

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761042Orig1s000

CHEMISTRY REVIEW(S)

**First Biosimilar for Etanercept****Recommendation: Approve**

BLA 761042
Review #1
Review Date: August 4, 2016

Drug Name/Dosage Form	GP2015
Strength	25 mg/0.5 mL and 50 mg/mL solution for injection in pre-filled syringes
Route of Administration	subcutaneous
Rx/OTC Dispensed	Rx
Indication	Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis
Applicant/Sponsor	Sandoz

Product Overview

GP2015 is a TNF receptor-Fc fusion protein. The TNF receptor contains both O- and N-linked glycans and the Fc portion contains the typical immunoglobulin N-linked glycan. GP2015 binds to both soluble TNF-alpha and TNF-beta (lymphotoxin alpha) and membrane bound TNF-alpha. GP2015 binding to soluble TNF blocks the ability of TNF to bind its receptors on the surface of cells, resulting in an inhibition of the downstream effects. Although the Fc portion of the molecule can induce effector functions such as antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC), the levels of these activities are low relative to intact antibodies and do not contribute to GP2015's mechanism of action.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Peter Adams	OBP/DBRR1
Drug Product	Peter Adams	OBP/DBRR1
Analytical Similarity	Peter Adams	OBP/DBRR1
Facilities	Zhong Li/Peter Qiu	OPF/DIA
Drug Substance Microbiology	Reyes Candau-Chacon/Patricia Hughes	OPF/DMA
Drug Product Microbiology	Candace Gomez-Broughton/Patricia Hughes	OPF/DMA
Labeling	Jibril Abdus-Samad/Peter Adams	OBP
Immunogenicity	Brian Janelsins/Jee Chung	OBP/DBRR1
Business Regulatory Process Manager	Keith Olin	OPRO
Application Technical Lead	Marjorie Shapiro	OBP/DBRR1



Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE / DIVISION
RPM	Leila Hann/Jessica Lee	ODEII/DPARP
Cross-disciplinary Team Lead	Nikolay Nikolov	ODEII/DPARP
Medical Officer	Rachel Glaser	ODEII/DPARP
Medical Officer	Gary Chiang	ODE II/DGIEP
Pharm/Tox	Andrea Benedict/Marcie Woods	ODEII/DPARP
Clinical Pharmacology	Yunzhao Ren/Ping Ji	OCF/DCPII
Statistics	Kathleen Fritsch/Yongman Kim/Gregory Levin	OB/DBIII
CMC Statistics	Meiyu Shen/Yi Tsong	OB/DBIV

- a. Names
 - i. Proprietary Name: Erelzi
 - ii. Trade Name: Erelzi
 - iii. Non-Proprietary/USAN: etanercept –xxxx (suffix to be determined)
 - iv. CAS registry number: 185243-69-0.
 - v. Common name: GP2015
 - vi. INN Name: etanercept
 - vii. Compendial Name:
 - viii. OBP systematic name: FUS: MABFRAG HUMAN (IGG1 FC); RPROT P20333 (TNR1B_HUMAN) [GP2015]

- b. Pharmacologic category: TNF- α antagonist

Communications with Sponsor:

Communication / Document	Date
Information Request #1 (Q1-10 OBP, Q11-18 DS Micro)	November 19, 2015
Information Request #2 (Q1-5 Immunogenicity, Q6-10 DP Micro, Q11-15 OBP)	December 11, 2015
Telecon (follow up to 12/11/15 IR)	December 17, 2015
Information Request #3 (Q1-4 DS Micro, Q5-8 OBP)	February 26, 2016
Information Request #4 (Q1-8 OBP)	March 10, 2016
Information Request #5 (Q1 DIA)	March 31, 2016
Telecon	April 7, 2016
Information Request #6 Follow up to tcon (Q1-2 OBP)	April 8, 2016
Information Request #7 (Q1-2 DS Micro, Q3 OBP)	April 8, 2016
Information Request #8 (Q1- 2 DS Micro)	May 2, 2016
Information Request #9 (Q1- 7 DP Micro)	May 19, 2016
Information Request #9 (Q1-3 DP Micro)	June 17, 2016
Information request #10 (Q 1- 3, DP Micro, PMC communication)	June 17, 2016
Information request #11 (Q1-4 OBP, PMC communication)	July 25, 2016
Telecon (stability and potency criteria for new ref standards)	August 4, 2016

Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original Application	July 30, 2015
Amendment 8	December 11, 2015, response to IR #1 (Q1-18)
Amendment 9	January 15, 2016, response to IR #2 (Q1-15)
Amendment 12	January 29, 2016, response to IR #2 (Q13) and tcon, updated information to correct errors
Amendment 15	March 2, 2016, response to IR #2 (Q13)
Amendment 17	March 10, 2016, response to IR #3 (Q5-8)
Amendment 19	March 22, 2016 response to IR#3 (Q1-4)
Amendment 20	March 31, 2016 response to IR #4 (Q1-8)
Amendment 21	April 6, 2016 response to IR #5 (Q1)
Amendment 23	April 13, 2016 response to IR #7 (Q3)
Amendment 24	April 22, 2016 response to IR #7 (Q1-2)
Amendment 25	April 28, 2016, response to IR #6 (Q1-2)
Amendment 29	June 3, 2016 response to IR #8 (Q1-7)
Amendment 31	June 24, 2016 response to IR #9 (Q1-3)
Amendment 32	July 7, 2016 response to IR #8 (Q7)
Amendment 34	July 29, 2016 response to IR #11 (Q1-4)
Amendment 35	August 9, 2016, response to 8/4 tcon, update to DS and DP stability and extension of expiration date.

Signature Block:

Name and Title	Signature and Date
Application Technical Lead Marjorie A. Shapiro, Ph.D. Division of Biotechnology Products Research and Review I Office of Biotechnology Products, CDER	<p>Digitally signed by Marjorie A. Shapiro -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300081252, cn=Marjorie A. Shapiro -S Date: 2016.08.12 11:37:38 -04'00'</p>
Division Director Kathleen A. Clouse Division of Biotechnology Products Research and Review I Office of Biotechnology Products, CDER	<p>Digitally signed by Kathleen A. Clouse Strebel -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300054511, cn=Kathleen A. Clouse Strebel -S Date: 2016.08.12 12:54:14 -04'00'</p>



Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(k)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III	(b) (4)	(b) (4) Glass Syringe System	2, 3, 6	adequate	6/21/2016	Sterilization of syringe barrel, plunger stopper, and needles shield were reviewed. Also reviewed by CDRH
	Type III		Plunger stopper (b) (4)	3, 6			Review of plunger stopper sterilization was included in DMF (b) (4) review as part of the (b) (4) Syringe system Also reviewed by CDRH
	Type III		Rubber needle shield (b) (4)	3, 6			Review of rubber needle shield (b) (4) was included in DMF (b) (4)

			(b) (4)				review as part of the (b) (4) Syringe system Also reviewed by CDRH
(b) (4)	Device MF	(b) (4)	(b) (4) Autoinjector for GP2015 50 mg/1.0 mL (GP2015 (b) (4) 50 Auto Injector)	3, 6			Adequate information in BLA, reviewed by CDRH

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

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

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

3. CONSULTS:

DISCIPLINE/TOPIC	DATE REQUESTED	STATUS	RECOMMENDATION	REVIEWER
Device (prefilled syringe and autoinjector)	9/22/15	Complete 6/27/16	approve	Sarah Mollo
CDRH OC/Compliance status evaluation of (b) (4) (b) (4)	9/4/2015	Complete 12/6/2015	No device inspection is needed for the approvability of BLA-761042.	Shanika Booth

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

- a. Recommendation : **Approve**
- b. Summary of Complete Response issues **Not Applicable**
- c. Action letter language
 - Manufacturing location:
 - Drug substance –Sandoz GmbH, Langkampfen, Austria (FEI 3004828473)
 - Drug product – Novartis Pharma Stein AG, Switzerland (FEI 3002653483)
 - Combination Product – (b) (4)
 - Fill size and dosage forms: 25 mg/0.5 mL and 50 mg/mL solution for injection in pre-filled syringes. 50 mg/mL solution for injection in autoinjector.
 - Dating period:
 - Drug product – 24 months at 5±3°C followed by 28 days at 25±2°C
 - Drug substance – (b) (4) months at (b) (4) °C
 - Stability option (select one below):
 - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.
 - Exempt from lot release
 - Yes
 - We exempt specified according to 601.2a
- d. Benefit/Risk Considerations

The analytical similarity evaluation included comprehensive methods that assessed the primary structure and post-translational modifications, higher order structure, size variants, hydrophobic variants, charge variants and glycoform variants. Table A lists critical quality attributes, the determination of the criticality risk ranking and the statistical Tier used to assess the similarity data between GP2015, US-licensed Enbrel and EU-approved Enbrel.

Each attribute was given a criticality score (See Section II for additional details), which was converted to a risk score for the purposes of the analytical similarity exercise. The risk scores were based on the abundance of a specific attribute such that the criticality score was reduced by 15-60 points if the abundance of that attribute is present at <5%, <2% or <0.5%

The methods that were assessed by equivalence testing (Tier 1) include TNF-alpha neutralization using a reporter gene assay and TNF-alpha binding using surface plasmon resonance (SPR).

The remaining methods were assessed using the quality range (mean ± X SD, Tier 2) or by qualitative comparisons (Tier 3).

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Table A. Methods used to assess analytical similarity

Quality Attribute	Specific Attribute Measured	Criticality /Risk	Method	Tier
Primary Structure	<ul style="list-style-type: none">• Amino acid sequence• Disulfide mapping• Site of glycosylation and chemical modification• Free Thiols	High	<ul style="list-style-type: none">• LysC peptide mapping coupled with Reverse phase ultra-performance liquid chromatography (RP-UPLC) with fluorescence and mass spectrometry (MS) detection, tandem MS/MS	3
Post Translational Modification (Glycosylation)	<ul style="list-style-type: none">• Terminal GlcNAc-variants• Alpha-galactosylation• High Mannose Glycans• Tri-antennary glycan Structures• Non-fucosylated glycan variants• Overall Sialylation• Sialylation N-glycans• Sialylation O-glycans• Sialic acids (NGNA)• Beta-galactosylation	High/High Moderate/ Moderate or Low Low	<ul style="list-style-type: none">• NP-HPLC• DMB – labeling (NANA, NGNA)• AEX (relative retention time)• WAX (0S, 1S, 2S)	2/3

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High Order Structure	<ul style="list-style-type: none"> • Secondary and Tertiary structure • Molecular weight of glycosylated protein 	High/High	<ul style="list-style-type: none"> • Far- and Near-UV circular dichroism • Differential Scanning Calorimetry • Fourier transform infrared spectroscopy (FTIR) • Hydrogen Deuterium Exchange • NMR • X-ray crystallography 	3
	<ul style="list-style-type: none"> • Wrongly bridged disulfide bonds 	High/High	<ul style="list-style-type: none"> • Non-reducing peptide map 	3
Size Variants	<ul style="list-style-type: none"> • Main Peak Purity • Aggregation Products • Degradation Products 	High/ Moderate	<ul style="list-style-type: none"> • SEC • SEC-MALLS • SDS-PAGE • AUC • FFF-MALLS 	3
Bioactivity	<ul style="list-style-type: none"> • TNF-alpha neutralization • TBF-beta neutralization • TNF-alpha binding • FcRn binding • CDC Activity • ADCC • FcγRIIIa binding • FcγRIIa binding • Other FcγR receptors 	Very high High Moderate	<ul style="list-style-type: none"> • Reporter Gene assay • SPR • SPR • Cell based • SPR 	1/2/3



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Product related Substances and impurities	<ul style="list-style-type: none"> • Acidic Variants • Oxidation • PENNYK Deamidation • Deamidation • Basic Variants • Proline Amide • Succinimide • N-terminal Variants • C-terminal Lys Variants • Glycation 	<p>Moderate/Moderate</p> <p>Low/Low</p> <p>Low/Very</p> <p>Low</p>	<ul style="list-style-type: none"> • CZE • Peptide mapping 	2/3
Drug product attributes	<ul style="list-style-type: none"> • Protein content • pH • Osmolality • Color • Turbidity 	High/High	<ul style="list-style-type: none"> • Compendial Methods 	2/3

Analytical similarity conclusions: GP2015 is highly similar to US-Enbrel.

TNF-alpha neutralization (RGA reporter gene assay) and TNF-alpha binding (surface plasmon resonance) are the designated Tier 1 methods evaluated by equivalence testing.

TNF-alpha binding between GP2015 and Enbrel met the criteria for statistical equivalence and the TNF-alpha binding data support a finding that GP2015 is highly similar to US-licensed Enbrel. In addition, TNF-alpha binding between GP2015 and EU-approved Enbrel and between US-licensed Enbrel and EU-approved Enbrel met the criteria for statistical equivalence, which supports the analytical portion of the scientific bridge for non-clinical and clinical studies conducted with EU-approved Enbrel.

For TNF-alpha neutralization, GP2015 and US-licensed Enbrel did not meet the criteria for equivalence, although GP2015 was equivalent to EU-approved Enbrel and US-licensed Enbrel was equivalent to EU-approved Enbrel. However, all the GP2015 lots were within the quality range (mean ± 3SD) of US-license Enbrel, but average mean potency for GP2015 was higher than for US-license Enbrel.



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The reason for the lack of a demonstration of equivalence was due to differences in the presence of the product related impurity identified by reverse phase chromatography termed "post peak". US-licensed Enbrel, as well as EU-approved Enbrel generally contain higher levels of this hydrophobic variant than GP2015. This hydrophobic variant is known to have reduced potency relative to

the main peak. The "post peak" contains wrongly bridged disulfide bonds. Sandoz identified 4 wrongly bridged disulfide bonds that can occur between 5 different cysteine residues in the TNFR portion of the molecule. Sandoz showed a correlation between the presence of one of the wrongly bridged disulfide bonds, termed the T7 peptide, with a reduction of potency in the TNF-neutralization assay. Thus, a structure function relationship was established between wrongly bridged disulfide bonds and potency in the TNF-alpha neutralization assay.

Most disulfide bonds are structural and are important for the correct folding of a protein. However, some disulfide bonds are allosteric, which control the function of a protein when they are reduced or oxidized in vivo in the blood. Examples of proteins with allosteric disulfide bonds include antibodies and other proteins, tissue factor and viral glycoproteins responsible for viral entry into cells. Reports in the literature also provide evidence that TNFR1, TNFR2 and other members of the TNFR family contain allosteric disulfide bonds.

Therefore, Sandoz was asked to provide data that would demonstrate that the wrongly bridged disulfide bonds could refold in vivo.

Data were provided for an in vitro system using mild redox conditions that mimic the in vivo environment. These data demonstrated a reduction of levels of wrongly bridged disulfide bonds and restoration of potency in GP2015 process intermediates that contain high levels of the T7 peptide, US-licensed Enbrel and EU-approved Enbrel lots.

Based on these data and knowledge of the levels of the T7 peptide in a subset of GP2015, US-licensed Enbrel and EU-approved Enbrel, a computed potency model was developed taking into account the correct refolding of the disulfide bonds. Using the computed potency model, GP2015 and US-licensed Enbrel met the criteria for statistical equivalence. In addition, using the computed potency model, GP2015 and EU-approved Enbrel and US-licensed Enbrel and EU-approved Enbrel met the criteria for statistical equivalence. Therefore, differences in levels of post-peak hydrophobic variant do not preclude a conclusion that GP2015 is highly similar to US-licensed Enbrel. Furthermore, the comparisons support the analytical portion of the scientific bridge for non-clinical and clinical studies conducted with EU-approved Enbrel.

Other quality attributes assessed by the quality range analysis and by qualitative comparisons also support a finding that GP2015 is highly similar to US-licensed Enbrel, notwithstanding minor differences in clinically inactive components.

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

1. To develop and implement an analytical method for release and stability testing of GP2015 drug substance and drug product that can adequately assess levels of hydrophobic variants, including wrongly bridged disulfide bond variants. The final validation report and release and stability acceptance criteria will be submitted as a PAS by December 31, 2017.
2. Repeat the microbial retention study using a more suitable surrogate solution. Attributes of the surrogate solution that are known to affect microbial retention (surface tension, viscosity, ionic strength, etc.) should model the drug product as closely as possible while preserving viability of the challenge organism. Alternatively, use of a reduced exposure time or modified process conditions (e.g., temperature) may be appropriate. Provide the summary data, the associated report, and justification for any modifications to the study. If any filtration parameters are changed as a result of the study, update the BLA file accordingly. The final report will be submitted as a CBE30 by September 30, 2017.

II. Summary of Quality Assessments

The control strategy for GP2015 is based on the identification of critical quality attributes (CQAs), manufacturing and clinical experience, characterization data, analytical method understanding, process understanding, and stability data.

Control elements include: **Design Control**, where process steps are specifically designed to influence the formation or removal of a specific quality attribute; **Process Control**, where elements are put in place to control process steps, including critical process parameters, and ensures production within defined ranges of all process parameters; **Raw Material Control** includes tests performed on raw materials to ensure consistency in quality attributes; **In-Process Testing** to ensure certain levels of specific quality attributes against an alert limit, action limit or acceptance criterion; **Release Testing** that ensures a quality attribute is consistently within an established range; **Stability Testing**, that ensures the established limit is not exceeded prior to the end of shelf life; **Process Performance Qualification testing** of specific quality attributes of process intermediates or DS during process validation; **Characterization** includes additional studies that are not covered by the previous control elements; and **Monitoring** after successful completion of PPQ and will be included in the Continued Process Verification plan.

