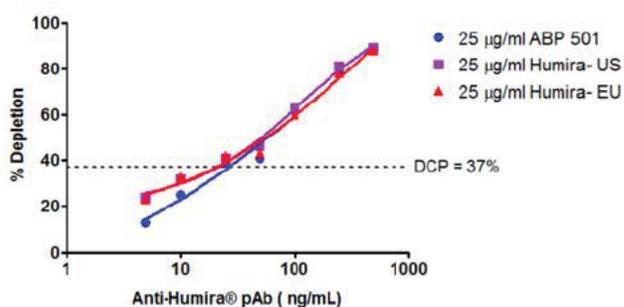


Table 6. Drug Tolerance: Specificity Assay Sensitivity at DCP in the presence of 25 µg/mL of Drug (Phase 1)

	ABP 501 [25 µg/mL]	Humira®-EU [25 µg/mL]	Humira®-US [25 µg/mL]
[anti-Humira® Pab] ng/mL	26.6	21.3	20.7

Drug tolerance results for the assays for the Phase 3 are listed in Table 15. The screening assay was able to detect at least 10 ng/mL of anti-Humira® antibody above the CP of 1.15, in the presence of 25 µg/mL of ABP 501, Humira®-EU and Humira®-US.

Table 15. Anti-Humira® pAb Average Drug Tolerance Sensitivity: Assay Sensitivity at CP=S/N 1.21 and DCP=30% in the presence of 25 µg/mL of Drug (Phase 3)

	25 µg/mL Drug Tolerance Sensitivity at CP S/N=1.21			25 µg/mL Drug Tolerance Sensitivity at DCP=30%		
	Prep 1 (ng/mL)	Prep 2 (ng/mL)	Mean (ng/mL)	Prep 1 (ng/mL)	Prep 2 (ng/mL)	Mean (ng/mL)
ABP 501	18.0	10.0	14.0	57.0	21.6	39.3
Humira®-EU	14.6	NA	14.6	42.5	NA	14.6
Humira®-US	23.9	29.2	26.6	24.1	37.4	30.8

Reviewer Comment: The following conclusions were drawn:

- The screening assay was able to detect at least 10 ng/mL of anti-Humira® antibody above the CP of 1.15, in the presence of 25 µg/mL of ABP 501, Humira®-EU and Humira®-US (Figure 13)
- The specificity assay was able to detect at least 27 ng/mL of anti-Humira® antibody at the DCP of 37% in the presence of 25 µg/mL of ABP 501, Humira®-EU and Humira®-US. (Table 6)
- Anti-Humira pAb detectable in presence of 25 µg/mL drug are 39.3 ng/mL for ABP 501, 30.8 ng/mL for US-licensed Humira, and 14.6 ng/mL for EU-approved Humira.

Trough concentrations are approximately 4-5 µg/mL throughout clinical studies. Thus, assessment of 25 µg/mL drug tolerance is considered appropriate.

Assay Range

A dose-response curve using concentrations ranging from 1 to 200 µg/mL was analyzed to detect a high-dose hook effect for the screening assay.

Reviewer's Comments: Amgen claimed that no hook effect was observed from the data (Table 20 in the submission).

This is considered adequate.

Lower Limit of Reliable Detection

The lower limit of reliable detection (LLRD) is the lowest concentration of the positive control antibody that can be reliably detected above the assay CP in any given serum sample.

Reviewer Comment: The following conclusions were drawn:

- Four out of 6 donors, 3 from the rheumatoid arthritis and 3 from the psoriasis combined CP population, spiked with 20, 25 or 40 ng/mL anti-Humira® pAb met the CP criteria
- For the LLRD determination 18 donors each from the rheumatoid arthritis and psoriasis combined CP population were spiked with 20 ng/mL anti-Humira® pAb antibody and tested against ABP 501 conjugates only. All 18 psoriasis donors recovered above the CP and DCP criteria at 20 ng/mL, while 16 out of 18 rheumatoid arthritis donors recovered above the CP and DCP criteria at 20 ng/mL
- For spiking at 25 ng/mL anti-Humira® pAb, all 18 psoriasis donors and 18 rheumatoid arthritis donors recovered above the CP and DCP criteria at 25 ng/mL

Amgen claimed that 25 ng/mL was determined to be the Low Positive Control (LPC) Concentration. This is considered adequate.

Specificity of the Assay

Reviewer’s Comments: The following conclusions were drawn:

- Specificity in the presence of soluble ligand (TNF-α): Concentrations of TNF-α that were 12.5 ng/mL or greater were detected as false positives when spiked into negative control serum (Table 7). S/N responses of TNF-α concentrations less than 12.5 ng/mL were below the assay CP and DCP.
- Interference by Positive Control and Negative Control: No interferences were observed by high levels of unrelated antibodies. The ability of the assay to specifically detect anti-Humira® pAb antibodies is shown in Table 25.
- Serum Interference Factors: the presence of bilirubin, intra-lipid or hemoglobin do not interfere with the assay’s ability to detect anti-Humira® specific antibodies

This is considered adequate.

**Table 25. Specificity Results:
Cross-reactivity and Interference from Irrelevant Antibodies**

5 µg/mL Irrelevant Antibody (IrrAb)	[ATA] ng/mL	Mean ECL	Irr Ab S/N	Control S/N	%DCP	CV%	Result	Pass/Fail*	Cross Reactivity ?	Interference ?
anti-Enbrel pAb	0	64.0	1.27	1.00	13	2	NEGATIVE	Pass	No	NA
	25	163.0	3.23	1.73	37	5	POSITIVE	Pass	NA	No
anti-Rituxen pAb	0	58.5	1.16	1.00	5	13	NEGATIVE	Pass	No	NA
	25	159.5	3.16	1.73	38	4	POSITIVE	Pass	NA	No
anti-infliximab pAb	0	103.5	2.05	1.00	9	9	NEGATIVE	Pass	No	NA
	25	215	4.26	1.73	32	1	POSITIVE	Pass	NA	No
anti-infliximab pAb	0	40.5	1.07	1.00	3	9	NEGATIVE	Pass	No	NA
	25	83.5	2.21	2.17	56	1	POSITIVE	Pass	NA	No
	250	468.5	12.41	10.83	92	1	POSITIVE	Pass	NA	No

*According to Analytical Validation Plan Acceptance Criteria: Pass if [ATA=0] = Negative, [ATA=25] = Positive

Sample and Reagent Stability

Reviewer Comment: Amgen reported that negative control serum spiked at 0 and 25 ng/mL of anti-Humira® pAb is able to withstand at least 10 freeze/thaw cycles, one week at 2° to 8°C, and 72 hours at ambient room temperature on the bench top without compromising immunological reactivity or affecting the background response (Table 27).

This is considered adequate.

Precision

Precision was measured by evaluating the negative control (NC), low positive control (LPC), and high positive control (HPC) throughout validation and assessed by calculating the %CV. Intra-assay and inter-assay %CV was investigated and acceptance criteria was defined to be that all control replicates must have a %CV less than or equal to 20%. Precision was measured for each assay (ABP 501, Humira®-EU and Humira®-US).

Reviewer Comment: Amgen reported the precision results in the submission and the summary is listed below. This is considered adequate.

Validation Experiment (continued)		Results	
Precision		S/N	ECL
ABP 501 Intra-Assay Precision CV (28 replicates)	Negative Control (NC)	N/A	19%
	LPC = 25 ng/mL	18%	12%
	HPC= 250 ng/mL	19%	9%
Humira®-EU Intra-Assay Precision CV (8 replicates)	Negative Control (NC)	N/A	9%
	LPC = 25 ng/mL	10%	8%
	HPC= 250 ng/mL	16%	13%
Humira®-US Intra-Assay Precision CV (12 replicates)	Negative Control (NC)	N/A	12%
	LPC = 25 ng/mL	4%	18%
	HPC= 250 ng/mL	14%	8%
ABP 501 Inter-Assay Precision CV (15 days)	NC	N/A	18%
	LPC = 25 ng/mL	10%	12%
	HPC= 250 ng/mL	19%	9%
Humira®-EU Inter-Assay Precision CV (3 days)	NC	N/A	8%
	LPC = 25 ng/mL	16%	11%
	HPC= 250 ng/mL	18%	13%
Humira®-US Inter-Assay Precision CV (6 days)	NC	N/A	15%
	LPC = 25 ng/mL	11%	13%
	HPC= 250 ng/mL	20%	14%

Ruggedness And Robustness

Ruggedness is described as the reproducibility of test results obtained by analysis of the same samples under a variety of conditions, such as laboratory, analysts, instruments, reagent lots, days, etc.