Table 1 in Section A provides a summary of CQA identification and risk management. For the purposes of this table, CQAs are limited to attributes intrinsic to the drug substance (active pharmaceutical ingredient).

The identification and risk management of process related impurities and general drug substance and/or drug product attributes are described in separate risk tables in Section B Drug Substance Quality Summary and Section C Drug Product Quality Summary.

Product variants are defined as variants that are fully active, or close to fully active. Product impurities are defined as product variants that are inactive or have greatly reduced activity. Reverse-phase chromatography identifies the main peak, pre- and post-peaks. The post peak is present in GP2015 to a lesser extent than in Enbrel. This post-peak is known to have reduced potency.

Three tools were used for the risk assessment and criticality ranking: Tool A was impact and uncertainty scoring for product variants and Tool B was impact and uncertainty scoring for process- and excipient related impurities. For both Tools A and B, the criticality assignment was based on scores as follows:

- Very High: 121-140
- High: 86-120
- Moderate: 56-85
- Low: 31-55
- Very Low: 2-30

Tool C was used for the criticality assessment of other attributes such as potency, identity, strength & composition,¹ and appearance & description. These attributes are considered to be of very high criticality unless justified otherwise and were given a score of 140. Note that for the Tables in this section, the criticality ranking is reported, not the risk ranking that was done for purposes of analytical similarity.

Table 1 lists only CQAs ranked very high, high or moderate.

¹ "Strength and composition" is the phrase Sandoz used in its S.4.5 module in describing its control strategy.



QUALITY REVIEW



A. CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA (Type)	Risk	Origin	Control Strategy	Other
TNF-alpha Neutralization (Potency)	MOA - Impact on efficacy	Intrinsic to molecule Impacted by wrongly-bridged disulfide bonds in TNFR portion, aggregates and degradation products.		(b) (4)
TNF-beta Neutralization (Potency)	MOA - Impact on efficacy	Intrinsic to molecule		
TNF-alpha binding	MOA - Impact on efficacy	Intrinsic to molecule		
Glycosylation -Alpha Galactosylation -Terminal GlcNAc -Overall Sialylation -Triantennary Glycans -Afucosylated Glycans -High Mannose	Impact on immunogenicity Impact on PK/PD Impact on PK/PD Impact on PK/PD Impact on ADCC Impact on PK/PD and	Cell Line and Bioreactor		



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Glycans	ADCC		(b) (4)
Higher Order Structure -Aggregates -Degraded Products -Wrongly Bridged Disulfide Variants	Impact on biological activity, PK/PD, and immunogenicity	Intrinsic to molecule DS manufacture: may be formed during cell culture or some purification steps	
Bioactivity FcRn binding CDC and ADCC Activity FcγR binding (all variants)	Impact on PK/PD Possible impact on bioactivity, not considered MOAs for this product.	Intrinsic to molecule	



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<p>Other Variants -Acidic variants -Oxidation -Deamidation</p>	<p>Impact on PK/PD Impact on PK/PD, immunogenicity</p>	<p>Formed during cell culture and possibly during some purification steps.</p>	<p>(b) (4)</p>
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B. Drug Substance [USAN Name] Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

APPEARS THIS WAY ON ORIGINAL



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

CQA (Type)	Risk	Origin	Control Strategy	Other
Visual Appearance: color and clarity (General)	Impact on safety and immunogenicity	Intrinsic to molecule, formulation and manufacturing processes		(b) (4)
Protein Quantity (General)	Impact on efficacy	Manufacturing process		
DNA (Process Impurity)	Impact on safety and immunogenicity	Cell Culture		
Host Cell Proteins (Process Impurity)	Impact on safety, immunogenicity and stability	Component of Cell Culture Media		
Protein A (Process Impurity)	Impact on safety and immunogenicity	(b) (4)		
(b) (4) (Process Impurity)	Impact on safety and immunogenicity	Cell Culture		
Endotoxin	Impact on safety	Endotoxin can be introduced		



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(Contaminant)		throughout the manufacturing process	(b) (4)
Bioburden (Contaminant)	Impact on safety	Bioburden can be introduced throughout the manufacturing process	
Mycoplasma (Contaminant)	Impact on safety	Cell Culture	
Virus Contamination (Contaminant)	Impact on safety	Cell Culture	
(b) (4)	Impact on safety	Cell Culture medium (b) (4)	



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			(b) (4)
(b) (4)	Impact on safety	Cell Culture - stock solution	(b) (4)
	Impact on safety	Cell Culture - stock solution	(b) (4)
	Impact on safety	Raw Materials	

a. Description

GP2015 is a TNF Receptor-Fc Fusion protein produced in CHO cells. It is a homo-dimer containing 934 amino acid residues with a molecular mass of ~125 kDa. The N-terminal portion of the molecule is the TNF receptor followed by the Hinge Region, CH2 and CH3 domains of a human IgG1 molecule. It contains 29 intra- and inter-chain disulfide bonds. It contains the typical N-glycan structure and heterogeneity of an antibody in the Fc portion and has 2 N-glycosylation sites and multiple O-glycosylation sites on the TNFR portion of the molecule.

b. Mechanism of action

Etanercept binds soluble TNF-alpha and TNF-beta with high affinity. It also binds membrane bound TNF-alpha. Etanercept-bound TNF is blocked from binding the TNFR on cells, inhibiting the downstream effects of TNF signaling. In addition to blocking TNF signaling, there is a potential for antibody effector function through the Fc portion of the molecule. While etanercept can be shown to have complement dependent cytotoxicity and antibody dependent cellular cytotoxicity activities, both activities are low relative to anti-TNF monoclonal antibodies and even lower when compared to mAbs whose primary MOA includes effector function. Antibody effector function does not contribute to the overall mechanism of GP2015.

c. Potency Assay

The potency assay is a TNF-alpha neutralization reporter gene assay. HEK293 cells expressing the TNF receptor were transfected with a luciferase reporter gene construct under transcriptional control of the NF- κ B dependent promoter. When the cells are incubated with TNF-alpha, stimulation of the cells results in luciferase expression. Serial dilutions of GP2015 and a fixed concentration of TNF-alpha are added to the cells and incubated for 16-24 hours. The addition of GP2015 will inhibit luciferase expression, which is detected by the addition of a luciferase substrate whose signal is detected on a luminescence reader. Potency is reported relative to the GP2015 reference standard. This method is used for both GP2015 DS and DP release and stability testing.

d. Reference material(s)

A two-tier reference standard system is in place, which is consistent with ICH Q6B. The primary reference standard (PRS), GP2015.02REF, was developed from a Phase III (b) (4) lot, B170075, which was used in Clinical studies GP15-103, GP15-104 and GP15-302. The current working reference standard (WRS), GP2015.01WST, was developed from lot #B213820, which is representative of the commercial process. The WRS was appropriately qualified against the PRS.

e. Critical starting materials or intermediates

(b) (4)

(b) (4)

f. Manufacturing process summary

(b) (4)

g. Container closure

The container closure system is (b) (4) with (b) (4) screw closure. A toxicity assessment of the extractables identified no substances of concern.

h. Dating period and storage conditions

The data support an expiration dating period of 36 months at (b) (4) °C.

C. Drug Product [Established Name] Quality Summary

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



QUALITY REVIEW



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

CQA (Type)	Risk	Origin	Control Strategy	Other
Content (General)	Impact on efficacy	DP manufacture BDS and filling		(b) (4)
Visible Particles (b) (4)	Impact on immunogenicity and safety	DS/DP manufacture		
Sub-visible Particles (b) (4)	Impact on immunogenicity and safety	DS/DP manufacture		
pH (General)	Impact on product stability and conformation, potential impact on PK/PD	DS/DP manufacture		
Extractable Volume (General)	Impact on efficacy	DP manufacture		



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			(b) (4)
Osmolality (General)	Impact on stability	DP manufacture	
Bioburden (Contaminant)	Impact on safety	BDS and DP manufacture	
Sterility (Contaminant)	Impact on safety and efficacy (degradation or modification of the product by contaminating microorganisms)	Contaminants may be introduced throughout the manufacturing process through input materials, BDS, during processing or through a container closure failure	



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Endotoxin (Contaminant)	Impact on safety	Contaminants may be introduced throughout the manufacturing process through input materials, BDS, during processing or through a container closure failure	(b) (4)
Container Closure Integrity	Impact on safety	Container closure system designed and tested to maintain integrity and thus the sterility of the product throughout shelf-life.	
(General)	Impact on product safety, immunogenicity and therapeutic dose	DP manufacture and Pre-filled syringes.	
Density (General)	Impact on therapeutic dose	DP manufacture	
Viscosity (General)	Impact on therapeutic dose	DP and PFS manufacture	



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Gliding Force (General)	Impact on therapeutic dose	DP and PFS manufacture	(b) (4)	
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- a. Strength
Erelzi is supplied as etanercept-xxxx (established name to be determined) 25 mg/0.5 mL solution for injection and 50 mg/mL solution for injection in pre-filled syringes and a 50 mg/1.0 mL solution for injection in an autoinjector (AI).
- b. Summary of Product Design
Erelzi is supplied as 25 mg/0.5 mL solution for injection and 50 mg/mL solution for injection in pre-filled syringes and a 50 mg/mL solution for injection in an autoinjector (AI). The 50 PFS and AI have an overfill of (b) (4)% and the 25 mg PFS has an overfill of (b) (4)% to ensure an accurate extractable volume to receive the appropriate dose.

The Quality Target Product Profile (QTPP) ensures product quality and safety by the following:

- Product meets and maintains quality attribute targets during manufacture, transport, storage shelf-life and use
 - DP does not interact with packaging components to compromise safety and efficacy
 - DP that is sterile and with low-endotoxin levels
 - Acceptable appearance
 - PFS assembled with needle safety device or in autoinjector
 - DP that is suitable for subcutaneous administration and meets pharmacopeial requirements for parenteral administration
 - Sufficient shelf life at 2-8°C plus 28 days at 25±2°C to support commercial use
- c. List of Excipients
50 mM citrate buffer
29 mM sucrose
26 mM NaCl
25 mM L-Lysine
- d. Reference material(s)
Same as for DS

- e. Manufacturing Process

(b) (4)

- f. Container Closure
DP is stored in 1 mL (b) (4) glass syringes (b) (4).
The staked hypodermic needle is stainless steel (b) (4) and the 27G x 1/2" needle is glued to the glass syringe body. It had a rubber needle

shield in a rigid needle shell made of (b) (4) that protects the rubber needle shield. The plunger stopper is comprised of (b) (4) rubber.

g. **Expiration Date & Storage Conditions**

The shelf life for both 25 and 50 mg PFS and AI is 24 months at 2-8°C plus 28 days at 25±2°C

h. **List of co-packaged components, if applicable**
Not applicable

D. Novel Approaches/Precedents

Release testing for drug product sterility uses a rapid microbial method (RMM). This is the first biotechnology product approval in CDER using this method. The RMM has been approved for some small molecule drug products.

E. Any Special Product Quality Labeling Recommendations

None



QUALITY REVIEW



F. Establishment Information

OVERALL RECOMMENDATION: Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Sandoz GmbH (FEI 3004828473) and Novartis Pharma Stein AG (FEI 3002653483) proposed for GP2015 DS and DP manufacture. All proposed manufacturing and testing facilities are acceptable on the basis of their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facilities assessment perspective.

DRUG SUBSTANCE					
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	PRELIMINARY ASSESSMENT	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
DS Manufacturing DS and DP release and stability testing	Sandoz GmbH, Schafteuau Biochemiestrassen 10 6336 Langkampfen Austria	301698247 3004828473	Acceptable	A 2 item FDA-483 issued. Firm's responses deemed adequate Inspection classified VAI	Approve
Release of DS DS and DP release and stability testing	Sandoz GmbH, Kundl Biochemiestrassen 10 6250 Kundl Austria	300220969 3002806523	Acceptable	A 2 item FDA-483 issued. Firm's responses deemed adequate Inspection classified VAI	Approve
DS release testing	(b) (4)	(b) (4)	Inspection waived	NA Previous inspection in (b) (4) classified NAI	Approve



QUALITY REVIEW



	(b) (4)				
DS release testing			N/A	Inspection performed in (b) (4) to support BLA 761042 Inspection classified NAI	Approve
DS and DP release and stability testing			Inspection waived	NA Previous inspection in (b) (4) classified NAI	Approve
DS and DP release and stability testing	Novartis Pharma AG Lichtstraße 35 4056 Basel Switzerland	482347168 3002807772	Inspection waived	NA	Approve
DS and DP release and stability testing for bioactivity Preparation of WCB; Storage of WCB and MCB			Acceptable	(b) (4) inspection for BLA (b) (4) NAI, no FDA-483 issued	Approve
DRUG PRODUCT					

**QUALITY REVIEW**

FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER		INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
DP Manufacturing IPC, Release and Stability testing	Novartis Pharma Stein AG Schaffhauserstrasse 4332 Stein Switzerland	488152505 3002653483	Inspection waived	NA Previous inspection in (b) (4) classified NAI	Approve
Device Assembly IPC testing	(b) (4)	(b) (4)	Inspection waived	NA	Approve

G. Facilities

Prior Inspection History

Drug Substance

Sandoz GmbH Schafftenau (FEI 3004828473)

A pre-license inspection in support of BLA 761042 was conducted from 3/7-3/11/2016 in accordance with CP7356.002M and covered Quality, Facilities and Equipment, Production, Materials, and Laboratory systems. A 2-item FDA-483 was issued. The firm's corrective action plan was deemed appropriate to correct the deficiencies. The inspection was classified VAI. A GMP surveillance inspection was conducted from 3/10-18/2014 in accordance with CP7356.002A and CP7356.002F and covered the Quality, Production, Laboratory Control, Materials, and Facility and Equipment systems. No FDA-483 was issued. The inspection was classified NAI. Previous inspections in 2012 and 2010 were classified as VAI.

(b) (4)

The inspection from (b) (4) was a pre-license inspection in support of BLA (b) (4) conducted in accordance with CP 7346.832 and ICH Q7, and covered Quality, Facilities and Equipment, Production, Materials, and Laboratory systems. No FDA-483 was issued. The inspection was classified NAI. Previous inspections in 2015 and 2012 were classified as NAI.

Novartis Pharma AG (FEI 3002807772)

The inspection from 1/12-14/2015 was a pre-approval and GMP surveillance inspection was conducted in accordance with CP7356.002 and CP7346.832 and covered the Quality and Lab Control systems. No FDA-483 was issued. The inspection was classified NAI. Previous inspections in 2013 and 2012 were classified as NAI.

Sandoz GmbH Kundl (FEI 3002806523)

The inspection from 3/7-11/2016 covered the Quality and Laboratory Control systems for microbiology testing. A 2-item FDA-483 was issued. The firm's corrective action plan was deemed appropriate to correct the deficiencies. The inspection was classified VAI. Previous inspections in 2014 and 2012 were classified as VAI.

(b) (4)

The inspection from (b) (4) was a pre-approval and GMP surveillance inspection conducted in accordance with CP7356.002 and CP7346.832 and covered the Quality and Lab Control systems. No FDA-483 was issued. The inspection was classified NAI. Previous inspections in 2009 and 2006 were classified as VAI and NAI, respectively.

(b) (4)

The inspection from [REDACTED] (b) (4) was a GMP surveillance inspection conducted in accordance with CP7356.002M and covered the Facility/Equipment, Quality, Lab and Material systems. No FDA-483 was issued. The inspection was classified NAI. Previous inspections in 2011 and 2009 were classified as VAI and NAI, respectively.

[REDACTED] (b) (4)

The facility had not been inspected by FDA prior to 1/2016.

Drug Product

Novartis Pharma Stein AG (FEI 3002653483)

The inspection of the firm's sterile facility from 3/17-25/2014 was a pre-approval and GMP surveillance inspection conducted in accordance with CPs 7356.002, 7356.002A, 7356.002M, and 7356.002F, and 7346.832 with coverage of the all (b) (4) drug systems for sterile operations and pre-approval coverage and BLAs and NDAs. No FDA-483 was issued. The inspection was classified NAI. Previous inspections in 2012 and 2010 were classified as VAI and NAI, respectively.

[REDACTED] (b) (4)

The inspection from [REDACTED] (b) (4) was a GMP surveillance inspection conducted in accordance with CP 7356.002A and covered the Quality, Laboratory, Packaging and Labeling systems. A 10-item FDA-483 was issued. The firm response was deemed adequate in addressing the deficiencies. The inspection was downgraded from pOAI to VAI. Previous inspections in 2012 and 2010 were classified as NAI and VAI, respectively.