Robustness is described as the capacity of a method to remain unaffected by variations in method parameters such as incubation times.

Reviewer Comment: The following conclusions were drawn:

- The combined CP and DCP, obtained from analysis of healthy, rheumatoid arthritis and psoriasis donor serum, were derived from data that incorporated use of multiple analysts, plate lots, biotinylated and ruthenylated conjugate lots (ABP 501, Humira®-EU, and Humira®-US) read buffer lots, and MSD instruments (MSD Sector Imager 6000 (2) and MSD Quickplex). These analyses demonstrate consistent, precise and reliable assay performance as described in RPT-034104, RPT-048397, RPT-048398, RPT-048438, and RPT-048523 (see Addendums)
- From the robustness study, there was a potential impact due to a 30 minutes delay in plate read after addition of read buffer. This resulted in a %CV of 23% for NC, 15% for LPC and 22% for HPC evaluated across all conditions. When results are removed for the 30 minute read delay after addition of read buffer the %CV is 5% for NC, 7% for LPC and 7% for HPC.

This is considered adequate.

5.3.1.4.2. Neutralizing Antidrug Antibody Assay

a. Cell-based Assay for Phase 1 Study (Method ICDCB)

The cell-based bioassay for neutralizing activity utilized an A549 cell line, an adherent, TNF α -responsive adenocarcinomic human alveolar basal epithelial cell line, that expresses both TNFR1 and TNFR2. Binding of TNF α to TNF receptors induced phosphorylation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B). Phosphorylation of NF κ B subsequently activated downstream signaling. ABP 501 inhibited TNF α -induced NF κ B phosphorylation in A549 cells. Neutralizing antibody activity attenuated the ABP 501 mediated inhibition of NF κ B phosphorylation and caused an increase in signal.

The binding-antibody assay results, which were available before the neutralizing activity assay was performed, demonstrated that ADAs induced by ABP 501, adalimumab (US), and adalimumab (EU) bound equivalently to drug from all 3 sources. Therefore, neutralizing activity was tested only against ABP 501.

Reviewer Comment: This approach is considered acceptable.

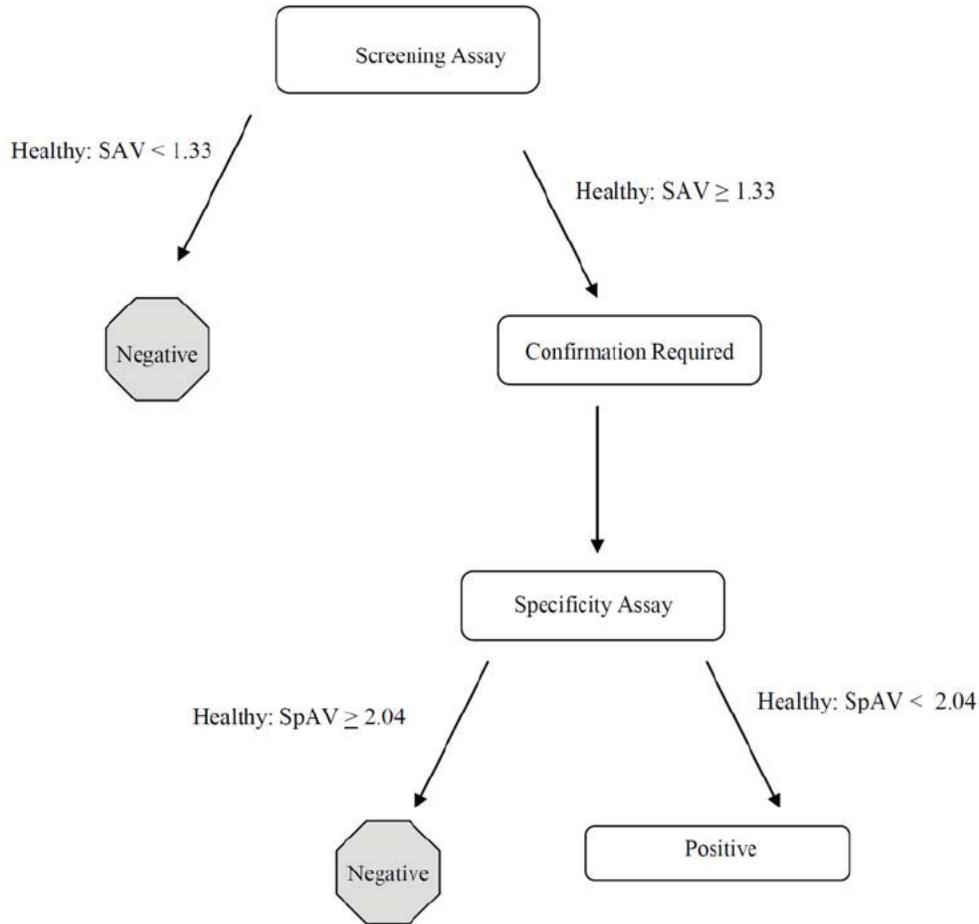
An ECL sandwich immunoassay was used to detect the level of NF κ B phosphorylation in A549 cell lysates. Serum samples were tested for the ability to inhibit the function of ABP 501 using the addition of TNF α and ABP 501 in the screening assay. Serum samples were also tested by directly adding them to A549 cells in the absence of TNF α and ABP 501 in the specificity assay. The screening bioassay assessed the neutralization of ABP 501, while the specificity bioassay confirmed if the increase was due to neutralizing activity specific to the drug. The combined results of the screening and specificity bioassays were used to determine positivity.

Criteria for Determining Final Results: Samples with a screening assay value above the screening assay cut point can be given an intermediate result of “confirmation required.” The combined results of the screening and specificity bioassays are used to determine whether the final sample result is negative or positive as shown in the below table and Appendix A (NAb assay decision tree).

Assay Cut Points

Population	Cut Point	
Healthy	Screening Assay Value (SAV)	1.33
	Specificity Assay Value (SpAV)	2.04

Appendix A. NAb Assay Decision Tree



Validation of a Cell-Based Assay for the Detection of ABP 501 Neutralizing Antibodies in Human Serum Samples via Meso-Scale Discovery Electrochemiluminescence Assay (Report MVR-AKZ2)
 Summary of the assay validation results is listed in the below table.

Species/Matrix:	Healthy Human Serum		
Analysis Method:	Electrochemiluminescent measurement using Meso-Scale Discovery NF-κB kit		
Data Capture of RLU (ECL)	MSD Sector Imager 6000		
Additional Data Analysis and Calculations:	MSD Discovery Workbench (MSD6000) Version 3.0.18, Microsoft® Excel 2003 and 2010,		
Screening Assay Cut Point ¹	≥ 1.33		
Specificity Assay Cut Point ¹	< 1.32		
Minimum Required Dilution	1:5 (20% serum, starting concentration)		
Precision	Inter-Assay	0.500 µg/mL	18.6%
		0.310 µg/mL	18.5%
		0.155 µg/mL	11.9%
	Intra-Assay	0.310 µg/mL	2.84%
		0.500 µg/mL	3.21%
Assay Sensitivity	155 ng/mL		
LLRD	500 ng/mL		
Validation of the ACP and LLRD (False-positive and False-negative rates)	7.41% (n = 2) of the unspiked healthy human serum individuals had an overall result of "positive." 0.00% of the samples spiked at the LLRD had an overall result of "negative."		
Drug Tolerance 1000 ng/mL PC (2X LLRD)	Neutralizing antibodies can be detected in samples in the presence of up to 320 ng/mL of excess ABP 501.		
	500 ng/mL PC (LLRD)	Neutralizing antibodies can be detected in samples in the presence of up to 160 ng/mL of excess ABP 501.	
Hemolysis Interference	No effect from hemolysis on the detection of neutralizing antibodies to ABP 501		
Lipemia Interference	No effect from lipemia on the detection of neutralizing antibodies to ABP 501		

¹ A sample that meets both of these assay cut point criteria, in addition to %CV criteria as stated in the method report, would be considered overall "positive."

Reviewer Comment: Amgen submitted the ICDCB 36 validation report in the submission.

The following conclusions were drawn:

- **Assay Cut Points:** Assay cut points were established for the screening assay cut point (SACP) and the specificity assay cut point (SpACP). Twenty-seven individual healthy human serum samples were analyzed independently using statistical analysis. These data were used to calculate a cut point of 1.33 for the SAV and 1.32 for the SpAV.
- **Relative Assay Sensitivity:** Relative assay sensitivity is the lowest concentration which gives a response equivalent to the SACP that was calculated by interpolation from each antibody curve. Sensitivity was evaluated by spiking anti-adalimumab antibody into neat pooled RA human serum. The relative assay sensitivity was determined to be 155.3 ng/mL.
- **Establishment of ACP and LLRD (Selectivity/Matrix Interference):** Selectivity is the ability of an assay to measure the analyte of interest in the presence of other matrix constituents. It is characterized by the recovery of analyte (represented by a positive control) from matrix samples containing potential interference factors. The LLRD was tested with 0.500 µg/mL anti-adalimumab and the 27 unspiked and spiked samples that were analyzed in the screening and specificity assays. It was found that the final false-negative rate for the assay was 0% and the final false-positive rate for the assay was 7.41%, which meets validation plan acceptance criteria. Therefore, LLRD was determined to be 500 ng/mL.
- **Drug Tolerance:** The potential of ABP 501 to interfere with the detection of neutralizing antibodies was evaluated by analyzing anti-adalimumab antibody in the presence of increasing concentrations

of ABP 501. It was found that **the LLRD (500 ng/mL antibody) can tolerate 160 ng/mL of excess ABP 501. At 2X LLRD (1000 ng/mL antibody), 320 ng/mL of excess ABP 501 can be tolerated.**

- **Precision:** Inter-assay precision and intra-assay precision were tested. Results are listed in the below table.

Precision	Inter-Assay	0.500 µg/mL	18.6%
		0.310 µg/mL	18.5%
		0.155 µg/mL	11.9%
	Intra-Assay	0.310 µg/mL	2.84%
		0.500 µg/mL	3.21%

- **Hemolysis Interference:** To evaluate the effect of sample hemolysis on recovery of neutralizing antibodies, five individual healthy human serum samples were analyzed. No interference was observed for hemolyzed samples up to 10% hemolysis.
- **Lipemia Interference:** To evaluate the effect of lipemia on recovery of neutralizing antibodies, five individual lipemic samples obtained from a commercial source were spiked with 0.500 µg/mL of anti-adalimumab antibody. No interference was observed for lipemic samples.

Amgen concluded that this method was validated by (b) (4) and the data are acceptable according to the criteria described in the validation plan. The method is applicable for the detection of anti-adalimumab neutralizing antibodies from a minimum 20-µL (screening) and 20-µL (specificity) human serum aliquot.

This is considered adequate.

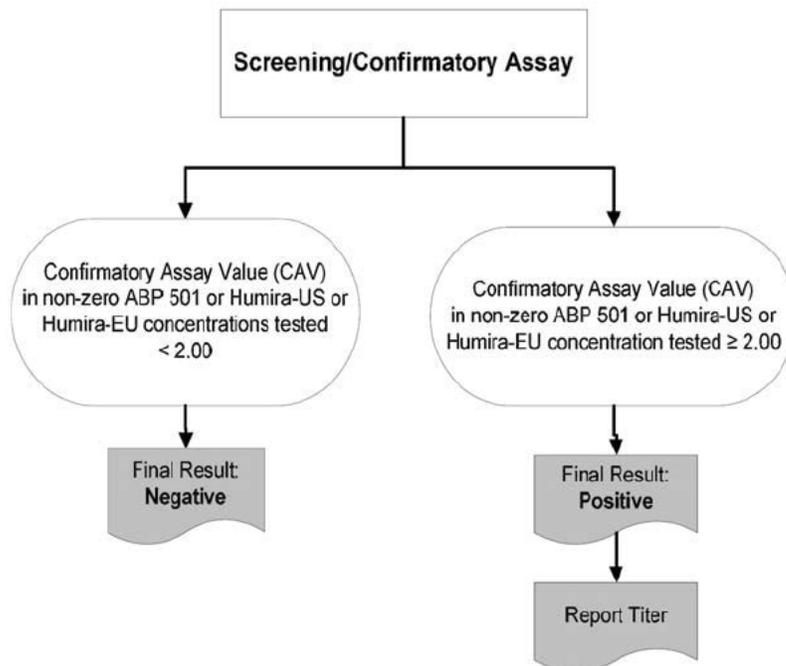
Target Binding Method for the Detection of Neutralizing Antibodies against ABP 501 and Adalimumab in Human Serum (MET-003554)

The purpose of this analytical method (MET) is to describe the electrochemiluminescent (ECL) target binding assay to detect anti-therapeutic neutralizing antibodies (NAb)s against ABP 501 and adalimumab in human serum using the Meso Scale Discovery SECTOR Imager 6000 or equivalent instrument.

The method for the detection of anti-ABP 501 or anti-Humira NAb)s is a competitive binding assay that uses soluble TNF, rHu, Bio to form a complex with Ru-ABP 501, Ru-Humira-US, and Ru-Humira-EU. The complex is captured on a Streptavidin Gold MSD plate. The plate is washed to remove any unbound protein prior to adding the read buffer. Upon electrical stimulation, a series of electrical reactions occur in the wells that result in light emission. The resulting electrochemiluminescent (ECL) signal can be detected and quantified in ECL units using the Meso Scale Discovery 6000 reader. If anti-ABP 501 or anti-Humira NAb)s are present in the sample, they will compete with TNF, rHu, Bio for binding to Ru-ABP 501, Ru-Humira-US or Ru-Humira-EU, resulting in a reduction of ECL signal. To confirm that a sample contains anti-ABP 501 or anti-Humira NAb)s, an excess amount of ABP 501 or Humira is added to the sample, which will bind to anti-ABP 501 or anti-Humira antibodies and reduce the amount of available NAb)s to compete with TNF, rHu, Bio for Ru-ABP 501, or Ru-Humira-US, or Ru-Humira-EU binding and result in an increase of ECL signal.

The neutralizing antibody testing strategy involves a screening and a confirmatory assay run simultaneously. The purpose of the screening assay is to detect the interruption of ruthenylated ABP 501 (Ru-ABP 501) or ruthenylated Humira-US (Ru-Humira-US) or ruthenylated Humira-EU (Ru-Humira-EU) binding to biotinylated TNF (TNF-alpha, rHu, Bio) by anti-Humira and/or anti-ABP 501 neutralizing antibodies (NAb)s in human serum samples, whereas the confirmatory assay confirms that the interruption observed is due to the presence of anti-ABP 501 or anti-Humira NAb)s. The result obtained from the confirmatory assay is used to determine whether a sample is 'positive' or 'negative' for the presence of NAb)s against ABP 501 and/or Humira US and/or Humira EU as shown in Figure 2.

Figure 2. Result Determination Diagram



The result determination process diagram above does not necessarily reflect the assay flow as described in the analytical procedure

Analytical Method Validation Report for a Target Binding Method for the Detection of Neutralizing Antibodies against ABP 501 in Human Serum (MVR-000476)

Summary of assay parameters and validated method parameters are listed in the below table.

Assay Parameters	Results
Serum concentration in the assay	10%
Biotinylated TNF-alpha concentration in the assay	50 ng/well
Ruthenylated ABP 501 or Humira-US or Humira-EU concentration in the assay	50 ng/mL
ABP 501/Humira-US/Humira-EU concentration in the confirmatory assay	0.5 µg/mL
Validated Method Parameters	Results
Assay Sensitivity for ABP 501	0.6 – 0.7 µg/mL
Assay Sensitivity for Humira-US	0.8 µg/mL
Assay Sensitivity for Humira-EU	0.825 µg/mL
Lower Limit of Reliable Detection (LLRD)	0.85 µg/mL
Confirmatory Assay Cut Point	2.00
False Positive Rate	0%
False Negative Rate	0%
Drug Tolerance	0.85 µg/mL of anti-Humira neutralizing antibodies in neat serum in the presence of 156.3 to 312.5 ng/mL of excess drug. 5 and 10 µg/mL of anti-Humira neutralizing antibodies in neat serum in the presence of 2.5 and 5 µg/mL of excess drug, respectively.