Sandoz GmbH (FEI 3004828473)

See above under DS

[REDACTED] (b) (4)

See above under DS

Novartis Pharma AG (FEI 3002807772)

See above under DS

Sandoz GmbH (FEI 3002806523)

See above under DS

[REDACTED] (b) (4)

See above under DS

H. Lifecycle Knowledge Management

a. Drug Substance

- i. Protocols approved - Preparation and Testing of new Working Cell Banks; Preparation and Testing of new Working Reference Standards (Note: if a new Primary Reference Standard is needed, a post-approval supplement will be submitted); Annual GMP stability.
- ii. Outstanding review issues/residual risk – Need fulfillment of PMC to implement RPC or HIC method for DS and DP release and stability.
- iii. Future inspection points to consider: The following items were communicated to the sponsor during the BDS inspection at Sandoz GmbH, Schafstau and should be follow up at the next inspection:
 - Many of the WFI points of use in the water for injection (WFI) system of building (b) (4) are not routinely tested;
 - Deviations should be investigated case-by-case and copying the content of a deviation from a previous file should be avoided when new deviations are written. In addition, some of the deviations (for example bioburden investigations) are not adequately investigated;
 - Some of the presentation only included the good results. For example the presentation on the (b) (4) study did not include the contaminations;
 - The storage (b) (4) for drug substance storage are almost fully loaded and it is not clear if there will be storage space for future DS batches in the (b) (4) currently existing.

b. Drug Product

- i. Protocols approved - Annual GMP stability. No extension of shelf life needed.
- ii. Outstanding review issues/residual risk – Need fulfillment of PMC to implement RPC method for DP release and stability
- iii. Future inspection points to consider - None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

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



QUALITY REVIEW



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

BLA STN 761042

Proper Name: To be determined

Sandoz

Peter Adams, DBRR1/OBP Product Reviewer

Reyes Candau-Chacon OPF/DMA, DS Microbiology Reviewer

Candace Gomez-Broughton, OPF/DMA, DP Microbiology Reviewer

Patricia Hughes, Acting Branch Chief, DMA/OPF

Zhong Li, DIA/OPF, Facilities Reviewer

Peter Qiu, Branch Chief, DIA/OPF

Keith Olin, OPRO RBPM

Marjorie Shapiro, DBRR1/OBP, ATL

OPQ CMC BLA Review Data Sheet

1. **BLA#:** STN 761042
2. **REVIEW DATE:**
3. **PRIMARY REVIEW TEAM:**
 Medical Officer: Rachel Glaser, Gary Chiang and Nikolay Nikolov (Team Leader)
 Pharm/Tox: Andrea Benedict and Marcie Woods
 Product Quality Team: Peter Adams and Marjorie Shapiro
 CMC Microbiology: Maria Candau-chacon, Candace Gomez-Broughton and Patricia Hughes (Team leader)
 Immunogenicity: Brian Janelins and Jee Chung
 Facilities: Zhong Li and Peter Qiu
 Clinical Pharmacology: Yunzhao Ren and Ping Ji
 Statistics: Kathleen Fritsch, Yongman Kim and Gregory Levin
 OBP Labeling: Jibril Abdus-Samad and Peter Adams
 RPM: Leila Hann and Jessica Lee
4. **MAJOR 21st Century Review DEADLINES**
Filing Meeting: September 3, 2015
Mid-Cycle Meeting: December 16, 2015
Wrap-Up Meeting: April 12, 2016
Primary Review Due: July 29, 2016
Secondary Review Due: August 5, 2016
CDTL Memo Due: August 12, 2016
BsUFA Action Date: August 27, 2016
5. **COMMUNICATIONS WITH APPLICANT AND OND:**

Communication/Document	Date
Information Request #1	November 20, 2015
Information Request #2	December 11, 2015
Teleconference (IR 12/11 follow-up)	December 17, 2015
Information Request #3	February 26, 2016
Information Request #4	March 10, 2016
Teleconference	April 7, 2016
Information Request #5 (follow-up to telecon)	April 8, 2016
Information Request #6	April 8, 2016
Information Request #7	July 25, 2016
Teleconference	August 4, 2016

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

Submission	Date Received	Review Completed (Yes/No)
Original Application	July 30, 2015	Yes
Amendment 8	December 11, 2015, response to IR #1 (Q1-18)	Yes
Amendment 9	January 15, 2016, response to IR #2 (Q1-15)	Yes
Amendment 12	January 29, 2016, response to IR #2 (Q13) and tcon, updated information to correct errors	Yes
Amendment 15	March 2, 2016, response to IR #2 (Q13)	Yes
Amendment 17	March 10, 2016 response to IR#3 (Q5-8)	Yes
Amendment 20	March 31, 2016 response to IR #4 (Q1-8)	Yes
Amendment 23	April 15, 2016 response to IR #7 (Q3)	Yes
Amendment 27	April 28, 2016, response to IR #6 (Q1-2)	Yes
Amendment 35	July 29, 2016 response to IR #11 (Q1-4)	Yes
Amendment 36	August 8, 2016 response to tcon (Q1-3)	Yes

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

- a. Proper Name: Erelzi
- b. Trade Name: Erelzi
- c. Non-Proprietary/USAN: etanercept – xxxx (suffix to be determined)
- d. CAS name: 185243-69-0
- e. Common name: GP2015
- f. INN Name: etanercept
- g. Compendial Name:
- h. OBP systematic name: FUS: MABFRAG HUMAN (IGG1 FC); RPROT P20333 (TNR1B_HUMAN) [GP2015]
- i. Other Names:

8. **PHARMACOLOGICAL CATEGORY:** TNF-a antagonist

9. **DOSAGE FORM:** solution in a single use vial

10. **STRENGTH:** 25mg/0.5mL and 50mg/mL

11. **ROUTE OF ADMINISTRATION:** SC

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)	(b) (4)	Glass Syringe System	yes	No review required. Sufficient information in the BLA, reviewed by CDRH.
(b) (4)	(b) (4)	Plunger stopper	yes	No review required. Sufficient information in the BLA, reviewed by CDRH

		(b) (4)		
	(b) (4)	Rubber needle shield (b) (4)	yes	No review required. Sufficient information in the BLA, reviewed by CDRH
Device MF #				
	(b) (4)	(b) (4) Autoinjector for GP2015 50 mg/1.0 mL (GP2015 (b) (4) 50 Auto Injector)	yes	No review required. Sufficient information in the BLA, reviewed by CDRH. CDRH recommends approval

13. INSPECTIONAL ACTIVITIES

A preapproval inspection (PAI) of the Sandoz GmbH facilities in Langkampfen (Austria) for bulk drug substance (BDS) manufacturing of Erelzi was conducted by Maria Candau-Chacon and Maria Jose Lopez-Barragan of DMA/OPF Zhong Li of DIA/OPF and Peter Adams, DBRR1/OBP. The site is responsible for the manufacturing of Drug Substance and release testing. A FDA-483 form was issued with two observations: (1) There is no demonstration of microbial control of (b) (4) during storage and (2) Hold times are not adequately established. Four additional recommendations were made to the firm during the inspection that should be followed up at the next inspection: (1) Many of the WFI points of use in the water for injection (WFI) system of building (b) (4) are not routinely tested; (2) Deviations should be investigated case-by-case and copying the content of a deviation from a previous file should be avoided when new deviations are written. In addition, some of the deviations (for example bioburden investigations) are not adequately investigated; (3) Some of the presentation only included the good results. For example the presentation on the (b) (4) study did not include the contaminations; and (4) The storage (b) (4) for drug substance storage are almost fully loaded and it is not clear if there will be storage space for future DS batches in the (b) (4) currently existing.

14. CONSULTS REQUESTED BY OBP

Dr. Sarah Mollo, ODE/CDRH reviewed the prefilled syringe with needle safety device and autoinjector device constituents of this combination product. CDRH recommends approval.

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
X	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control

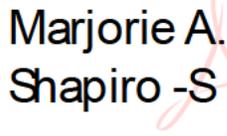
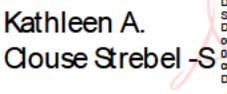
	Process Analytical Technology
	Expanded Change Protocol

16. PRECEDENTS

None

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Primary Reviewer Peter L. Adams, Ph.D. Division of Biotechnology Products Research and Review I Office of Biotechnology Products, CDER	 Digitally signed by Peter Adams-S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Peter Adams-S, 0.9.2342.19200300.100.1.1=0011335608 Date: 2016.08.12 12 06:47 -04'00'
Application Technical Lead Marjorie A. Shapiro, Ph.D. Division of Biotechnology Products Research and Review I Office of Biotechnology Products, CDER	 Digitally signed by Marjorie A. Shapiro -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300081252, cn=Marjorie A. Shapiro -S Date: 2016.08.12 16:10 38 -04'00'
Division Director Kathleen A. Clouse Division of Biotechnology Products Research and Review I Office of Biotechnology Products, CDER	 Digitally signed by Kathleen A. Clouse Strebel -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1 1300054511, cn=Kathleen A. Clouse Strebel -S Date: 2016.08.12 12 59 19 -04'00'

B. CC Block

Recipient	Date
Jessica Lee BLA RPM DPARP	Provided Electronically
Nikolay Nikolov, MC. CDTL DPARP	Provided Electronically

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products recommends approval of this 351(k) BLA application 761042 for GP2015 (Erelzi), manufactured by Sandoz, Inc., as a biosimilar to US-licensed Enbrel®. The data submitted in the BLA support the conclusion that GP2015 is highly similar to US-licensed Enbrel® and that the manufacture of Erelzi (etanercept-xxxx; suffix to be determined) is well controlled and leads to a product that is pure and potent. The product is free of endogenous and infectious adventitious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing are sufficiently validated and a consistent product has been manufactured from multiple production runs. It is recommended that Erelzi (etanercept-xxxx) be approved for human use under conditions specified in the package insert.

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

We recommend an expiration dating period of 24 months for Erelzi drug product when stored 2-8°C followed by 28 days at 25±2°C.

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

II. List Of Deficiencies To Be Communicated

None

III. List Of Post-Marketing Commitments/Requirement

1. To develop and implement an analytical method for release and stability testing of GP2015 drug substance and drug product that can adequately assess levels of hydrophobic variants, including wrongly bridged disulfide bond variants. The final validation report and release and stability acceptance criteria will be submitted as a PAS by December 31, 2017.
2. Repeat the microbial retention study using a more suitable surrogate solution. Attributes of the surrogate solution that are known to affect microbial retention (surface tension, viscosity, ionic strength, etc.) should model the drug product as closely as possible while preserving viability of the challenge organism. Alternatively, use of a reduced exposure time or modified process conditions (e.g., temperature) may be appropriate. Provide the summary data, the associated report, and justification for any modifications to the study. If any filtration parameters are changed as a result of the study, update the BLA file accordingly. The final report will be submitted as a CBE30 by September 30, 2017.

IV. Review Of Common Technical Document-Quality Module 1

Environmental Assessment or Claim Of Categorical Exclusion

A categorical exclusion from the requirement of an environment assessment is requested by Sandoz under 21 CFR Part 25.31(b). The request is based on an action that increases the use of the active moiety, but the active concentrations of the substance at the point of entry into the aquatic environment will be less than 1 part per billion.

A calculation is provided showing that the levels will be not exceeded and uses a formula presented in *Guidance for Industry-Environmental Assessment of human Drug and Biologics Applications, dated July 1998*. Therefore approval of this submission will not increase the overall use of the active moiety.

The claim of a categorical exclusion is accepted.

V. Primary Container Labeling Review

A separate primary container labeling review was performed Jibril Abdus-Samad, OBP.

VI. Review Of Common Technical Document-Quality Module 3.2

The review of module 3.2 is provided below.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

A separate review of the immunogenicity assays was performed by Dr. Brian Janelins, DBRR1 who concluded "The development and validation of the immunogenicity assays used to assess the immunogenicity of GP2015 and EU-approved Enbrel (i.e., etanercept) are acceptable and the immunogenicity data obtained from the clinical trials suggest that both products are similar from an immunogenicity perspective, i.e., the data regarding anti-drug antibody (ADA) incidence in patients treated with GP2015 or EU-approved Enbrel are supportive of finding no clinically meaningful differences between GP2015 or EU-approved Enbrel." ADAs from 600 ng/mL up to 24,000 ng/mL can be detected in the presence of trough levels of GP2015 (4-10 µg/mL) Lower levels of ADA (200 ng/mL) can be detected in the presence of 1 µg/mL GP2015.

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DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

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

S. DRUG SUBSTANCE

3.2. S.1.1 Nomenclature

- Descriptive Name: etanercept is TNFR2:Fc fusion protein targeted against soluble and membrane bound forms of tumor necrosis factor- α and lymphotoxin β . Etanercept consists of the extracellular domain of the tumor necrosis factor 2 receptor and the Fc region of an IgG1 antibody.
- Generic Name (USAN, INN, JAN): etanercept-xxxx (suffix to be determined)
- Trade Name: Erelzi
- Synonyms:
- Laboratory Codes: GP2015

3.2.S.1.2 Structure

GP2015 is a dimeric TNFR2:Fc fusion protein consisting of 467 amino acids that includes the extracellular domain of TNFR2 (1-235) and IgG1 Fc region (236-467). The Fc region is truncated and includes the human IgG1 hinge, CH2 and CH3 domains of the Fc region. The protein sequence is given below with the TNFR2 sequence is in black and the Fc in red.

```

1  LEAQVAFTPY APEFGSTCRLL REYYDQTAQM CCSKCSPGQH AKVFCTKTSD
51  TVCDSCEDST YTQLWNWVPE CLSCGSRCS DQVETQACTR EQNRICTCRP
101 GWYCALSKQE GCRLCAPLRK CRPGFGVARP GTETSDVVCV PCAPGTFBNT
151 TSSTDICRPH QICNVVAIPG NASMDAVCTS TSPTRSMAPG AVHLPQPVST
201 RSQHTQPTPE PSTAPSTSFL LEMGPSPPAE GSTGDEPKSC DKHTCPCPCP
251 APELLGGPSV FLFEPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD
301 GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA
351 PIEKTISKAK GQPREPQVYT LPPSRBEMTK NQVSLTCLVK GFYPSDIAVE
401 WESNGQPENN YKTTTPVLDL DGSFFLYSKL TVDKSRWQGG NVFSCSVMHE
451 ALHNHYTQKS LSLSPGK

```

3.2.S.1.3 General Properties

- GP2015 drug product is clear to yellowish in color;
- Three N-linked glycans Asn 149 and Asn 171 in the TNFR2 portion and Asn 317 in the Fc region;
- O-linked glycans between Thr 179 and Ser 239 in the TNFR2 portion;
- 13 intra-chain disulfide bonds per monomer and 3 inter chain disulfide bonds, for a total of 29 disulfide bonds throughout the molecule;
- The extinction coefficient was established experimentally;
- The mechanism of action involves the binding and neutralization of TNF- α

3.2.S.2 Manufacture

(b) (4)



263 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

3.2.R REGIONAL INFORMATION (U.S.A.)

Reviewer comment: In addition to the batch records, documents in the Regional section include: the CQA assessment; analytical similarity studies between GP2015 and US-licensed Enbrel and analytical similarity studies between US-licensed Enbrel and EU-approved Enbrel; comparability studies of GP2015 DS after manufacturing changes; GP2015 DS and DP small scale model qualification studies; GP 2015 DS and DP process characterization studies; and descriptions of analytical methods and validation of methods that are not included in Module 3.2.S.4.2 and Module 3.2.P.5.2. Review of the comparability studies, small scale model qualification and process characterization studies are reviewed in the associated sections in 3.2.S and 3.2.P. Module 3.2.R also includes reports summarizing device-related technical and scientific information regarding the final combination products and their device constituent parts. This information was reviewed by CDRH.

The document describing the analytical similarity studies is titled "Biosimilarity with Reference Product". This document was updated several times in response to information requests. Unless otherwise noted, the tables and figures in the review were copied from the version submitted 1/29/16. Other tables and figures were copied from the responses to information requests that were separate from the updated "Biosimilarity with Reference Product" document.

3.2.R.3 Analytical Similarity

GP2015, proposed biosimilar to etanercept, has the same presentation US-licensed Enbrel with a pre-filled syringe (both 50mg and 25mg) and an auto-injector (50mg). US-licensed Enbrel is also supplied as a 25 mg/vial lyophilized form for multiple use, but GP2015 is not currently supplied in this format. GP2015 is formulated in 50 mM citrate buffer, 29 mM sucrose, 26 mM NaCl, 25 mM L-lysine, pH 6.3. This differs from the US-licensed Enbrel formulation that consists of 25 mM sodium phosphate, pH 6.3, 100 mM sodium chloride, 25 mM L-arginine hydrochloride and 1% sucrose.

To support a demonstration of biosimilarity, Sandoz provided data from three pharmacokinetic studies (GP15-101, GP15-102 and GP15-103). GP15-102 is the pivotal PK study comparing GP2015 to US-license Enbrel, while GP2015 was compared to EU-approved Enbrel in GP15-101 and GP15-103. In order to bridge the PK data between GP2015, US-licensed Enbrel and EU-approved Enbrel, a pre-planned cross study comparison between GP15-101 and GP15-102 was performed.

Sandoz also provided data from GP15-302, which was designed to demonstrate efficacy for GP2015 and compare the safety and immunogenicity between GP2015 and EU-approved Enbrel in patients with moderate to severe chronic plaque-type psoriasis. It included 531 randomized patients, with the efficacy endpoints assessed up to Week 12, immunogenicity assessments up to Week 18 and safety data available up to week 42. As EU-approved Enbrel is used as the comparator in clinical study GP15-302, a three-way analytical bridge linking GP2015, US-licensed Enbrel and EU-approved Enbrel was performed.