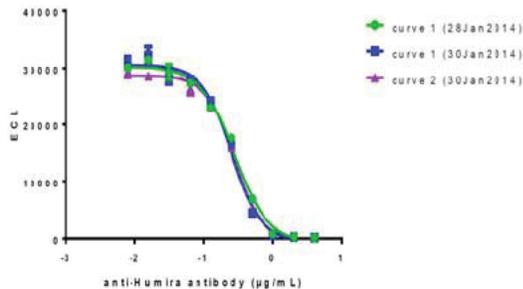
Reviewer Comment:

Drug tolerance demonstrates a “true sensitivity” 5-10 µg/mL in the presence of serum drug concentrations. This is considered adequate.

Anti-Humira Positive Control Antibody Curves

The goal of this experiment was to assess the ability of a rabbit polyclonal positive control neutralizing antibody to inhibit the binding of ruthenylated ABP 501 to biotinylated TNF alpha. The antibody concentrations tested in neat human serum were 0, 0.0078, 0.0156, 0.0313, 0.0625, 0.125, 0.25, 0.5, 1, 2 and 4 µg/mL. Results are shown in Figure 1 below.

Figure 1. Anti-Humira Antibody Titration Curves in the Range of 0 to 4 µg/mL.



Reviewer Comment: Amgen reported that the 50% inhibitory concentrations (IC 50) for curves 1, 2 and 3 were 0.2774, 0.2494 and 0.2705 µg/mL, respectively. This is considered appropriate.

Establishment of Assay Sensitivity

To assess and establish assay sensitivity, positive control antibody was spiked with concentration range from 0.2 to 0.8 µg/mL, in 0.1 µg/mL increments, into neat pooled human serum and samples were tested against ABP 501, Humira-US and Humira-EU. Results are shown in Figures 3 and 4. A sample with a Confirmatory Assay Value (CAV) value greater or equal to 2.00 indicated a ‘positive’ result for anti-Humira neutralizing antibodies while a sample with a CAV value of less than 2.00 indicated a ‘negative’ result for anti-Humira neutralizing antibodies.

Figure 3. Establishment of Assay Sensitivity for ABP 501 (Expt#2)

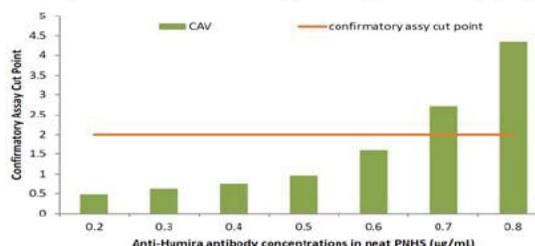
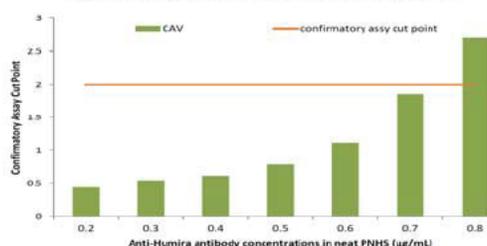


Figure 4. Establishment of Assay Sensitivity for Humira-US



Reviewer Comment: Amgen concluded that since ABP 501 assay sensitivity was determined to be 0.6 µg/mL in the first experiment and 0.7 µg/mL in the second experiment, a range of 0.6 to 0.7 µg/mL will be considered to be the assay sensitivity for ABP 501 Nab detection.

This is considered adequate.

Establishment of Lower Limit of Reliable Detection (LLRD)

Individual human donor serum samples spiked with 0.6, 0.85 and 1.2 µg/mL of anti-Humira positive control antibody were tested in the screening and confirmatory assays against ABP 501 to determine the LLRD concentration.

As shown in Figure 6, the lowest concentration of NAb at which all 6 donors tested positive against ABP 501 was 0.85 µg/mL. In the second experiment, 6 different donors spiked with 0.85 µg/mL of NAb tested positive when evaluated against Humira-US and Humira-EU (Figure 7) and the confirmatory cut point of 2.00 was applied. This set of experiments served as an LLRD establishment as well as cross-validation of Humira-US and Humira-EU against ABP 501. The LLRD of 0.85 µg/mL was confirmed to be valid for ABP 501, Humira-US and Humira-EU.

Figure 6. Establishment of Lower Limit of Reliable Detection (LLRD) Concentration (0.6, 0.85 and 1.2 µg/mL)

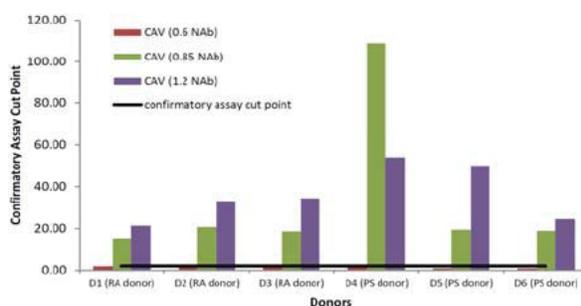
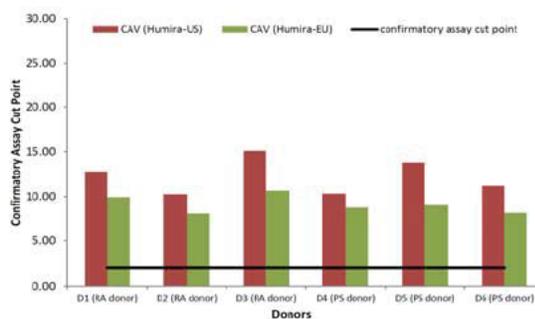


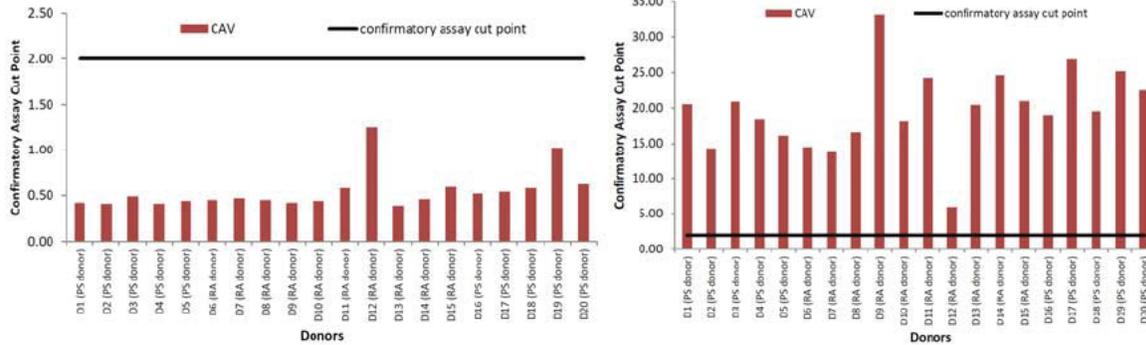
Figure 7. Cross Validation of Humira-US and Humira-EU at 0.85 µg/mL LLRD



The goal of this experiment was to validate the confirmatory assay cut point of 2.00. A total of 20 serum samples from 10 rheumatoid arthritis donors and 10 psoriasis donors were evaluated in 2 experiments: unspiked sample and sample spiked with 0.85 µg/mL of anti-Humira antibody.

All CAV values were less than 2.00 for all unspiked donors (Figure 8). All CAV values were greater than 2.00 for all donors spiked with 0.85 µg/mL of anti-Humira neutralizing positive control antibody (Figure 9). When the confirmatory cut point of 2.00 was applied, all samples spiked with 0.85 µg/mL of positive control antibody tested “positive” and all unspiked donor samples tested “negative” for the presence of NAb, therefore yielding a 0% false negative rate.

Figure 8. Validation of Confirmatory Assay Cut Point and LLRD (Unspiked donors) Figure 9. Validation of Confirmatory Assay Cut Point (LLRD spiked donors)

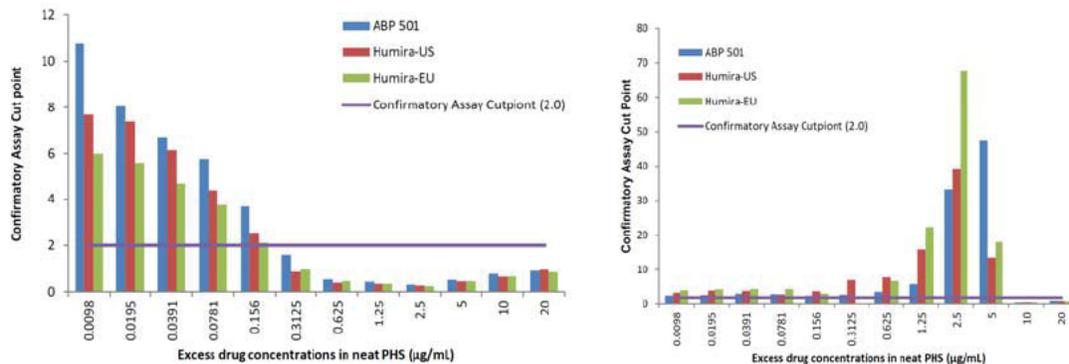


Reviewer Comment: This is considered adequate.

Drug Product Interference

Drug tolerance experiment was performed using all 3 drugs, ABP 501, Humira-US and Humira-EU at 3 different concentrations of reference positive control antibody. Anti-Humira antibody was diluted to 0.85 µg/mL, 5 µg/mL, and 10 µg/mL in pooled human serum. Excess ABP 501, Humira-US and Humira-EU were spiked into neat serum at 0.0098, 0.0195, 0.0391, 0.0781, 0.1563, 0.3125, 0.6250, 1.25, 2.5, 5, 10, and 20 µg/mL, respectively.

Figure 11. Drug Tolerance with ABP 501, Humira-US and Humira-EU at LLRD Figure 13. Drug Tolerance with ABP 501, Humira-US and Humira-EU at 10 µg/mL of NAb



Reviewer Comment: Amgen reported the assay was able to detect the following:

- 0.85 µg/mL (LLRD) of anti-Humira neutralizing antibody in neat serum in the presence of 0.156 - 0.3125 µg/mL of excess drug (Figures 10 and 11)

- 5 µg/mL of anti-Humira neutralizing antibody in the presence of 2.5 µg/mL of excess drug (Figure 12)
- 10 µg/mL of anti-Humira neutralizing antibody in the presence of 5 µg/mL of excess drug (Figure 13)

Refer to the Figures 11 and 13 are shown above.

This is considered adequate.

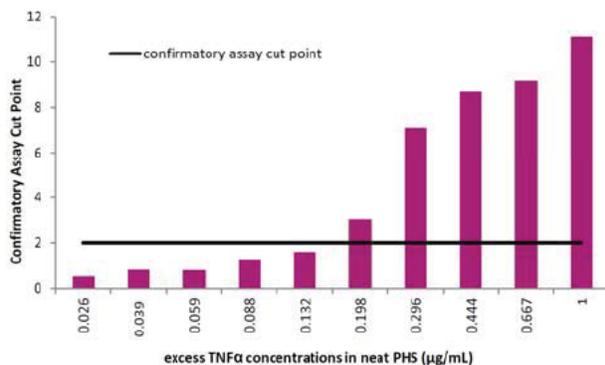
Target Interference

The goal of this experiment was to assess the effects of excess amounts of TNF-alpha in a test sample and determine at what concentration of TNF the assay would yield a false positive result in a NAb negative sample. TNF-alpha was spiked into neat pooled normal serum at the following concentrations: 0.026, 0.039, 0.059, 0.088, 0.132, 0.198, 0.296, 0.444, 0.667 and 1 µg/mL.

Reviewer Comment: The cut point selection is appropriately balance between minimizing false positives between TNF-alpha interference and assay sensitivity.

Results are shown in Figure 14.

Figure 14: Target Interference (TNFα)



Reviewer Comment: Amgen claimed that the assay is able to tolerate up to 0.132 µg/mL of TNF-alpha in neat pooled normal serum not containing any NABs. All of the concentrations of TNF tested above 0.132 µg/mL yielded false positive results.

This is considered adequate.

Titrating of Samples Spiked with Positive Control Antibody

The goal of this experiment was to determine the reproducibility of titers generated by samples spiked with positive control antibody generated by testing against ABP 501, Humira-US and Humira-EU.

Reviewer Comment: Amgen reported that testing results (Table 1 in the submission) demonstrated the reproducibility of titers. Automation and manual testing generated similar results therefore the automated platform is considered to be validated and suitable to be used in this assay.

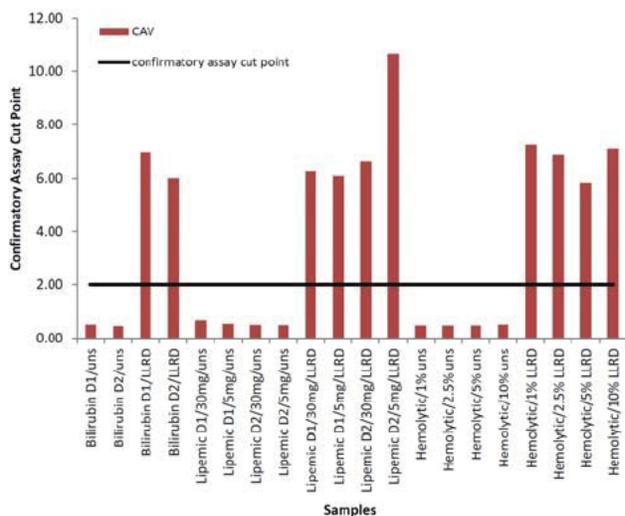
This is considered adequate.

Bilirubin, Lipid and Hemolysis Interference

The goal of this experiment was to assess the effects of excess amounts of bilirubin, lipids and hemolysis in a test sample on the ability of the assay to detect anti-Humira antibodies at 0.85 µg/mL (LLRD) and 1.7 µg/mL (2x LLD) of NAb and also to determine whether these agents would cause potential false positive results in unspiked human serum.

As shown in Figure 15 the assay was able to detect samples containing 0.85 µg/mL of anti-Humira neutralizing antibodies as 'positive' and unspiked samples as 'negative' in the presence of high content of bilirubin, lipid and hemolysis. The assay was able to detect anti-Humira antibodies at LLRD and all unspiked samples tested 'negative'. Hence, these agents when present in excess amounts in test samples did not interfere with the assay results. Results from experiment using 1.7 µg/mL of anti-Humira antibody (2x LLRD) yielded identical results but are not shown in this validation report.

Figure 15: Bilirubin, Lipid and Hemolysis Interference



Reviewer's Comments: This is considered adequate.

Selection of Confirmatory Assay Cut Point

A Confirmatory Assay Value (CAV) of 2.00 was selected to maximize the assay's sensitivity to detect NAbs as well as its ability to tolerate endogenous TNF levels.

As shown in Figure 9, CAVs ranging from 5.97 to 33.20 were obtained with 20 donor sera spiked with reference positive control antibody at LLRD (0.85 µg/mL). Derivation of statistical cut point would have impaired assay sensitivity since a mean CAV significantly greater than 2.00 (calculated value=19.8) was obtained from this and other experiments. This would have corresponded to assay sensitivity greater than 1 µg/mL. On the other hand, a CAV lower than 2.00 (e.g. 1.5) reduced the assay's ability to tolerate endogenous TNF-alpha from 132 ng/mL to 88 ng/mL (Figure 14). Therefore, an arbitrary cut point of 2.00 was selected based on the consideration that it allowed improved (i) assay sensitivity and (ii) tolerance of endogenous TNF.