In order to demonstrate analytical similarity Sandoz performed extensive characterization studies, including analysis of GP2015, US-licensed Enbrel and EU-approved Enbrel in direct

'head-to-head' studies, as well as generating data from additional lots of US-licensed Enbrel and EU-approved Enbrel not used in the head-to-head studies and using historical data generated from GP2015 DS and DP development and clinical lots. The GP2015 lots used in the head-to-head analysis include the six GP2015 DS process validation lots ((b) (4)), 6 DP process validation lots (manufactured from three of the DS validation lots and one additional lot) and two DP lots used in clinical studies: lots CB50B2 used in GP15-302 and lot PVB50B3 used in GP15-104 and GP15-302. Three lots each of US-licensed Enbrel and EU-approved Enbrel were used in the head-to-head studies, with one lot of US-licensed Enbrel included in GP15-104 and two lots of EU-approved Enbrel used in GP15-302. Table 3-1, not copied.

Reviewer comment: GP2015 DP lots CB50B2 and PVB50B3 were derived from manufactured prior to the validation campaign. The remaining drug product lots are derived from drug substance validation lots listed Table 3-1. None of the GP2015 lots listed in Table 3-1 were used GP15-102 clinical trial. However, DP lot BW6918, which was analyzed by several, if not all of the analytical methods, was used in GP15-102. GP15-104 was an additional PK study comparing GP2015 to EU-approved Enbrel.

The US-licensed Enbrel and EU-approved Enbrel lots, including both dosage forms (PFS and lyophilized) were analyzed over a period of eight years. Sandoz noted a shift in the ranges of some quality attributes, such as bG2 glycans and charge variants, in these lots over time. Since the GP2015 manufacturing process was developed prior to the shift in these quality attributes, the entire range of the attributes from "pre-shift" and "post-shift" lots was used in the analytical similarity assessment of these attributes.

Reviewer Comment: The expiration dates for the US-licensed Enbrel and the EU-approved Enbrel are in 2015 and 2016 and the analysis conducted in 2014 was within the expiration period. The approach to use the entire range of the attributes observed in "pre-shift" and "post-shift" lots is acceptable.

The extended characterization studies included methods for identity confirmation, and purity determination (Table 3-3 not copied), heterogeneity of the products and stability indicating degradation products (Table 3-4 not copied), binding and in vitro biological methods, (Table 3-5, not copied) and general methods and methods for DS process related impurities (Table 3-6, not copied.) Methods used for release and stability testing were validated, while the other characterization methods are described as being "scientifically sound" and were suitable for their intended use.

Reviewer Comment: The methods used for release and stability testing are reviewed in the appropriate sections, 3.2.S.4 or 3.2.P.5. Adequate descriptions of the characterization methods are provided.

3.3 Evaluation of analytical similarity

Reviewer Comment: Information request #1, dated 11/20/15, requested that Sandoz assign TNF binding and the TNF- α RGA assay to Tier 1 and for Tier 2 methods, use the quality range (mean

$\pm X SD$) instead of Tolerance Intervals. Their updated approach was submitted on 1/29/16, which is reviewed here instead of the approach described in the original BLA submission.

The evaluation of analytical similarity involved the categorization of quality attributes according to their risk to activity, PK/PD, safety and immunogenicity. This criticality assessment was used to assign each quality attribute to one of three tiers, which use different statistical approaches to assess the quality attributes, Table 3-7. The criticality score is further modified based on the abundance of the quality attribute. For an attribute at the lower end of the criticality category that is present at <5%, it can be reduced by one category, for example from Tier 2 to Tier 3. For an attribute present at <2%, the category could also be reduced by one level and for an attribute present at <0.5%, it could be reduced by two levels, Table 3-8, not copied.

Table 3-7 Tier assignment

Criteria for assignment	Tier	Proposed statistical evaluation tool
Quality attributes with very high or high risk score (> 85) representing the clinical mode of action and having the highest impact on clinical performance.	Tier 1	Equivalence testing
Very high or high risk score (> 85) not representing the mode of action and numerical read-out.	Tier 2	Mean \pm 3 SD
Moderate risk score (56 – 85) and numerical read-out	Tier 2	Mean \pm 3 SD
Quality attributes with moderate, high or very high risk scores without numerical read-out and quality attributes with low or very low risk score (< 56)	Tier 3	Descriptive evaluation Comparison of chromatograms, spectra, gels, etc.; attributes without numerical readout Numerical evaluation: attributes with low or very low risk score

Reviewer Comment: The revised approach to the criticality assessment and placement of quality attributes into Tiers is acceptable.

Tier 1, 2 and 3 Methods

Tier 1 is a statistical equivalence test comparing the means of the two products.

Tier 2 uses quality ranges (mean \pm 3SD)

Tier 3 is for quality attributes not amenable to quantitative analysis or for attributes that can be quantitated, but are present at very low levels.

Reviewer Comment: The equivalence test uses the method recommended by OTS/OB/DBVI. These analyses were reviewed by Dr. Meiyu Shen, who also performed an independent analysis. Using the mean \pm 3SD for Tier 2 methods is also acceptable. We performed an independent analysis of the Tier 2 methods calculating the mean \pm 1.5 SD, 2SD and 3SD. All methods were within \pm 3SD, but some had narrower ranges.

Critical Quality Attribute Assessment

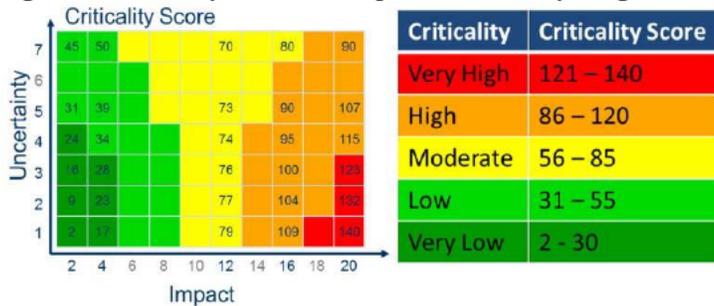
The critical quality attribute assessment was provided in a separate document in 3.2.R. A risk ranking approach was used to assess the impact that changes in an attribute will have on product quality and safety according principles outlined in ICHQ9. Three tools (tools A, B, and C) were used in the assessment of the criticality. Product related variants and process related impurities were assessed using tools A and B, respectively. Quality attributes that are related to potency, identity, strength and composition along with appearance and description are considered to be high criticality and were assessed using tool C.

The two elements of Tool A are the impact and uncertainty scoring of quality attributes. Impact scoring definitions range from none (2), low (4), moderate (12), high (16) and very high (20) impact on biological activity, PK/PD, immunogenicity and safety, Table 2-1, not copied. The definitions for uncertainty scoring none (1), very low (2), low (3), moderate (4), high (5) and very high (7), , not copied. Tool B uses the same impact scoring as Tool A, but the uncertainty scoring only has none (1), low (3) and very high (7), Tables 2-3 and Table 2-4, not copied. The formula used to calculate the criticality score for quality attributes using either tool (Figure 2-1) is given below, along with the criticality score contour plot (Table 2-2).

Figure 2-1 Criticality scoring using the 1st order full-factorial equation.



Figure 2-2 Criticality score contour plot and criticality categories



The matrix plot (to the left) summarizes the criticality scores calculated based on impact and uncertainty. The table to the right defines the criticality categories based on the criticality scores.

Reviewer comment: The approach that was outlined for the assessment of critical quality attributes is reasonable. However, no explanation was given regarding how the values were obtained for the formula in Figure2-1.

IR #1, dated 11/19/2015, contained the following comment:

CQA Assessment, Section 2.3, describes the calculation of criticality scores for variants

and impurities. In general, we agree with the criticality (very high, high, moderate, low, or very low) assignments for each quality attribute shown in Table 3-1. However, you should provide an explanation.

In the response dated 12/10/2015, Sandoz indicated that the tools used for the criticality assessment of the quality attributes were published by the CMC working group (A-Mab case study). Sandoz is using a modified version of tool #1 where quality attributes with a low uncertainty to have a high impact are assigned a high criticality score. The response is adequate.

For Tool C, quality attributes are assigned to be of high criticality and are assigned different criticality categories, which are justified according to the impact on safety and efficacy. Elements that do not contribute directly to the mechanism of action can be assigned a lower criticality score. Quality attributes associated with potency, composition and strength are assigned high criticality. The definition of the criticality scores ranges from low (14), moderate (71), high (103) and very high (140), Table 2-5, not copied, and descriptions of each of the criticality categories.

The criticality assessment for GP2015 is given in Table 3-1, not copied, which lists the applicability (DS/DP), quality attribute, the criticality scores for efficacy, PK/PD, immunogenicity, safety, and stability, and the overall criticality score, criticality ranking (very high to very low) and the assessment tool. In cases where tool C was applied, the attributes were considered as 'CQA by definition'. For methods assessing sterility, bioburden and adventitious agents, only, the criticality score is only determined for safety and the other categories are excluded. Where warranted, other methods assess the criticality for a subset of the efficacy, PK/PD, immunogenicity, safety, and stability categories.

Specific examples of risk based criticality assessment of GP2015 quality attributes include examples in each criticality category: very high (TNF-alpha neutralization), high (degradation products) moderate (host cell protein), low (excipient related impurities) and very low (lysine variants). The assessment of degradation products, which has a high criticality, is shown as an example, Table 4-2.

Table 4-2 Degradation products

DS, DP; tool A		
Efficacy		
Impact	X	Uncertainty
16	X	3
100		
I) Degradation products are inactive variants and show no potency in the TNF-alpha RGA.*		
U) Effect of QA was shown in <i>in vitro</i> studies.*		
PK/PD		
Impact	X	Uncertainty
16	X	4
95		
I) Impact on PK/PD profile is expected. PK is mainly driven by the Fc domain, which is intact for the observed fragments. Until now, fragments derived from the receptor region were observed. PD can be influenced by degradation products.		
U) QA is present in the reference product.		
Immunogenicity		
Impact	X	Uncertainty
2	X	7
45		
I) No impact on immunogenicity expected		
U) No information available		
Safety		
Impact	X	Uncertainty
	X	
Criticality score		
	100	High

3.2. R 4 Results of Extended Characterization Study

R.4.1 Physicochemical Characterization

Reviewer Comment: Sandoz included analytical data from US-licensed Enbrel and EU-approved Enbrel. The analytical bridge between EU-approved Enbrel to US-licensed Enbrel and GP2015 is provided in a separate PDF document – “Justification for the use of EU-authorized Enbrel in the nonclinical program and the clinical efficacy and safety study for the development of GP2015” , which is reviewed together with the analytical similarity data in the PDF “Biosimilarity with Reference Product.” The analytical data in the analytical bridge PDF is limited to quality attributes classified as Tier 1. For quality attributes classified as Tier 2 and 3, Sandoz refers to ‘Biosimilarity with Reference Product’ . No distinction was made between the US-licensed Enbrel and EU-approved Enbrel for statistical analysis and an information request asked for clarification. However, Tables 7-1 and 7-2 at the end of the “Biosimilarity with Reference Product” PDF list the results for all lots and are divided into GP2015 DP and DS results followed by EU-approved Enbrel and US-licensed Enbrel lots. For our purposes, we analyzed the results from EU-approved Enbrel and US-licensed Enbrel lots separately.

Justification for the use of EU-authorized Enbrel in the nonclinical program and the clinical efficacy and safety study for the development of GP2015

Analytical bridge

EU-approved Enbrel was used as the comparator for the pivotal clinical trial GP15-302. Therefore, bridging data from analytical studies are necessary, in which GP2015, U.S.-licensed Enbrel and EU-approved Enbrel are compared. The results of these analytical studies are included in the section “Justification for the use of EU-authorized Enbrel in the nonclinical program and the clinical efficacy and safety study for the development of GP2015.”

The data for the three pairwise comparisons (GP2015-US-licensed Enbrel, GP2015-EU-approved Enbrel, and US-licensed Enbrel EU-approved Enbrel) are summarized in Tables 2-1, 2-2 and Table 2-3, not copied, although they do not include numerical data or statistical analysis. A more detailed assessment of select quality attributes is provided for the TNF- α neutralization

assay, TNF- α binding and content. In addition to the summary of the data supporting the analytical bridge, a summary of the bridging PK data is included.

Reviewer's comment: *For the analytical bridge, Sandoz included the assessment of TNF neutralization, binding and content, as they were initially assigned a Tier 1 ranking. Quality attributes assigned Tier 2 and 3 are referred to in the "Biosimilarity to Reference Product" section. The number of lots included for TNF binding is not sufficient for Tier one statistical analysis. A comment to Sandoz was included in the information request (IR#1, 11/20/15). The initial statistical analysis of the data for the TNF- α reporter gene assay show that GP2015 is not equivalent to the US-licensed Enbrel. The clinical PK bridging studies are also included in Module 5 and will be reviewed by Dr. Yunzhao Ren.*

An IR (#1) was communicated to Sandoz on 11/20/2015 that contained the following question:

We note that your statistical analysis of the three-way comparison is restricted to bioactivity, TNF- α binding, and content. Data from this limited number of analytical attributes is not sufficient to establish a robust 3-way analytical bridge (i.e., pair-wise comparisons of GP- 2015, US-licensed Enbrel, and EU-approved Enbrel) necessary to justify the relevance of data obtained using EU-approved Enbrel to support a demonstration of biosimilarity to US-licensed Enbrel. The 3-way analytical bridge should include testing of all the quality attributes assessed in the analytical similarity exercise, which are ranked and subsequently analyzed using FDA's recommended statistical approach.

In the response (12/10/2015) Sandoz agreed and supplied data from the testing of the all the quality attributes assessed in the analytical similarity exercise. The quality attributes that were assessed by Tier 1 or Tier 2 methods are listed in Table 4-1.

Table 4-1 Statistical evaluation US-licensed and EU-authorized Enbrel

Attribute	Analytical readout	Comparison EU authorized Enbrel® - US licensed Enbrel®
Disulfide bridging	Non-reducing peptide mapping	Ranges highly overlapping
N-glycosylation	NP-HPLC	Non-fucosylation: ≥ 90% of Enbrel/EU within quality range of Enbrel/US Alpha-galactosylation: ranges highly overlapping; Enbrel/EU slightly outside; smaller sample size of Enbrel/US Terminal GlcNAc variants: ranges highly overlapping; Enbrel/EU slightly outside; smaller sample size of Enbrel/US
Oxidation	RP-HPLC, Peptide Mapping	≥ 90% of Enbrel/EU within quality range of Enbrel/US
Deamidation	Reducing Peptide Mapping	≥ 90% of Enbrel/EU within quality range of Enbrel/US
Overall sialylation	DMB-labeling (NANA, NGNA)	≥ 90% of Enbrel/EU within quality range of Enbrel/US
Sialylation N-glycans	WAX (0S, 1S, 2S)	≥ 90% of Enbrel/EU within quality range of Enbrel/US
Content	UV/Vis spectroscopy	86% of Enbrel/EU within quality range of Enbrel/US; also 1 US/Enbrel data points exceeds the upper limit of the quality range, but max values are comparable
TNF-alpha neutralization	TNF-alpha reporter gene assay	Ranges highly overlapping; Enbrel/EU outside with only 5 data points; smaller data basis for Enbrel/US (see also Section 2.2)
TNF-beta neutralization	TNF-beta reporter gene assay	Ranges highly overlapping; Enbrel/EU outside with only 1 data point; limited sample size
TNF-alpha binding	Surface plasmon resonance	Ranges overlapping; only very limited sample size (see also Section 2.1)
CDC	Cell based CDC assay	87% of Enbrel/EU within quality range of Enbrel/US; not mode of action

S.4.1.1 Primary Structure

Protein sequence: The primary structure of US-licensed Enbrel and GP2015 was determined by peptide mapping using a combination of limited proteolysis and mass spectrometry (ms/ms). Limited proteolysis involved the use of multiple enzymes (chymotrypsin, trypsin/chymotrypsin, trypsin, and AspN/GluC) in order to achieve 100% coverage. The results are consistent with US-licensed Enbrel and GP2015 having the same primary sequence. The MS/MS fragment ion coverage for GP2015 (GP2015.02REF) and US-licensed Enbrel (lot 1035224) are shown in Figures 4-4 and 4-7 of the submission, not copied.

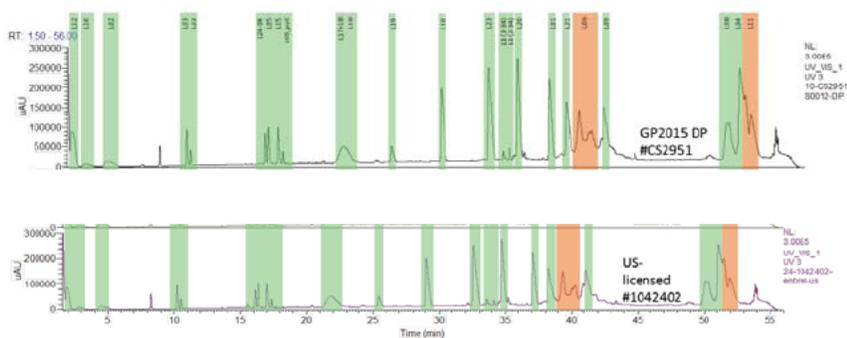
Reducing peptide mapping: The method was used to both confirm identity and to establish the heterogeneity of the amino and carboxyl termini. Deviations from the theoretical masses of the

cleaved peptides are given in Table 4-3, not copied, for mass data. Overlays of chromatograms for six lots of the GP2015 drug substance and eight lots of GP2015 drug product along with three lots of the US-licensed and EU-approved Enbrel are provided and representative chromatograms from Table 4-4 are shown below. Both MS and UV detection are used to obtain semi-quantitative data concerning the relative levels of the variants present in the sample and this is shown in Table 4-5, not copied.