Figure 9. Validation of Confirmatory Assay Cut Point (LLRD spiked donors)

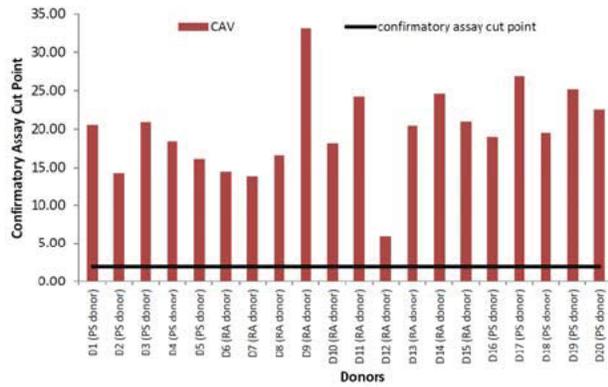
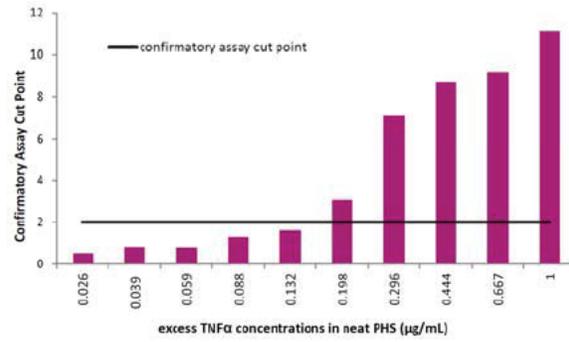


Figure 14: Target Interference (TNF α)



Reviewer Comment: This is considered adequate.

Overall Conclusion for Immunogenicity Assays:

Analytical methods used for the detection of anti-drug antibody (ADA) and neutralizing antibody activity against ABP 501, US-licensed Humira, and EU-approved Humira are found to be appropriate to assessing in the ABP 501 clinical studies.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUN T PARK
09/09/2016

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

Date: 08/16/2016

From: Steven Fong, Ph.D., Microbiologist, OPQ/OPF/DIA Branch 1
Lakshmi Narasimhan, Ph.D., Microbiologist, OPQ/OPF/DMA Branch IV
Jun Park, Ph.D., Biologist, OPQ/OBP/DBRR Branch II

To: BLA File 761024/0

Through: Ruth Moore, Ph.D., Acting Branch Chief, OPQ/OPF/DIA Branch 1

Subject: Inspection waiver memo for manufacture of ABP-501 DP at the Amgen Manufacturing Ltd facility in Juncos, Puerto Rico.

Applicant: Amgen Inc.

Facility: Amgen Manufacturing Ltd
Road 31, Kilometer 24.6
Building 1
Juncos, Puerto Rico 00777
FEI #1000110364

Product: ABP 501

Dosage: 20 mg or 40 mg of ABP 501 delivered in prefilled syringes containing, respectively, 0.4 mL or 0.8 mL of 50 mg/mL DP formulation.

Indication: Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, and plaque psoriasis.

Waiver Recommendation

ABP 501 DP will be manufactured in Building (b) (4) at Amgen Manufacturing Ltd in Juncos, Puerto Rico (AML (b) (4)). The proposed commercial manufacturing scheme is similar to the approved processes for other aseptically filled products at AML (b) (4), including (b) (4)

(b) (4). The most recent inspection of AML (b) (4) was conducted 01/12-23/2015 by the SJN-DO. At the conclusion of the inspection a Form FDA 483 was issued that cited deficiencies regarding air sampling of syringe stopper placement components, post-use surface monitoring of sterile product contact tools, and general surface monitoring procedures. The firm's response was determined to be adequate and the inspection was classified VAI for profiles CTX, GLA, TCM, and SVS. Based on the firm's compliance history, its current acceptable status for profile SVS, and the fact that the proposed

manufacturing procedure for ABP 501 is similar to that for other licensed, sterile products produced at AMI (b) (4), we recommend that inspection of AMI (b) (4) for DP manufacture be waived for STN 761024/0.

Summary

BLA 761024 was submitted by Amgen Inc. to provide information and data to support manufacture of ABP 501 DS at Amgen Inc. in Thousand Oaks, CA (FEI 2026154), and ABP 501 DP at AMI (b) (4) FEI #1000110364). AMI is also proposed as an autoinjector assembly facility. The current waiver recommendation is in regards to ABP 501 DP manufacture at AMI (b) (4) only. It does not pertain to autoinjector assembly. For an assessment of AMI as an autoinjector assembly site please refer to the CDRH consult review for this BLA.

Facility Information

Manufacture of ABP 501 DP will take place in a prefilled syringe (PFS) manufacturing area at AMI (b) (4). The manufacturing process consists of the following: (b) (4)

[REDACTED]

The rooms, sterilization equipment, and filling machines have previously been approved for manufacture of other licensed PFS DPs, including (b) (4) (b) (4) ®. The syringe components (barrel, plunger-stopper, and needle shield) are provided pre-sterilized by the vendor, (b) (4).

Evaluation of criteria that may warrant inspection

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

The AMI (b) (4) site is a multi-product facility approved for the manufacture of the following U.S.-distributed biologics under license (b) (4)

[REDACTED]

2. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

As noted above under “Waiver Recommendation”, at the conclusion of the 01/12-23/2015 surveillance inspection a Form FDA 483 was issued citing three (b) (4) manufacturing GMP deficiencies. The Agency determined that these deficiencies were adequately addressed by the firm. The inspection was classified VAI.

3. *The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities / buildings / areas.*

As noted in *Facility Information* and the response to item 1, the PFS manufacturing area in AMI (b)(4) has previously been approved for multi-product, (b)(4) manufacture of other sterile injectable products.

4. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment.*

The proposed (b)(4) manufacturing scheme for ABP 501 DP is similar to the approved processes for other PFS products manufactured at AMI (b)(4), including (b)(4). The manufacturing process for (b)(4) is also similar except that this product is (b)(4).

Steven Fong, Ph.D., Microbiologist, OPF/DIA Branch 1: **Steven Fong -S**
Digitally signed by Steven Fong-S
 DN: c=US, ou=U.S. Government, ou=HHS, ou=FDA, ou=People,
 cn=Steven Fong-S, 0.9.2342.19200300.100.1.1=2000287433
 Date: 2016.08.16 13:12:45 -04'00'

Lakshmi Narasimhan, Ph.D., Microbiologist, OPF/DMA Branch IV: **Lakshmi Narasimhan -S**
Digitally signed by Lakshmi Narasimhan-S
 DN: c=US, ou=U.S. Government, ou=HHS, ou=FDA,
 ou=People, o=FDA, ou=People, cn=Lakshmi Narasimhan-S,
 0.9.2342.19200300.100.1.1=2000443745
 Date: 2016.08.22 08:40:14 -04'00'

Jun Park, Ph.D., Biologist, OBP/DBRR: **Jun T. Park -S**
Digitally signed by Jun T. Park-S
 DN: c=US, ou=U.S. Government, ou=HHS, ou=FDA, ou=People,
 cn=Jun T. Park-S, 0.9.2342.19200300.100.1.1=2000443745
 Date: 2016.08.16 13:16:57 -04'00'

Joel Welch, Ph.D., ATL, OBP/DBRR: **Joel T. Welch -S**
Digitally signed by Joel T. Welch-S
 DN: c=US, ou=U.S. Government, ou=HHS,
 ou=FDA, ou=People, cn=Joel T. Welch -S,
 0.9.2342.19200300.100.1.1=2000443745
 Date: 2016.08.21 08:40:14 -04'00'

Patricia Hughes, Ph.D., Branch Chief (Acting), OPF DMA Branch IV: **Patricia F. Hughestroost -S**
Digitally signed by Patricia F. Hughestroost-S
 DN: c=US, ou=U.S. Government,
 ou=HHS, ou=FDA, ou=People,
 0.9.2342.19200300.100.1.1=1300096
 547, cn=Patricia F. Hughestroost-S
 Date: 2016.08.29 07:38:36 -04'00'

Ruth Moore, Ph.D., Branch Chief (Acting), OPF/DIA Branch I: **Zhihao Qiu -S**
Digitally signed by Zhihao Qiu-S
 DN: c=US, ou=U.S. Government, ou=HHS,
 ou=FDA, ou=People, cn=Zhihao Qiu -S,
 0.9.2342.19200300.100.1.1=2000438274
 Date: 2016.08.22 09:36:01 -04'00'

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

Application BLA
761024

Submission Type: 351 (k)

Established/Proper Name:
ABP 501

Applicant: Amgen

Letter Date: February 7, 2016

OND Office: DPARP

Chemical Type:
Biologic

Stamp Date: November 25, 2015 **Strength:** (b) (4) mg & 40 mg

Original BLA

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not Applicable
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?		X	

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	X	<input type="checkbox"/>	
2.	Botanical ¹	<input type="checkbox"/>	X	
3.	Naturally-derived Product	<input type="checkbox"/>	X	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	X	
5.	PET Drug	<input type="checkbox"/>	X	
6.	PEPFAR Drug	<input type="checkbox"/>	X	
7.	Sterile Drug Product	X	<input type="checkbox"/>	
8.	Transdermal ¹	<input type="checkbox"/>	X	
9.	Pediatric form/dose ¹	<input type="checkbox"/>	X	
10.	Locally acting drug ¹	<input type="checkbox"/>	X	
11.	Lyophilized product ¹	<input type="checkbox"/>	X	
12.	First generic ¹	<input type="checkbox"/>	X	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
13.	Solid dispersion product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
14.	Oral disintegrating tablet ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Modified release product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
16.	Liposome product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Biosimilar product ¹	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Biosimilar product to Humira® (adalimumab)
18.	Combination Product _____	<input checked="" type="checkbox"/>	<input type="checkbox"/>	ABP 501 fomulation in PFS and autoinjector
19.	Other _____	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

Regulatory Considerations				
20.	USAN Name Assigned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Adalimumab- (b) (4)
21.	End of Phase II/Pre-NDA Agreements	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	<input type="checkbox"/>	Not available
24.	Comparability Protocol(s) ²	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
25.	Other _____	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Quality Considerations				
26.	Drug Substance Overage	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The autoinjector contains a prefilled syringe which is filled to ensure a deliverable volume of 0.8 mL.
27.	Design Space	Formulation	<input type="checkbox"/>	<input checked="" type="checkbox"/>
28.		Process	<input type="checkbox"/>	<input checked="" type="checkbox"/>
29.		Analytical Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>
30.		Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>
31.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
33.	Alternative Microbiological Test Methods	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Container closure integrity
34.	Process Analytical Technology ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	<input checked="" type="checkbox"/>	<input type="checkbox"/>
36.		Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>
37.		Microbial	<input type="checkbox"/>	<input checked="" type="checkbox"/>
38.	Unique analytical methodology ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
39.	Excipients of Human or Animal Origin	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
40.	Novel Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Nanomaterials ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Hold Times Exceeding 30 Days	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
43.	Genotoxic Impurities or Structural Alerts	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
44.	Continuous Manufacturing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
45.	Other unique manufacturing process ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
47.	New delivery system or dosage form ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
48.	Novel BE study designs	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
49.	New product design ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
50.	Other _____	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <ul style="list-style-type: none"> <input type="checkbox"/> Facilities and Equipment <input type="checkbox"/> Adventitious Agents Safety Evaluation <input type="checkbox"/> Novel Excipients <input type="checkbox"/> Regional Information <ul style="list-style-type: none"> <input type="checkbox"/> Executed Batch Records <input type="checkbox"/> Method Validation Package <input type="checkbox"/> Comparability Protocols 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: <input type="checkbox"/> Name of facility, <input type="checkbox"/> Full address of facility including street, city, state, country <input type="checkbox"/> FEI number for facility (if previously registered with FDA) <input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person. <input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and <input type="checkbox"/> DMF number (if applicable)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <input type="checkbox"/> Is a manufacturing schedule provided? <input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
DRUG SUBSTANCE INFORMATION					

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

C. FILING CONSIDERATIONS					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	
6.	<p>Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> general information <input type="checkbox"/> manufacture <ul style="list-style-type: none"> ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment 	X	<input type="checkbox"/>	<input type="checkbox"/>	
DRUG PRODUCT INFORMATION					
7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Description and Composition of the Drug Product <input type="checkbox"/> Pharmaceutical Development 	X	<input type="checkbox"/>	<input type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

C. FILING CONSIDERATIONS					
	<ul style="list-style-type: none"> ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development <input type="checkbox"/> Manufacture <ul style="list-style-type: none"> ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? <input type="checkbox"/> Control of Excipients <input type="checkbox"/> Control of Drug Product <ul style="list-style-type: none"> ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution <input type="checkbox"/> Reference Standards or Materials <input type="checkbox"/> Container Closure System <ul style="list-style-type: none"> ○ Include data outlined in container closure guidance document <input type="checkbox"/> Stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment <input type="checkbox"/> APPENDICES <input type="checkbox"/> REGIONAL INFORMATION 				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: <ul style="list-style-type: none"> • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided? 	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

C. FILING CONSIDERATIONS					
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <ul style="list-style-type: none"> <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination <input checked="" type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production <input type="checkbox"/> novel excipients 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
17.	Are the following information available for Biotech Products: <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For 	<input checked="" type="checkbox"/>			

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

C. FILING CONSIDERATIONS				
	<p>example:</p> <ul style="list-style-type: none">○ LAL instead of rabbit pyrogen○ Mycoplasma <p>Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples</p>			

Inspection View								
Task Number	Task Name	Corr	Assignments	Pln Comp	Act Comp	Task Status	Actions	Additional Information
Parent: Manufacturing Facility Inspection (2)								
7	Application Specific Inspection Criteria	If you are finished with this check the Task Set to Cor	Steven Fong IM - Filing PM/Coordinator	11/29/15	1/19/16	Complete	Go to Form	
70	Overall Manufacturing Inspection Recommendation		Steven Fong IM - OPF Reviewer OPF Reviewer	9/20/16	9/13/16	Complete	Go to Form	Recommendation: Approve
Parent: Facility: AMGEN INC FEI: 2026154 DUNS: 039976196 FACILITY STATUS: PENDING (1)								
10	Enter Profile Codes		Steven Fong IM - Facility Profile Reviewer Facility Profile Reviewer	12/4/15	1/19/16	Complete	Go to Form	
Parent: Profile Evaluation for AMGEN INC - CBI BIOTECHNOLOGY DERIVED API (STERILE & NON-STERILE) FEI: 2026154 DUNS: 039976196 FACILITY STATUS: PENDING (6)								
12	Enter Facility Specific Criteria CBI BIOTECHNOLOGY DERIVED API (STERILE & NON-STERILE)		Steven Fong Zhihao Peter Qiu	12/9/15	5/24/16	Complete	Go to Form	
13	Office of Process and Facilities Decision/Request CBI BIOTECHNOLOGY DERIVED API (STERILE & NON-STERILE)		Steven Fong Zhihao Peter Qiu	12/14/15	5/24/16	Complete	Go to Form	
14	District Office Decision/Request CBI BIOTECHNOLOGY DERIVED API (STERILE & NON-STERILE)		OPF Division of Inspection/B1	12/24/15	5/24/16	Complete	Go to Form	
15	Inspect Facility and Receive FACTS Results		Patricia Hughes Troost Steven Fong Viviana Matta Zhihao Peter Qiu	8/30/16	9/13/16	Complete		
16	District Office Recommendation CBI BIOTECHNOLOGY		Patricia Hughes Troost	9/9/16	9/13/16	Complete	Go to Form	Recommendation: Approve Facility Reason: Based on File Review

Showing All (37) of 37

	DERIVED API (STERILE & NON-STERILE)	Viviana Matta Zhihao Peter Qiu					
17	Office of Process and Facilities Recommendation CBI BIOTECHNOLOGY DERIVED API (STERILE & NON-STERILE)	Viviana Matta IM - OPF Reviewer	9/19/16	9/13/16	Complete	Go to Form	Recommendation: Approve Facility Reason: District Recommendation
Parent: Facility: AMGEN MANUFACTURING LIMITED FEI: 1000110364 DUNS: 785800020 FACILITY STATUS: PENDING (1)							
19	Enter Profile Codes	Steven Fong IM - Facility Profile Reviewer Facility Profile Reviewer	12/4/15	5/4/16	Complete	Go to Form	
Parent: Profile Evaluation for AMGEN MANUFACTURING LIMITED - SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS FEI: 1000110364 DUNS: 785800020 FACILITY STATUS: PENDING (6)							
21	Enter Facility Specific Criteria SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	Steven Fong IM - OPF Reviewer	12/9/15	1/19/16	Complete	Go to Form	
22	Office of Process and Facilities Decision/Request SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	Steven Fong IM - OPF Reviewer OPF Reviewer	12/14/15	1/19/16	Complete	Go to Form	
23	District Office Decision/Request SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	German Rivera	12/24/15	2/2/16	Complete	Go to Form	
24	Inspect Facility and Receive FACTS Results	German Rivera	8/30/16	2/2/16	Complete		
Parent: Facility: AMGEN MANUFACTURING LIMITED - SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS FEI: 1000110364 DUNS: 785800020 FACILITY STATUS: PENDING (6)							
25	District Office Recommendation SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	German Rivera	9/9/16	2/2/16	Complete	Go to Form	Recommendation: Approve Facility Reason: Based on File Review
26	Office of Process and Facilities Recommendation SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS	Steven Fong IM - OPF Reviewer OPF Reviewer	9/19/16	2/4/16	Complete	Go to Form	Recommendation: Approve Facility Reason: District Recommendation