Reviewer Comment: Table 4-4 should be classified as a Figure rather than a Table as it contains chromatograms.

Variants L1 (1-34), L1(2-34) and L1 (3-34) appear to correlate with the age of the material, where higher amounts of L1(134) are present in older lots. Data from an analysis of EU-approved Enbrel and US-licensed Enbrel, Figure 4-8, not copied, show the relationship between the age of the lot and N-terminal clipping, with an increase in clipped species over the shelf-life of the EU-approved Enbrel.

Representative images of chromatograms excerpted from the Table 4-4:



Reviewer Comment: There are no significant differences between the chromatograms derived from US-licensed Enbrel, EU-approved Enbrel and GP2015 among the lots included in the analysis. This provides evidence for analytical similarity between GP2015, US-licensed Enbrel and EU-approved Enbrel.

C-terminal variants that occur as a result of clipping are predominantly L24-1K and L24-prolineamide, and there is no relationship with respect to the age of the sample. There are comparatively more C-terminal variants present in US-licensed Enbrel and EU-approved Enbrel lots compared to the GP2015 lots that were analyzed.

Reviewer Comment: The data in Figure 4-8, not copied, show a correlation between age and the % N-terminal variant, which is evident for EU-approved Enbrel. However, the trend is not evident for the US-licensed Enbrel, which is likely due to differences in the ages of the lots. The US-licensed Enbrel lots are more recent and don't span as broad a range of expiration dates. N-terminus – degradation products. The formation of diketopiperazine variants occur as a result of a chemical degradation reaction when proline is present as the second amino acid from the

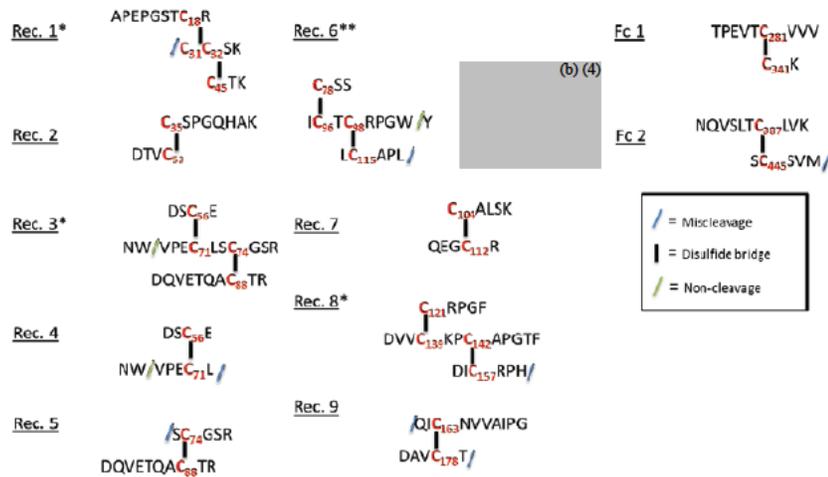
amino terminus. The degradation product has a molecular weight of 210 Da and is quantified using LC-ESI-MS. Sandoz contends that the levels of diketopiperazine present in a sample reflect the age of the protein, as two GP2015 drug product lots (CS2951 and DR0917) have higher values, 1.92% and 1.04%, respectively, and are closer to the expiry date relative to other GP2015 drug product lots tested. Diketopiperazine levels in the GP2015 drug substance lots (<LOQ to 0.06%) are lower than observed in the GP2015 drug products lots (0.31 – 1.92%) and the US-licensed Enbrel (0.76 – 1.29%) and EU-approved Enbrel lots (0.64 – 1.27%).

Reviewer Comment: Sandoz indicated that the levels of diketopiperazine present are reflective of the age of the sample. This is supported by the values obtained for GP2015 drug product lots CS2951 and DR0917, which have higher values than the other DP lots that were manufactured more recently. The values obtained for US-licensed Enbrel are consistent with the older GP2015 DP lots having higher levels of diketopiperazine as well. However, the same trends are not apparent for the GP2105 drug substance lots, but this may be due to storage at ^{(b) (4)}C where degradation is typically minimal compared to storage at 2-8°C. The assay was classified as Tier 3 and this is appropriate.

Disulfide bridging: A comparative analysis of the arrangement of disulfide bonds was undertaken using non-reducing peptide mapping. Three proteases (AspN, chymotrypsin and trypsin) were used for the digestion in combination with reverse phase HPLC and mass spectrometry to identify disulfide bonds. There are twenty nine disulfide bonds present (13 intra-chain and 3 inter-chain) and data from the analysis identified four extraneous disulfide bonds could be (C18-C74, C78-C88, C54-71; Figures 4-12 and 4-13)

Table 4-7, not copied, lists the 11 correctly bridged disulfide bonds and four extraneous disulfide bonds for GP2015 DS and DP lots and three lots each of EU-approved Enbrel and US-licensed Enbrel. The correctly folded and extraneous disulfide bonds are present in all of the test articles. One of the extraneous disulfide bonds, C78-C88, impacts the potency of etanercept. C78-C88 is contained in peptide T7. Table 4-8, not copied, shows the quantitative analysis of the levels of T7 variant present in the test articles. The levels of the T7 variant present in GP2015 drug substance and drug product lots (1.1- 1.4%) are lower than in the EU-approved Enbrel and US-licensed Enbrel (2.5-2.8%).

Figure 4-12 Structural representation of the correct GP2015 disulfide bridge Structures



Amino acids are indicated by single letter code. "Rec" indicates disulfide bridge structures that occur in the receptor region of GP2015. "Fc" indicates disulfide bridge structures that occur in the Fc region of GP2015. A number of structures contained miss-cleavages and non-cleaves as indicated in the legend. "*" indicates structures that cannot be unequivocally verified due to the presence of more than one disulfide bridge. "**" indicates two isoforms detected.

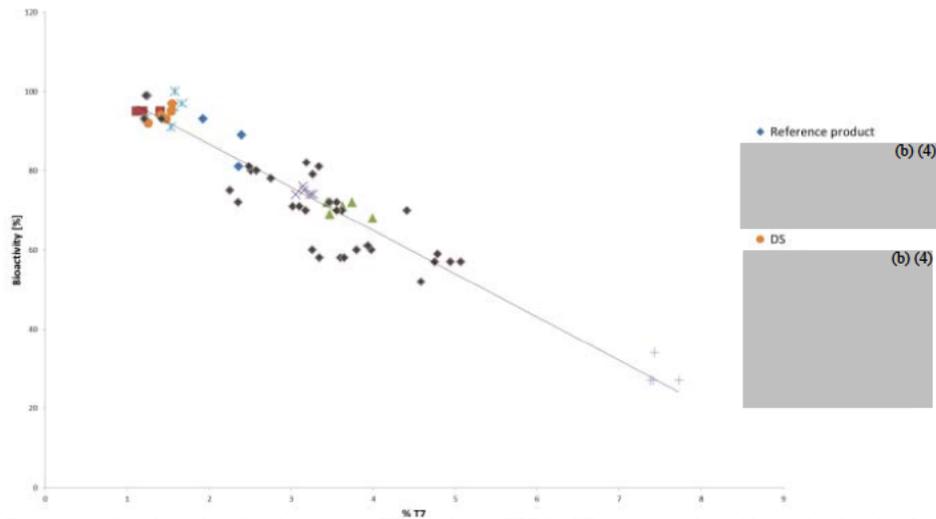
Figure 4-13 Structural representation of identified extraneous GP2015 disulfide bridge structures in the receptor region



Amino acids are indicated by single letter code. "Ex" indicates "extraneous" disulfide bridge structures that were not observed using X-ray crystallography. A number of structures contained miss-cleavages and non-cleaves as indicated in the legend.

Figure 4-15 shows a correlation between the levels of the T7 erroneous disulfide bond (C78-C88) and the negative impact this has on potency. Drug substance batches and samples from process intermediates were analyzed and peptide T7 quantitated using an internal peptide standard by HPLC UV/Vis detection

Figure 4-15 Correlation of wrongly bridged T7 with TNF-alpha RGA

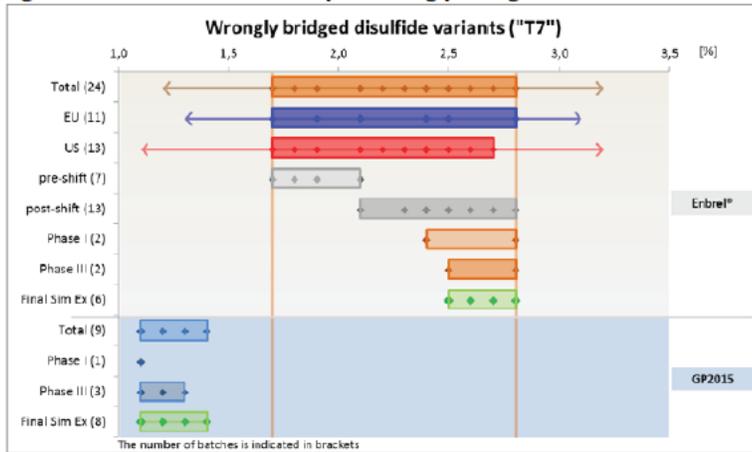


Representative data showing the percent T7 relative to T27 in different samples with varying levels of bioactivity ranging from approximately 20% to 95%. In addition to US-licensed Enbrel® and EU authorized Enbrel® (=“reference product” in figure legend) and GP2015 in-house reference material different IPC and development samples were analyzed.

Reviewer Comment: *The relationship between the T7 peptide levels and potency as assessed by the TNF- α RGA assay discussed greater detail in the functional characterization section. The lots analyzed differ in the levels of T7 peptide present and this shows the impact on potency as determined using the TNF- α RGA assay.*

A statistical analysis of the wrongly bridged disulfide bond variant T7 present in the GP2015 drug product was performed against the EU-approved Enbrel and US-licensed Enbrel. Given the importance of the attribute this was assigned to Tier 2 and the results are presented in Figure 4-16.

Figure 4-16 Schematic summary of wrongly bridged variants ("T7")



Brown horizontal arrows: Quality range (mean ± 3 SD) for the overall Enbrel® range; blue horizontal arrows: Quality range (mean ± 3 SD) for EU-authorized Enbrel® batches; red horizontal arrows: Quality range (mean ± 3 SD) for US-licensed Enbrel® batches; brown vertical lines: min-max range for the overall Enbrel® range

Reviewer Comment: Data are presented that show the impact of one of the extraneous disulfide bonds on the potency of etanercept. No information was provided regarding whether the three other extraneous disulfide bonds have an impact on the potency. An information request was sent (IR#3) and the response is discussed below.

This quality attribute has been assigned a Tier 2 status, as it was assigned high criticality and risk scores. The analytical data show that there are differences between GP2015 and US-licensed Enbrel in levels of the T7 peptide. However, these differences are acceptable based on the explanations provided in the submission and subsequent responses to the IRs regarding the assay and assessment of potency. Additional information is provided regarding the impact of the T7 levels on potency in the discussion of the TNF-potency results.

	GP2015	US-ENBREL	EU-ENBREL
mean (no. lots)	1.21(9)	2.5 (13)	2.21 (11)
range (+/- 3SD)	1.05 – 1.37	1.07-3.24	1.28-3.14

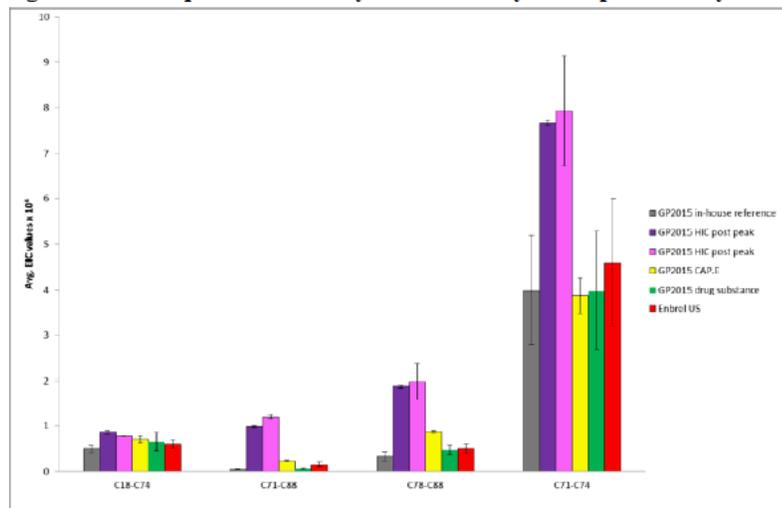
Table prepared by reviewer

An IR (#3) was communicated to Sandoz on 2/26/2016 that contained the following question:

You provided data showing the presence of the T7 peptide in the HIC post-^(b)₍₄₎ fraction peaks and, indirectly, the potency of the fractions. However, the Cys78-Cys88 disulfide bond (T7 peptide) is only one of four aberrant disulfide bonds that were identified in lots of GP2015 and US-licensed Enbrel. You did not provide data showing the impact of the other three aberrant disulfide bonds on potency or their levels relative to T7. In order to more fully understand the biological activity of the HIC post-peak, we recommend that you assess the post-peak fraction in the potency and binding assays.

In the response (3/10/2015), Sandoz provided the following information:

-  ^(b)₍₄₎
- The relationship between the RPC post-peak and potency was addressed in the response to IR # 2, see RPC. Samples of GP2015 and GP2015 process intermediates were used to demonstrate to the relationship between potency and levels of the T7 peptide (C78-C88). This included:
 - GP2015 HIC post-peak (high T7 level / low TNF-alpha RGA activity)
 - GP2015 CAP.E (medium T7 level / medium TNF-alpha RGA activity)
 - GP2015 DS (low T7 level / high TNF-alpha RGA activity)
- The same approach was used to show the relationship between potency and the three other WBV (C18-C^(b)₍₄₎, C71-C88, C71-C74). It was noted that the due to limitations of the method, the data could be used to examine relationships between the different samples, but not to compare to other WBVs.

Figure 1-2 Semi-quantitative analysis of WBVs by mass spectrometry

EIC: extracted ion chromatogram. The standard deviation (indicated by the black error bars) was calculated based on duplicate analysis. Two samples of HIC post-peak were analyzed which were derived from two different GP2015 batches.

The data in Figure 1-2 show that the relationship between the three other WBV's and the high, medium and low potency is maintained except for C71-C74 CAP.E. Additional evidence was provided graphically showing the correlation of the WBV C78-C88 (T7) with C71-C88 (MS data) with $R=0.97$ in Figure 1-3, not copied. C78-C88 (T7) with C71-C74 (MS data) with $R=0.907$ in Figure 1-4, not copied. Finally, C78-C88 (T7) with C18-C74 (MS data) with $R=0.798$ in Figure 1-5, not copied. This response is acceptable and demonstrates that the T7 peptide is representative of the correlation between WBVs and potency.

Free Cysteines: The presence of free cysteines was investigated using Ellman's reagent (DTNB) which reacts with free cysteines to generate a chromophore. The presence of free cysteines can be quantitatively measured by UV/VIS absorption. The reaction scheme is shown in Figure 4-17, not copied in review. Sandoz assigned this attribute Tier 3 status (low criticality) and the results show that GP2015 drug substance (0.13 to 0.17 mol free cysteine) and drug product (0.08 – 0.16) have slightly lower levels of free cysteines compared to the EU-approved and US licensed Enbrel (0.2 – 0.23 moles of free cysteine).

Reviewer Comment: Both GP2015 DS and DP were included in this analysis, which is not consistent with rationale provided for the disulfide bridging analysis, where Sandoz stated that both drug substance and drug product lots should not be included, so as to avoid duplication. While Sandoz should be consistent in their approach to determining which lots should be used in their analysis, this is not a concern for the overall demonstration of analytical similarity because 8 GP2015 DP lots were assessed and DS and DP data were not used in a statistical analysis.

Amino Acid Analysis: Amino acid analysis was carried out on single lots of US-licensed Enbrel and GP2015. Sandoz states that there is inherent variability in the method and the presence of glycans may impact serine and threonine levels. Table 4-10 lists the individual amino acids along with the theoretical value as a ratio. The results of the amino acid analysis were used to generate an extinction coefficient, which was then used to compare the values obtained for protein content, shown in Table 4-11.