Showing All (37) of 37

Parent: Profile Evaluation for AMGEN MANUFACTURING LIMITED - DKA DEVICE KIT ASSEMBLER FEI: 1000110364 DUNS: 785800020 FACILITY STATUS: PENDING (5)							
28	Enter Facility Specific Criteria DKA DEVICE KIT ASSEMBLER	Steven Fong IM - OPF Reviewer	12/9/15	5/4/16	Complete	Go to Form	
29	Office of Process and Facilities Decision/Request DKA DEVICE KIT ASSEMBLER	Steven Fong IM - OPF Reviewer	12/14/15	5/4/16	Complete	Go to Form	
30	District Office Decision/Request DKA DEVICE KIT ASSEMBLER	Frances de Jesus	12/24/15	5/9/16	Complete	Go to Form	
32	District Office Recommendation DKA DEVICE KIT ASSEMBLER	German Rivera	9/9/16	5/9/16	Complete	Go to Form	Recommendation: Approve Facility Reason: Based on File Review
33	Office of Process and Facilities Recommendation DKA DEVICE KIT ASSEMBLER	Steven Fong IM - OPF Reviewer	9/19/16	7/28/16	Complete	Go to Form	Recommendation: Approve Facility Reason: District Recommendation
Parent: Facility: (b) (4)			FACILITY STATUS: PENDING (1)				
35	Enter Profile Codes	Steven Fong IM - Facility Profile Reviewer Facility Profile Reviewer	12/4/15	1/19/16	Complete	Go to Form	
Parent: Profile Evaluation for (b) (4)			CTL CONTROL TESTING LABORATORY FEI: (b) (4) DUNS: (b) (4) FACILITY STATUS: PENDING (3)				
37	Enter Facility Specific Criteria CTL CONTROL TESTING LABORATORY	Steven Fong IM - OPF Reviewer	12/9/15	2/4/16	Complete	Go to Form	
38	Office of Process and Facilities Decision/Request CTL CONTROL TESTING LABORATORY	Steven Fong IM - OPF Reviewer OPF Reviewer	12/14/15	8/12/16	Complete	Go to Form	

Showing All (37) of 37

42	Office of Process and Facilities Recommendation CTL CONTROL TESTING LABORATORY	Steven Fong IM - OPF Reviewer OPF Reviewer	9/19/16	8/12/16	Complete	Go to Form	Recommendation: Approve Facility Reason: Based on Profile
Parent: Facility: (b) (4)		FEI: (b) (4)	DUNS: (b) (4)	FACILITY STATUS: PENDING (1)			
44	Enter Profile Codes	Steven Fong IM - Facility Profile Reviewer Facility Profile Reviewer	12/4/15	1/19/16	Complete	Go to Form	
Parent: Profile Evaluation for (b) (4)		CTL CONTROL TESTING LABORATORY FEI: (b) (4) DUNS: (b) (4) FACILITY STATUS: PENDING (3)					
46	Enter Facility Specific Criteria CTL CONTROL TESTING LABORATORY	Steven Fong IM - OPF Reviewer	12/9/15	2/4/16	Complete	Go to Form	
47	Office of Process and Facilities Decision/Request CTL CONTROL TESTING LABORATORY	Steven Fong IM - OPF Reviewer	12/14/15	2/4/16	Complete	Go to Form	
51	Office of Process and Facilities Recommendation CTL CONTROL TESTING LABORATORY	Steven Fong IM - OPF Reviewer OPF Reviewer	9/19/16	2/4/16	Complete	Go to Form	Recommendation: Approve Facility Reason: Based on Profile
Parent: Facility: (b) (4)		FEI: (b) (4)	DUNS: (b) (4)	FACILITY STATUS: PENDING (1)			
53	Enter Profile Codes	Steven Fong IM - Facility Profile Reviewer Facility Profile Reviewer	12/4/15	1/19/16	Complete	Go to Form	
Parent: Profile Evaluation for (b) (4)		CTL CONTROL TESTING LABORATORY FEI: (b) (4) DUNS: (b) (4) FACILITY STATUS: PENDING (3)					
55	Enter Facility Specific Criteria CTL CONTROL TESTING LABORATORY	Steven Fong IM - OPF Reviewer	12/9/15	2/4/16	Complete	Go to Form	
56	Office of Process and Facilities Decision/Request CTL CONTROL TESTING LABORATORY	Steven Fong IM - OPF Reviewer OPF Reviewer	12/14/15	2/4/16	Complete	Go to Form	

Showing All (37) of 37

60	Office of Process and Facilities Recommendation CTL CONTROL TESTING LABORATORY	Steven Fong IM - OPF Reviewer OPF Reviewer	9/19/16	2/4/16	Complete	Go to Form	Recommendation: Approve Facility Reason: Based on Profile
Parent: Facility: AMGEN TECHNOLOGY (IRELAND) FEI: 3002808497 DUNS: 896293920 FACILITY STATUS: PENDING (1)							
62	Enter Profile Codes	Steven Fong IM - Facility Profile Reviewer Facility Profile Reviewer	12/4/15	1/19/16	Complete	Go to Form	
Parent: Profile Evaluation for AMGEN TECHNOLOGY (IRELAND) - CTL CONTROL TESTING LABORATORY FEI: 3002808497 DUNS: 896293920 FACILITY STATUS: PENDING (3)							
64	Enter Facility Specific Criteria CTL CONTROL TESTING LABORATORY	Steven Fong IM - OPF Reviewer	12/9/15	2/9/16	Complete	Go to Form	
65	Office of Process and Facilities Decision/Request CTL CONTROL TESTING LABORATORY	Steven Fong IM - OPF Reviewer OPF Reviewer	12/14/15	2/9/16	Complete	Go to Form	
69	Office of Process and Facilities Recommendation CTL CONTROL TESTING LABORATORY	Steven Fong OPF Reviewer IM - Facility	9/19/16	2/9/16	Complete	Go to Form	Recommendation: Approve Facility Reason: Based on Profile
Showing All (37) of 37							

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

Steven Fong -S Digitally signed by Steven Fong -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
cn=Steven Fong -S, 0.9.2342.19200300.100.1.1=2000287433
Date: 2016.01.14 13:20:35 -05'00'

Steve Fong, Ph.D., Facilities Reviewer, Division of Inspectional Assessment, Office of Process and Facilities

Bo Chi -A Digitally signed by Bo Chi -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Bo Chi -A,
0.9.2342.19200300.100.1.1=1300194820
Date: 2016.01.14 12:50:02 -05'00'

Bo Chi, Ph.D., Drug Substance Microbiology Reviewer, Division of Microbial Assessment, Office of Process and Facilities

Lakshmi Narasimhan -S Digitally signed by Lakshmi Narasimhan -S
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Lakshmi Narasimhan, Ph.D., Drug Product Microbiology Reviewer, Division of Microbial Assessment, Office of Process and Facilities

Jun T. Park -S Digitally signed by Jun T. Park -S
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Jun Park, Ph.D., Product Reviewer, Division of Review and Research II, Office of Biotechnology Products

Joel T. Welch -S Digitally signed by Joel T. Welch -S
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cn=Joel T. Welch -S, 0.9.2342.19200300.100.1.1=2000443745
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Joel Welch, Ph.D. (ATL), Division of Review and Research II, Office of Biotechnology Products