Table 4-10 Amino acid ratio for GP2015 and Enbrel®

Amino acid	Theoretical ratio	GP2015 #VB25B3	Enbrel® #1035224
Asx	70	72.9	71.6
Thr	84	78.1	78.7
Ser	94	77.1	78.9
Glx	98	95.9	95.9
Ile	16	15.6	15.9
Pro	98	101.7	106.1
Gly	48	48.7	48.8
Ala	48	46.3	46.6
Val	72	69.5	69.8
Cys	58	47.5	40.5
Met	14	11.9	9.7
Leu	54	53.7	54.2
Tyr	28	24.3	24.5
Phe	24	23.9	23.7
His	22	23.3	23.6

Table 4-11 Experimentally determined content for GP2015 and Enbrel®

Batch	Content ($\epsilon = 1.15 \text{ cm}^2 \text{ mg}^{-1}$) [mg/mL]	Content according to AAA [mg/mL]	Deviation [%]
GP2015 #VB25B3	50.7	56.59	11.6%
US-licensed Enbrel® #1035224	49.2	56.73	15.3%

Reviewer Comment: The values obtained for cysteine, methionine, threonine, serine and tyrosine are lower than the theoretical values while proline is higher. This is consistent with the variability of the method. Cysteine and methionine levels differ between the GP2015 and US-licensed Enbrel, which may be also be due to variability inherent with the method.

An IR (#1) was communicated to Sandoz on 11/20/2015 that contained the following comment:

Section 4.1.1.7 describes amino acid analysis studies. An experimentally determined extinction coefficient was calculated using data from amino acid analysis of a single lot each of US-licensed Enbrel and GP2015. Provide a justification for the experimental method used to determine the extinction coefficient, and the approach that was used for calculating the experimental extinction coefficient.

In the response (12/10/2015) Sandoz indicated that for the final analytical similarity assessment, amino acid analysis was used as an additional analytical method for content confirmation

between GP2015 and Enbrel (US or EU not specified). This method is independent of the labeled content of Enbrel. Sandoz argues that in order to match content of US-licensed Enbrel, an analytical method independent of the labeled content is not well suited for experimental determination of the extinction coefficient. By using a method different from the reference product manufacturer, it is possible that an extinction coefficient which is significantly different to that used by the reference product manufacturer may be obtained. Data from the amino acid analysis will not be used to determine the extinction coefficient and therefore the data will not be used for the assessment of biosimilarity.

Ideally, a biosimilar sponsor will determine the theoretical extinction coefficient of the reference product and confirm this value experimentally for the proposed biosimilar product and the reference product. However, Sandoz's approach and response is acceptable.

4.1.2 Higher Order Structure.

CD Spectroscopy: An analysis of the test articles using circular dichroism is presented where spectra from the far UV region (190-250nm) are sensitive to changes in the secondary structure. Spectra in the near UV region (250-350nm) are sensitive to changes in the tertiary structure of the protein. Analysis was performed on five GP2015 drug substance lots and the spectra are shown in Figures 4-19 (far-UV) and 4-21 (near-UV) not copied. Overlays of the spectra of eight lots of the GP2105 drug product and three lots each of US-licensed Enbrel and EU-approved are shown in Figures 4-20 (far-UV) and 4-22 (near-UV), not copied. This is confirmed with the data provided in Table 4-12, not copied, which lists the peak minima and maxima for the near UV spectra. Overall, spectra in the near and far UV region do not show substantial differences among lots.

Differential Scanning Calorimetry: This method was used to assess the unfolding of the test articles. Representative peak maxima, melting temperatures and thermal profiles of six lots GP2015 drug substance lots are shown in Figure 4-23, not copied. Table 4-13 and Figure 4-24, not copied, show Tm1 and Tm2 for the six lots GP2015 drug substance, eight lots of GP2015 drug product and three lots each of US-licensed and EU-approved Enbrel. The results show that the test articles have similar thermal profiles.

Hydrogen/deuterium exchange and Mass Spectrometry (HDMS): HDMS was used to compare the protein structure and dynamics. Amide hydrogens that are present as part of the protein backbone exchange protons with the solvent. Deuterium is added to the solution and the rate of exchange is dependent on solvent exposure and in turn, reflects the local structural environment. After the exchange reaction is stopped by changing to an acidic environment at 0°C, pepsin digestion is followed by RP-HPLC analysis using mass spectrometry. One lot GP2015 drug product (#VB25B3) and one lot of US-licensed Enbrel (1035224) were analyzed. Sequence coverage for cleavage with pepsin was 80.5% and the presence of O- and N-linked glycans, along with disulfide bonds, contributed to the complexity of the analysis.

Figure 4-27 shows the heat map comparing GP2015 DP with US-licensed Enbrel. The darker colors indicate a higher rate of exchange and therefore, a more dynamic region of the protein. Difference plots of GP2015 versus US-licensed Enbrel, Figure 4-29, not copied, show no significant differences between the GP2015 and the US-licensed Enbrel.

Figure 4-27 Heat map of hydrogen / deuterium exchange experiment of GP2015 (top) and Enbrel® (bottom)



heat maps of GP2015 (DP #VB25B3) (top of colored row set) as well as US-licensed Enbrel®(#1035224) (bottom of colored row set). The sets of colored rows indicate different incubation times starting from 0 seconds up to 240 min. Darker colors indicate higher exchange.

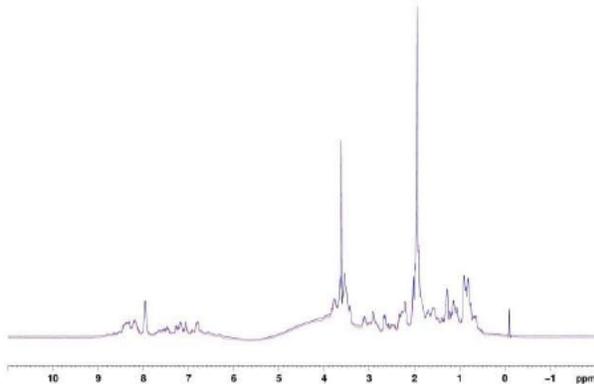
Fourier-transform Infrared Spectroscopy (FTIR): Analysis using FTIR provides information about the secondary structure of a protein, where infrared radiation is absorbed and the resulting spectrum yields a characteristic 'fingerprint'. There are characteristic bands present in the spectrum which includes Amide I (1720-1600cm-1) and Amide II (1600-1480cm-1), which are sensitive to changes in the secondary structure and conformation. It was noted that this method is sensitive to changes in the buffer composition, and as a consequence, the buffer was exchanged prior to sample analysis. Overlays of the FT-IR spectra for eight lots of GP2015 drug product and three lots each of EU-approved Enbrel and US-licensed Enbrel are shown in Figure 4-30, not copied. There are no differences evident in the overlay of the spectra and similarly, overlays of the zoomed in 2nd derivative spectra shown in Figure 4-33, not copied, show no significant differences. Table 4-14 shows the peak positions of amide I and amide II signals for each of the lots.

Table 4-14 Peak positions of amide I and amide II signals

	Batch	Peak amide I [cm ⁻¹]	Peak amide II [cm ⁻¹]
GP2015 drug product	#CS2951	1643.27	1551.28
	#DR0917	1643.25	1551.31
	#VB50B1	1643.20	1551.42
	#VB50B2	1643.21	1551.45
	#VB50B3	1643.24	1551.40
	#VB25B1	1643.22	1551.44
	#VB25B2	1643.22	1551.44
	#VB25B3	1643.23	1551.53
Enbrel [®]	#G75422	1643.11	1551.45
	#H76640	1643.05	1551.28
	#H50892	1643.02	1551.35
	#1035224	1643.21	1551.20
	#1040542	1643.18	1551.33
	#1042402	1643.14	1551.24

1D-Nuclear Magnetic Resonance Spectroscopy (NMR): This approach is generally used for determining the structure of small molecules. The complexity of large proteins precludes using 1D-NMR to determine the three dimensional structure. However, 1D-NMR can be used to obtain a structural fingerprint and these data can be used to assess the sameness of two protein samples. An overlay of a 1D ¹H NMR spectrum of GP2015 (lot #VB25B3, blue trace) and US-licensed Enbrel (lot #1035224, red trace) are similar between GP2015 and US-licensed Enbrel, Figure 4-36.

Figure 4-36 1D ¹H NMR spectrum (overlay) of GP2015 drug product #VB25B3 and Enbrel[®] #1035224



GP2015 drug product #VB25B3 (blue); US-licensed Enbrel[®] #1035224 (red)

Reviewer comment: Given there are no apparent differences between the spectra, it can be concluded that GP2015 and US-licensed Enbrel have similar higher order structure as determined by 1D-NMR.

X-ray Crystallography: Sandoz provided data showing the three dimensional structures of both US-licensed Enbrel (lot #1035224) and GP2015 drug product (lot #VB25B3). In order to facilitate crystallization and determine the structure, only the TNFR2 portion was co-crystallized with TNF- α . The molecular model was derived from X-ray data for GP2015 drug product, US-licensed Enbrel and EU-approved Enbrel. The structures were compared by determining the root mean square value (r.m.s), which provides a measure of similarity of higher order structure. There are minimal differences among the r.m.s values for GP2015, US-licensed Enbrel and EU-approved Enbrel, Table 4-15.

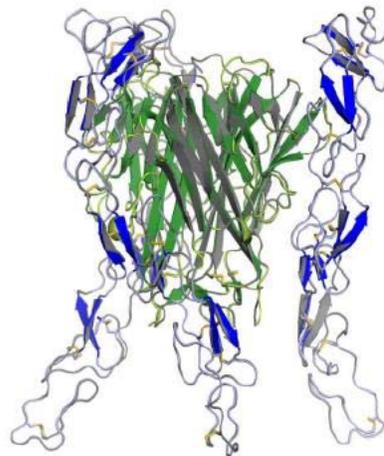
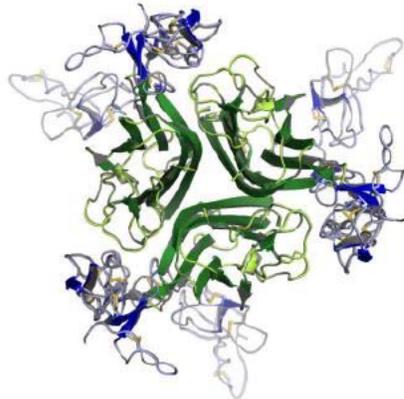
Table 4-15 Comparison of different etanercept - TNF-alpha complexes

	GP2015 DP #2G27062011	GP2015 DP #VB25B3	Enbrel® #G64164 (EU-authorized)	Enbrel® #1035224 (US-licensed)
GP2015 DP #2G27062011	0	0.31 Å	0.30 Å	0.28 Å
GP2015 DP #VB25B3	0.31 Å	0	0.27 Å	0.21 Å
Enbrel® #G64164	0.30 Å	0.27 Å	0	0.29 Å
Enbrel® #1035224	0.28 Å	0.21 Å	0.29 Å	0

The superimposed ribbon models of GP2015 (lot #VB25B3) and US-licensed Enbrel (#1035224) are shown in Figure 4-38. The GP2015 is colored blue, US-licensed Enbrel is colored grey and the TNF- α is green.

Reviewer Comment: The models show that the structures are similar. However, many details regarding basic information on the quality of the data used to generate the structural models was omitted. The report provided to Sandoz by the CTO that performed this study was reviewed while on inspection and the relevant data demonstrating the quality of the data used to generate the models were included in the report. The information in the report was adequate to support the model. The information in the report provided sufficient detail regarding the quality of the data that was used to generate the models.

Figure 4-38 X-ray structures of GP2015 (#VB25B3) and Enbrel[®] (US-licensed; #1035224)



4.1.3 Molecular Mass/Molecular size

MALDI-ToF: The intact mass measurement of the test articles was carried out using MALDI-ToF, including intact etanercept, desialylated etanercept, etanercept without N-glycans and, desialylated etanercept without the N-glycans. The molecular mass determinations for six lots of GP2015 drug substance, eight lots of drug product, along with three lots each of US-licensed Enbrel and EU-approved Enbrel are similar, Table 4-16, not copied. The intact mass among all lots ranged from 124095 Da up to 124634 Da. Similar or narrower ranges were seen in the molecular masses for the desialylated and deglycosylated products.

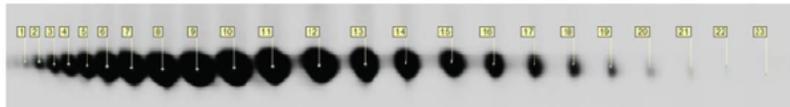
MALDI-ToF was also used to determine the number of O-linked glycans present on each molecule. The average mass of the O-glycan core 1 structure is 385.2 g/mol, which is used to determine the number of O-linked glycans where the mass of etanercept without N- and O-linked glycans is 102,418 Da. The results of this analysis show that all of the lots of GP2015 drug substance and drug product, US-licensed Enbrel and EU-approved Enbrel were found to contain 18 O-linked glycans, Table 4-17, not copied.

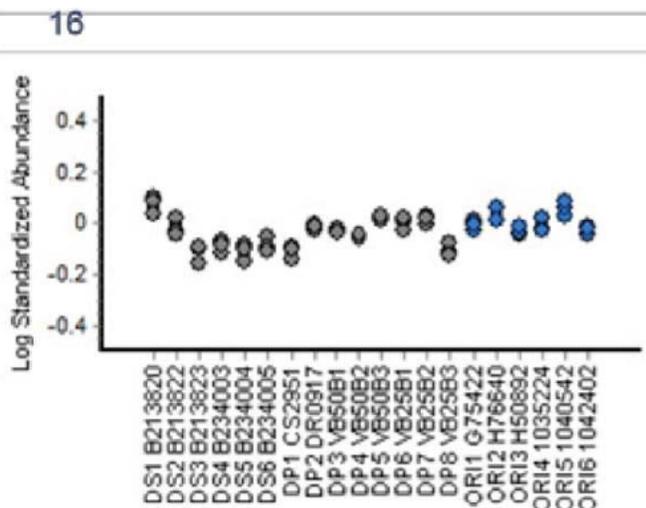
Reviewer comment: Based on the data provided it can be concluded that GP2015 has the same number of O-linked glycans. These data are supportive of a finding that GP2015 is highly similar to US-licensed Enbrel.

4.1.4 Charge

2D-Gel Electrophoresis (2D-DIGE): GP2015 drug substance and drug product lots were analyzed and compared to US-licensed Enbrel and EU-approved Enbrel using 2D-DIGE. After separation in two dimensions, the images of the individual lots were quantitated using the numbering system shown in Figure 4-44 (only the 2D_DIGE spots are shown along with data for spot #16). A relative quantitative analysis of the individual lots is given for each spot (Figure 4-44, not copied). Acidic variants (spots 1-4) are present at relatively lower levels in GP2015 compared to US-licensed and EU-approved Enbrel. This may be due to different levels of sialylated N-glycans or, alternatively, higher levels of C-terminal lysine variants in the US-licensed Enbrel. There are no significant differences in the relative abundances among GP2015, US-licensed Enbrel 1 and EU-approved lots in the major high abundance variants (spots 6-12). The spots in the basic region with lower abundance (18-21) are present at higher levels in US-licensed and EU-approved Enbrel lots compared to GP2015.

Figure 4-44 Relative quantitative analysis of main variants separated by 2D-DIGE





Reviewer Comment: There are differences in the levels of the acidic and basic variants GP2015 compared to US-licensed Enbrel samples. The explanation is that US-licensed Enbrel has a higher level of C-terminal lysine variants. This explanation is reasonable as levels of basic variants do appear to differ between the EU-approved Enbrel and the US-licensed Enbrel. There are also differences between GP2015 and US-licensed Enbrel and EU-approved Enbrel in levels of sialylated N-glycans, which can explain differences in acidic variants.

4.1.5 Heterogeneity Glycosylation

Enbrel is a complex glycoprotein containing both O- and N-linked glycans. There are multiple O-linked glycosylation sites in the TNFR region that occur between Thr179 and Ser239. The TNFR region has two N-glycans in addition to the N-linked glycan present in the Fc region.

O-glycosylation: The identity of the O-linked glycan sites and the occupancy was assessed using two different analytical approaches. The site occupancy was assessed using LC-ESI-MS following a tryptic digest and separation. Using this approach, it is not possible to unambiguously assign an O-linked glycan to specific threonine or serine residue. Instead, data are interpreted in the context being able to determine possible combinations of variants on specific peptides, which may contain zero, one or more O-glycans depending on the serine and threonine residues in that peptide. There are twenty-eight possible O-glycosylation sites Table 4-18, not copied. Overall, GP2015 drug substance and drug product lots were analytically similar to the US-licensed Enbrel and EU-approved Enbrel lots. The same O-linked glycans are present in GP2015 drug substance and drug product, US-licensed Enbrel and EU-approved Enbrel, Table 4-19.

Table 4-19 Identified O-Glycans in the analyzed samples

Structure O-glycan	#BZ1 3820	#BZ1 3822	#BZ1 3823	#BZ3-4003	#BZ3-4004	#BZ3-4006	#CS2851	#DR0917	#VB50B1	#VB50B2	#VB50B3	#VB25B1	#VB25B2	#VB25B3	#GT5422	#H76640	#H50892	#1035224	#1040542	#1042402
	Drug substance						Drug product						Enbrel®							
C1+1N	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
C1+1S	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
C1+1G	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
C1+2N	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
C1+1N+1G	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
C1+2S	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
C1+1S+1G	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
C1+2G	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

- ◆ NANA
- ◆ NGNA
- ◇ Neuraminic acid

N = Neuraminic Acid
 S = NANA = N-Acetylneuraminic Acid
 G = NGNA = N-Glycolylneuraminic Acid
 C1 = O-glycan core type 1
 Hex = Hexose

Reviewer Comment: In general, O-glycans are not as amenable to analysis N-glycans. Collectively, the data provide information on the similarity of the O-linked glycans. Recently published data regarding the analysis of O-linked glycans associated with etanercept found there are 12 O-linked-glycan sites. The majority of etanercept O-glycans are core 1 type and are capped with a 2-3 linked sialic acid (Houel, S.; et al, 86, 576-584 Analytical Chemistry). Another study estimated that there are 10 O-linked glycans (DiPaola, M. et al, 5, 180-186, 2013). However, Sandoz’s approach is adequate and demonstrates that the GP2015 O-glycosylation is similar to US-licensed Enbrel and EU-approved Enbrel.

N-glycosylation: Qualitative analysis: There are two N-linked glycosylation sites in the receptor portion of the molecule, at Asn149 and Asn171, along with the glycosylation site that is present in the Fc region, Asn317. Qualitative analysis of the N-linked glycans used a standard approach that involves release, separation of 2AB labelled glycans and detection using NP-HPLC-MS. The structures and mass of the N-glycans identified in GP2015, US-licensed Enbrel and EU-approved Enbrel are listed in Table 4-20 and Table 4-21, respectively, not copied in review. US-licensed and EU-approved Enbrel contain a glycan species (bG1-N-F) that was not detected in GP2015 DS lots, while GP2015 contains tNG3 and tNG4, which are not present in US-licensed and EU-approved Enbrel.

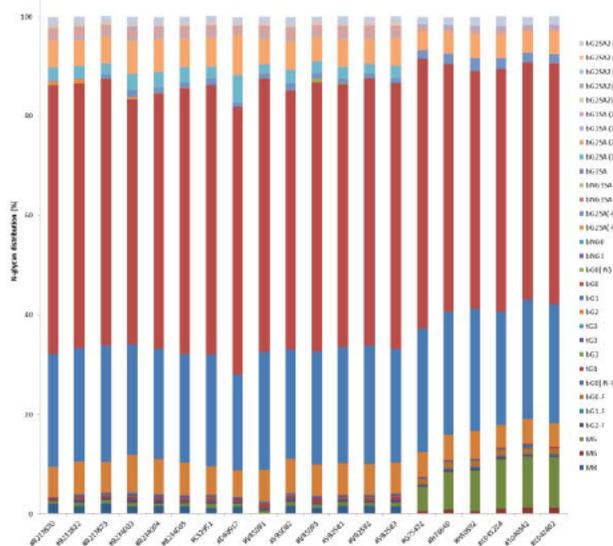
Reviewer Comment: The glycans that are unique to either GP2015 or US-licensed and EU-approved Enbrel are present at low levels that are not quantifiable and in addition, they are not known to be functionally important or present a risk in terms immunogenicity.

Quantitative Analysis: The outline of the analytical approach for the quantitative analysis of N-linked glycans on the TNFR and Fc portion of etanercept is shown in Figure 4-47, not copied and the of totals of each species are presented Table 4-22, not copied. Data of the N-glycans derived from the Fc portion are presented in Table 4-23 and the receptor portion in Table 4-24, not copied.

The analysis of the overall N-glycan distribution indicates that there are higher levels of mannose-5 and bG2-F present in the US-licensed and EU-approved Enbrel lots compared with GP2015 lots. In contrast, levels of the bG2 glycan are lower in the US-licensed and EU-approved Enbrel lots compared with the GP2015 lots with bG2 (GP2015 DP 41.4-44.1%; EU/US Enbrel 32.5-34.4%) and an isomer of bG2-F (GP2015 DP 8.8-10%; EU/US Enbrel 18.5-20.41%).

The analysis of the Fc region N-glycans shows relatively minor differences in the more abundant glycans, such as bG1 and bG0, Figure 4-49 There are higher levels of mannose 5 present in US-licensed and EU-approved Enbrel (1-10.1%) compared GP2015 DP (0.6-0.9%), while there are slightly higher levels of a less abundant glycans in GP2015 DP, including mannose 8 (1.1-1.6%), and bG2SA (2.1-5.5%), that are present at <0.1% in US-licensed and EU-approved Enbrel. There are slightly higher levels of the bG2SA structural isomer in GP2015 (5-8.2%) compared to US-licensed and EU-approved Enbrel lots (3.9-4.8%).

Figure 4-49 Comparison of N-glycan distributions on the Fc-parts of the molecule

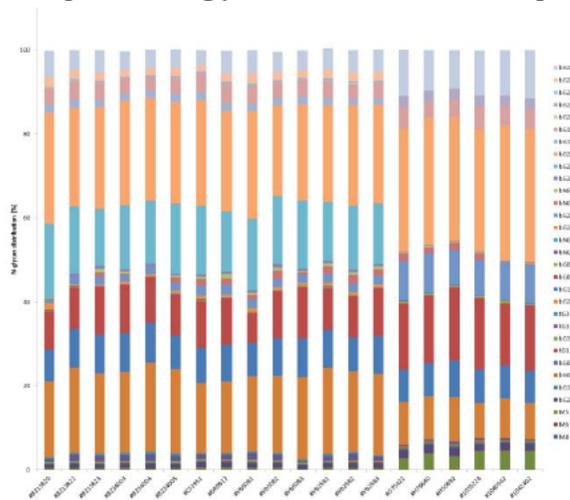


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Reviewer Comment: The differences in the levels of afucosylated glycans between GP2015 DP and US-licensed Enbrel and EU-approved Enbrel have implications for FcRγIII binding and ADCC. This is discussed in detail below in the relevant sections

The TNFR2 N-glycans are more variable between GP2015 and US- licensed and EU-approved Enbrel, Figure 4-50. The GP2015 lots contain significantly higher levels of two bG2SA isomers (14.0 – 17.0% and 1.4 – 1.8%) that are not present in the US-licensed and EU-approved Enbrel lots (<0.1%), while two additional bG2SA isomers are more similar among the lots (21.8 – 25.7% for GP2015 vs 29.3 – 31.1% for US-licensed and EU-approved Enbrel and 3.5 – 4.5% for GP2015 vs 4.0 – 5.4% for US-licensed and EU-approved Enbrel). There are also higher levels of bG2 in GP2015 (16.6 - 20.5% compared to US-licensed and EU-approved Enbrel lots (8.3 – 10.2%).

Figure 4-50 Comparison of N-glycan distributions on the Receptor-parts of the molecule



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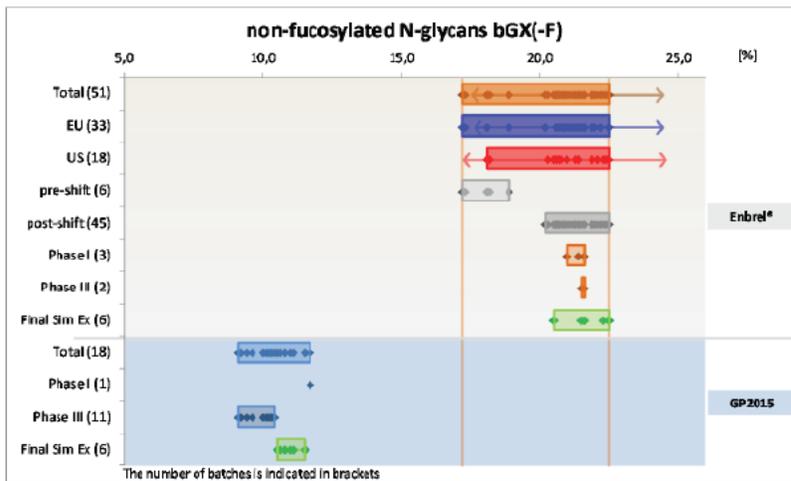
Reviewer Comment: The composition of the two N-linked glycans on the TNFR2 portion of the molecules differs between GP2015, US-licensed Enbrel and EU-approved Enbrel. This includes increased amounts of bG2 and isomers of bG2SA on GP2015 compared to US-licensed Enbrel and EU-approved Enbrel. There are relatively lower amounts of Mannose-5 present in GP2015 (GP2015 DP 0.2-0.6) compared to US-licensed Enbrel and EU-approved Enbrel (EU/US Enbrel 2.8-4.6%). There are relatively lower levels of bG0 present in GP2015 (GP2015 DP 7.2-12.2%) compared to EU-approved Enbrel and US-licensed Enbrel (EU/US Enbrel 14.9-17.4%)

Sandoz contends that as the glycans are not located near the TNFR2 binding site, they are unlikely to influence binding, see Figure 4-52 for X-ray structure, not copied). The absence of a significant difference in TNF-α binding is used to support this reasoning. However, as the receptor glycans are exposed, the impact of changes in glycan composition should be considered as changes may in turn impact the PK due to changes in clearance relative to the relative to the

US-licensed Enbrel. Changes in the degree of sialylation can impact the clearance. (Liu L., et al., 30 803-812, 2013 Pharm Res). However, the criteria for PK similarity were met, therefore, the impact of differences in high mannose and sialylated forms appears minimal. Overall, these differences in glycan structures are acceptable.

Statistical Evaluation of Glycans: Selected N-glycans were subjected to statistical evaluation using only GP2015 drug substance lots (GP2015 drug products lots were not included in the analysis). Non-fucosylated glycans were assessed as a Tier 2 quality attribute. The following N-glycans were included in the calculation of total non-fucosylated glycans, bGX(-F) = sum of bG0(-F), bG1(-F), bG1(-F), bG2(-F), [bG2(-F)+alpha Gal]. The relative abundances of the non-fucosylated N-glycans are shown in Figure 4-55. Based on the statistical analysis, it is evident that there is a significant difference in the levels of non-fucosylated N-glycans on the total protein in GP2015 drug substance lots compared the US-licensed and EU-approved Enbrel.

Figure 4-55 Relative abundances of non-fucosylated N-glycans for GP2015 drug substance and Enbrel



	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (lots)	11.04 (8)	20.90 (17)	20.89(33)
range (+/- 3SD)	9.52-12.56	17.1-24.70	17-22.5

Table prepared by reviewer

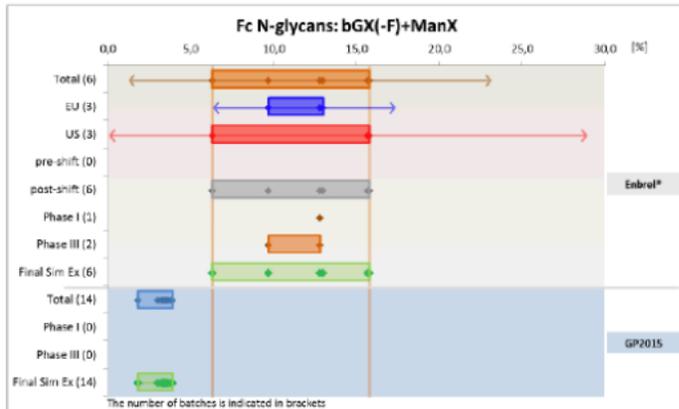
Reviewer Comment: The relative abundance of the non-fucosylated N-glycans includes the N-glycans present in both the receptor and Fc region. Only differences in the levels of non-fucosylated N-glycans on the Fc portion will have an impact on the interaction with FcγRIIIA receptor, which in turn affects ADCC. Therefore Sandoz should assess the data for the relative abundance of the non-fucosylated N-glycans that is limited to Fc N-glycan. In addition, the

calculation of the N-glycans should include all non-fucosylated N-glycans, e.g. Man5, to more accurately address the impact of the differences in N-glycan levels.

An IR (#1) was communicated to Sandoz on 11/20/2015 that contained the following question: The evaluation of non-fucosylated N-glycans did not include an assessment that was limited to the Fc region. In addition, the calculation of the non-fucosylated N-glycans does not include non-fucosylated glycans such as Man5. Differences in non-fucosylated N-glycans on the Fc-region of GP2015, US-licensed Enbrel, and EU-approved Enbrel could explain the differences in ADCC activity. Provide data separating the N-glycan structures of the Fc-region from the TNF receptor region of GP2015

In the response (12/10/2015), data were presented that showed the level of afucosylated glycans present in the Fc region was calculated by summing the following glycans Fc N-glycans bG0(-F), bG1(-F), bG2(-F), bG0(-N-F), isomers of bG2SA(-F), Man5, Man6, Man8, listed in Table 8-1, not copied. The sum of non-fucosylated glycans in GP2015 DP ranged from 1.9 – 4.3%, while the range for US-licensed and EU-approved Enbrel lots was 9.7 – 15.7%, with the largest difference in Man5. Data for the head-to-head analysis of 14 lots of GP2015 and 6 lots of US-licensed and EU-authorized Enbrel is shown in Figure 8-1 (also Figure 4-56 in updated Regional section submitted 1/29/16).

Figure 4-56 Quality range comparison for Fc-part N-glycans – bGX(-F)+ManX



Brown horizontal

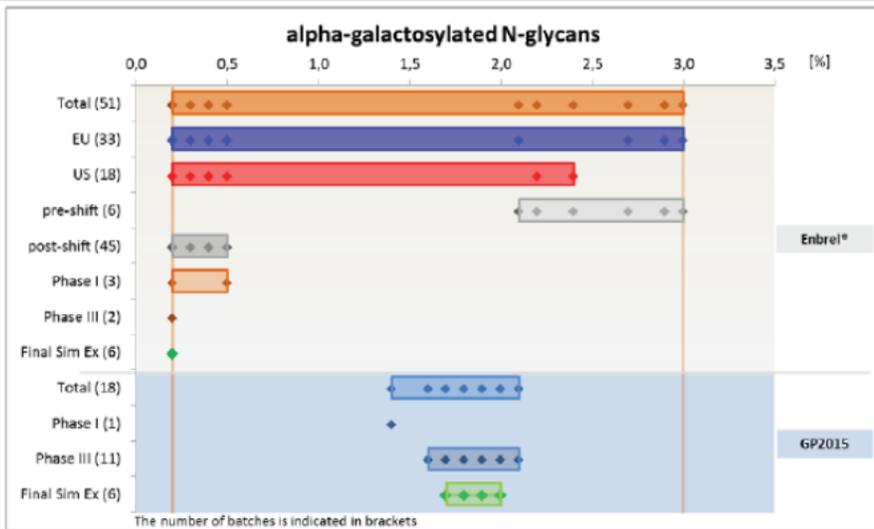
arrows: Quality range (mean ± 3 SD) for the overall Enbrel® range; blue horizontal arrows: Quality range (mean ± 3 SD) for EU-authorized Enbrel® batches; red horizontal arrows: Quality range (mean ± 3 SD) for US-licensed Enbrel® batches; brown vertical lines: min-max range for the overall Enbrel® range; bGX(-F)+ManX: sum of Fc N-glycans bG0(-F), bG1(-F), bG2(-F), bG0(-N-F), isomers of bG2SA(-F), Man5, Man6, Man8

Reviewer Comment: These data provide clearer evidence of the molecular basis for differences observed in ADCC levels between GP2015 and US-licensed and EU-approved Enbrel lots.

Alpha-galactosylated N-glycans, which are potentially immunogenic, were assessed as a Tier 2 quality attribute and assigned a high criticality score (see Table 3-9, not copied). The relative

abundance of alpha-galactosylated N-glycans is generally low ($\leq 3\%$), Figure 4-57 and the distribution in US-licensed and EU-approved Enbrel lots over the years of testing is variable, with lower levels in more recent lots. However, levels in GP2015 are inside the range of all US-licensed and EU-approved Enbrel lots.

Figure 4-57 Relative abundances of alpha-galactosylated N-glycans for GP2015 drug substance and Enbrel®



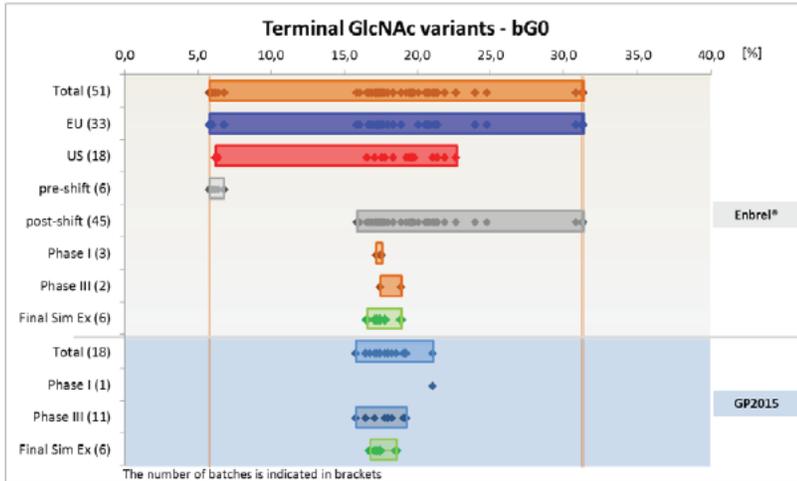
	GP2015	US-ENBREL	EU-ENBREL
mean (lots)	1.8 (18)	0.55 (18)	0.55 (33)
range (+/- 3SD)	-1.39-2.49	-1.39 - 2.49	-1.82-3.01

Table prepared by reviewer

Reviewer Comment: The relative abundances of the alpha-galactosylated N-glycans are within the range of the US-licensed Enbrel and EU-approved Enbrel.

The terminal GlcNAc variants represented by bG0 are assigned as a Tier 2 quality, Figure 4-58.

Figure 4-58 Relative abundances of terminal GlcNAc N-glycans (e.g. bG0) for GP2015 drug substance and Enbrel[®]



Reviewer Comment: Although there is a broad range for GlcNAc N-glycans in US-licensed Enbrel and EU-approved Enbrel, the levels in GP2015 are consistent and within the middle of the entire range.

	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (%) (lots)	17.8 (18)	17.9 (18)	18.1(33)
range (+/- 3SD)	14.1 – 21.7	4.3 – 31.5	0.9-35.3

Table prepared by reviewer

Glycation by boronate affinity chromatography: The relative amounts of glycosylated variants of GP2015, US-licensed Enbrel and EU-approved Enbrel were determined. The range of values obtained for US-licensed and EU-approved Enbrel (2.79-3.81%) was at least two-fold more than GP2015 drug substance and product lots (1.18-1.38%). Glycation is assigned as a Tier 3 quality attribute.

Sialic Acids: The levels of N-acetylneuraminic acid (NANA) and N-glycolylneuraminic acid (NGNA) on the terminal end of both the N- and O-linked glycans were assessed using three different analytical methods. Anion exchange chromatography of the intact molecule was used to assess sialylation by comparing the retention time relative to bovine serum albumin. The results show that GP2015 drug substance and drug product have slightly lower relative retention time (1.55-1.56 min) compared to US-licensed and EU-approved Enbrel (1.63-1.66 min). Table 4-26, not copied in review. Posttranslational modifications other than sialic acids can also impact the retention time.

Weak anion exchange chromatography: The sialylation of the N-linked glycans was assessed following digestion using PNGase F, labelling with 2-AB and chromatographic separation of mono, di- and tri-sialylated glycans. The resultant N-glycans were identified as having 0S, mono (1S) and di (2S). GP2015 DP had higher levels of 0S (61.2-63.2%) relative to US-licensed (49.1-54.5%) and EU-approved Enbrel (49.1-56.3%), and lower levels of 1S (30.5 - 32.5%) and 2S (6.1-6.6%) relative to US-licensed (1S 37.1 – 40.2%; 2S 8-10.7%) and EU-approved Enbrel (1S 36.2 – 38.6%; 7.5-10.9%), Table 4-27, not copied. The values obtained for the mol of sialic acids/mol N-glycans were slightly higher for US-licensed and EU-approved Enbrel (0.5-0.6) compared with GP2015 (0.4-0.5).

Reviewer Comment: An IR (#1) was sent to Sandoz on 11/20/2015 that contained the following question:

Table 4-27 includes a column " mol sialic acids/6 mol N-glycans" . Provide an explanation regarding the " 6 mol N glycans." Provide a rationale for including these data.

In the response (12/10/2015), Sandoz provided the following information:

There are 6 N glycosylated sites for the dimeric molecule. The average degree of sialylated N-glycans calculated per mol of etanercept is given in the following equation

$$\text{mol sialic acids/mol N - glycans} = \frac{\text{mol sialic acids/6 mol N - glycans}}{6}$$

The response is acceptable.

DMB labeling: The sialic acids are chemically released and labeled with the DMB reagent for fluorescent detection. The labeled sialic acid derivatives are separated using reverse phase chromatography. NGNA and NANA were quantitated and overall, there is little difference in the levels of NANA in US-licensed and EU-approved Enbrel (98.5%-99%) compared with GP2015 (99.2%), Table 4-28, not copied. The levels of NGNA in US-licensed and EU-approved Enbrel (0.1 – 1.5 %) were slightly higher in two lots compared to GP2015 (0.8%). Data from two additional "pre-shift" lots of EU-approved Enbrel (33469 and 35828) had higher levels of NGNA (1.2 – 1.5%) compared to remaining 6 lots (0.1%).

NGNA

	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (lots) mol/ mol GP2015	0.22 (6)	0.0 (3)	0.14 (5)
range (+/- 3SD)	0.09-0.34	0	-0.44-0.72

Table prepared by reviewer

NANA

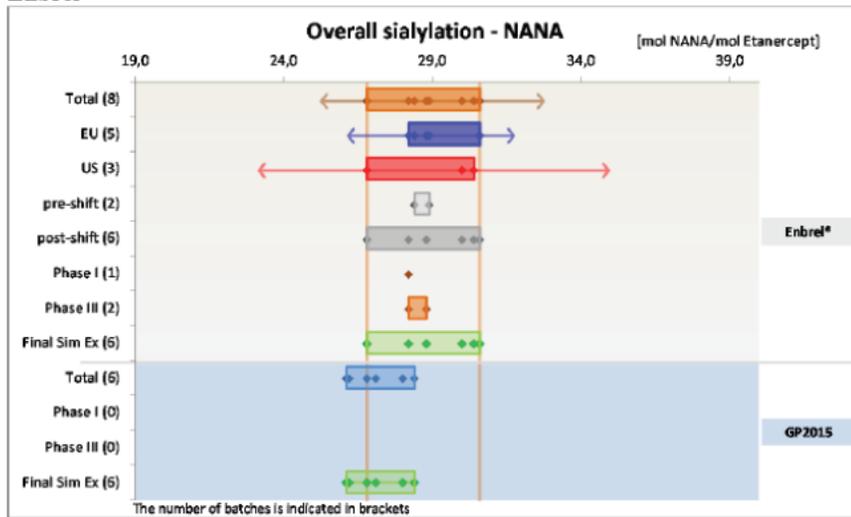
	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (lots) mol/mol GP2015	27.10 (6)	29.1 (3)	29 (5)
range (+/- 3SD)	24.3 – 29.9	23.2 - 32	26 – 31.8

Table prepared by reviewer

Reviewer Comment: NGNA is immunogenic in humans. While NGNA was detected in GP2015 lots, Sandoz showed that two of the “pre-shift” lots of EU-approved Enbrel contained levels (0.3-0.4mol/mol) which are slightly higher than those seen in GP2015. Therefore, the small difference in NGNA between GP2015 and US-licensed Enbrel and EU-approved Enbrel is unlikely to be meaningful.

A statistical evaluation of total non-sialylated N-glycans (0S, as well as, 1S and 2S and overall sialylation (NANA) shows that GP2015 was within the quality range (mean ± 3 SD) for 2S and overall sialylation (NANA), but slightly outside the quality ranges for 0S and 1S, Figures 4-67 – 4-70, only Figure 4-70 copied. Overall sialylation is classified as a Tier 2 quality attribute;

Figure 4-70 Absolute abundances of sialic acid NANA for GP2015 drug substance and Enbrel®



0S

	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (lots)	57.5 (17)	50 (15)	51.4 (29)
range (+/- 3SD)	45.2-69.7	41.4-58.6	40.7-62.1

Table prepared by reviewer

1S

	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (lots)	34.4 (17)	39.3 (15)	38.2 (29)
range (+/- 3SD)	27.7-41.6	34.3- 44.2	31 – 45.3

Table prepared by reviewer

2S

	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (lots)	8.1 (17)	10.8 (3)	10.3 (29)
range (+/- 3SD)	2.6 – 13.5	4.5 – 17.2	5.5 – 15.231.8

Table prepared by reviewer

Impact of sialylation on pharmacokinetics: As the degree of sialylation could have an impact on the pharmacokinetics, a series of studies were undertaken using rabbits to assess if there was difference in the PK profile. Figure 4-62, not copied, shows similar PK profiles between EU-approved Enbrel (lot E51371), GP2015 drug substance (#B056401) formulated in 50mM citrate, and GP2015 in the same formulation as EU-approved Enbrel. In addition, pre- and post-shift lots of EU-approved Enbrel showed no differences in the PK profile, Figure 4-63, not copied.

Reviewer Comment: The analytical data show that there are no significant differences in the overall degree of sialylation. However, there do appear to be some differences in the levels of the sialylated N-glycan subtypes. The OS N-glycans are slightly elevated in GP2015 (mean 57.5%) compared to US-Enbrel (mean 50%), while the 1S and 2S levels had slightly lower levels in GP2015. However, these differences in sialylated N-glycan subtypes did not impact PK. The combination of the analytical data from multiple methods including anion exchange, WAX and the PK data provide evidence to show that the overall degree of sialylation of GP2015 is supportive of a finding that GP2015 is highly similar to US-licensed Enbrel.

4.1.6 Heterogeneity amino acid sequence

Variability of the N-termini: Variability at the N-terminus was assessed and the results are summarized in Table 4-29, not copied. The variants include L1 (1-34), L1 (2-34) and L1 (3-34) and there are only minor differences between GP2015 drug substance and drug product lots. The levels of L1(3-34) are higher for US-licensed Enbrel (6.2-6.4%) and EU-approved Enbrel (8.6-9.8%) compared to GP2015 DP (4.2-5.1%). The levels of the L1 (1-34) in GP2015 (87.6-89.2%) are higher compared to EU-Enbrel (80.9-83.6%) and closer to US-Enbrel (89.8-90.2%). Differences between individual US-licensed and EU-approved Enbrel lots are more significant and thought to correlate with age (see section 4.1.1.2.) L1(2-34) is consistent between GP2015 (6.5-8%) and EU-approved Enbrel (7.7-9.4%), and lower for US-licensed Enbrel (3.6.-3.8%).

Reviewer Comment: The observed differences among the GP2015, US-licensed Enbrel and EU-approved Enbrel are likely due to differences in the ages of the products (Figure 4-8, not copied) and where the older US-Enbrel and EU-Enbrel lots had higher levels of clipped variants.

Variability of the C-terminus: The C-terminal variants were quantitated and there were no significant differences observed between the GP2015 drug substance and product lots, Table 4-30, not copied. The US-licensed and EU-approved Enbrel have higher levels of 1K GP2015.

C-terminal Lys (1K)

	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (%)	1.1	16.3	13.8
range (+/- 3SD)	-1.94-4.14	7.2-25.4	0.87 – 26.6 -

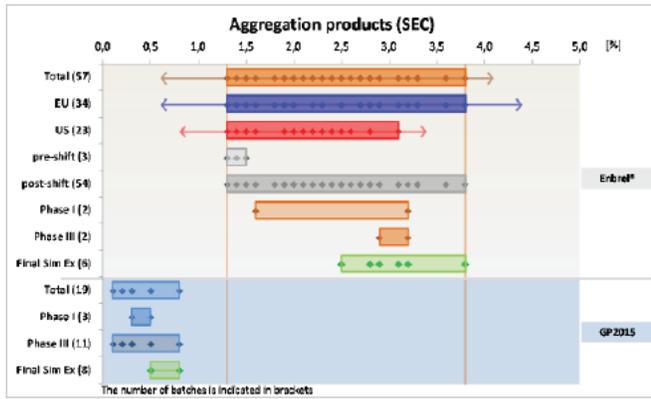
Table prepared by reviewer

Reviewer Comment: The presence or absence of C-terminal lysine does not have an impact on the biological function of the molecule and there is ample literature demonstrating that the C-terminal lysine of monoclonal antibodies is rapidly cleaved in vivo. It is highly likely that an Fc fusion protein will have the same properties.

4.1.7 Heterogeneity Size

Size exclusion chromatography (SEC): Analysis using SEC involved the quantitation of aggregates, degradation products and main peak purity. Representative chromatograms of GP2015 DP lots (#B213820, #VB50B3 and #CS2951), US-licensed Enbrel (#1040542) and EU-approved Enbrel (#G75422) are shown in Figures 4-72 and 4-73, not copied. The main peak purity is slightly higher in GP2015 drug substance and drug product lots (94.7-96.5%) compared to the US-licensed Enbrel lots and EU-approved (92.1-92.3%), while the levels of aggregates and degradation products were higher in US-licensed and EU-approved Enbrel lots (2.8 – 3.8% and 4.2-5.1%, respectively) compared to GP2015 lots (0.3-0.8% and 3.1-4.5%, respectively), Table 4-31, not copied and Figures 4-74 to 4-76.

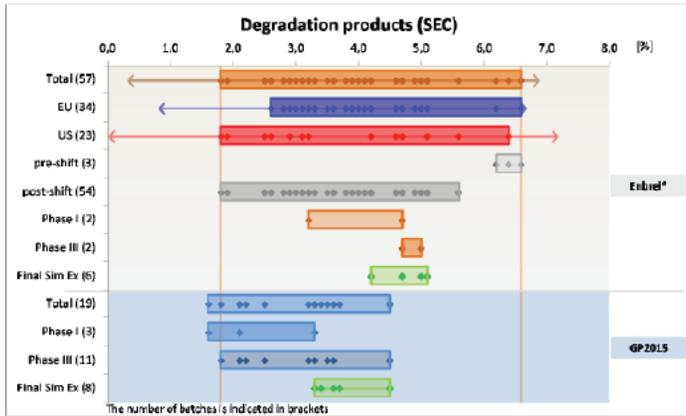
Figure 4-74 Quality range comparison of aggregation products for GP2015 drug product and Enbrel



	GP2015	US-ENBREL	EU-ENBREL
mean (lots)	0.37 (19)	2.1 (23)	2.5(34)
range (+/- 3SD)	-0.14-0.88	0.8-3.4	0.6-4.4

Table prepared by reviewer

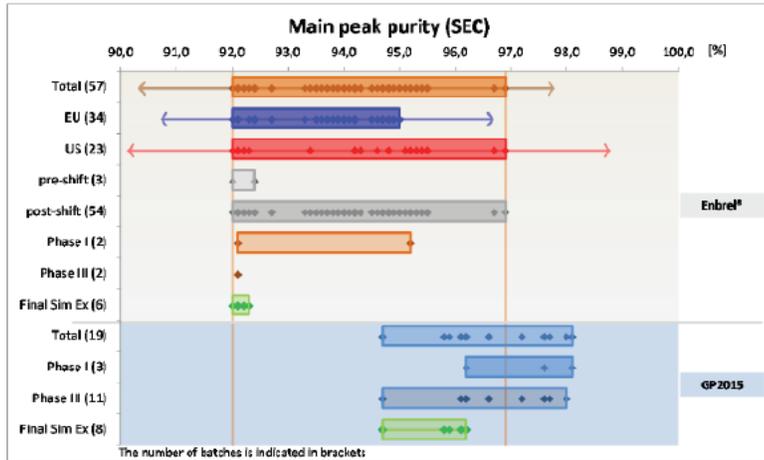
Figure 4-75 Quality range comparison of degradation products for GP2015 drug product and Enbrel



	GP2015	US-ENBREL	EU-ENBREL
mean (lots)	3 (19)	3.41 (23)	3.8 (34)
range (+/- 3SD)	0.61-5.35	-0.3-7.2	0.8-6.7

Table prepared by reviewer

Figure 4-76 Quality range comparison of the SEC purity (main peak) for GP2015 drug product and Enbrel



	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (lots)	96.65 (19)	94.5 (23)	93.70 (34)
range (+/- 3SD)	93.90-99.40	90.1-98.9	90.7-96.7

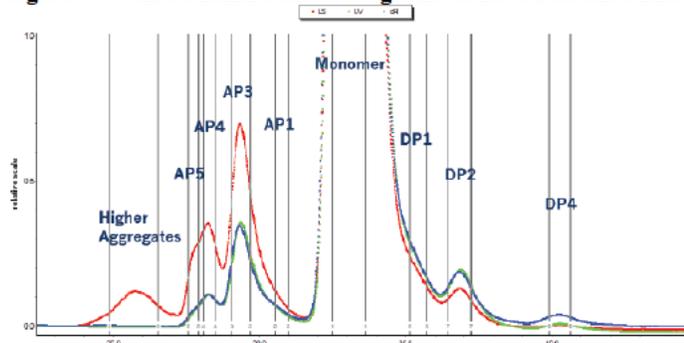
Table prepared by reviewer

Reviewer Comment: Although the data from the GP2015, US-licensed and EU-approved Enbrel lots tested in the final similarity exercise do not overlap, when GP2015 lots are compared to all US-licensed and EU-approved Enbrel lots tested, the % main peak for GP2015 falls within the overall all range. In general, GP2015 lots are more pure than US-licensed and EU-approved Enbrel lots. These differences may also be related to the age of the products at the time of testing.

Size exclusion chromatography – Multi angle laser light scattering (SEC-MALLS): The composition of the peaks identified by SEC were further characterized using SEC-MALLS. The elution profile for SEC-MALLS and the assignment of the peaks is shown in Figure 4-77.

The molecular mass of the monomer peak for GP2015 lots (116.7 to 117.8kDa) is within the range of values obtained for US-licensed Enbrel and EU-approved Enbrel lots (116.8-118.1kDa); the molecular mass of the AP3 peak for US-licensed Enbrel and EU-approved Enbrel (240.6-249.5) is slightly higher than seen in the GP2015 lots (207.7-235.9), Table 4-32, not copied.

Figure 4-77 SEC-MALLS chromatograms of EU-authorized Enbrel® batch #G75422



UV/vis signal (green), MALLS signal (red), refractive index (blue)

In addition, the relative peak areas of the aggregation products for US-licensed Enbrel and EU-approved Enbrel lots are greater than in GP2015, while the differences in the levels of the degradation products are minor, Table 4-33.

Table 4-33 Relative peak areas of aggregation and degradation products determined by SEC-MALLS

	Batch	Monomer	Higher aggregates	Aggregation and Degradation Products						
				AP5	AP4	AP3	AP1	DP1	DP2	DP4
				[%]						
Drug substance	#B213820	98.2	--	0.0	0.0	0.5	0.1	0.7	0.5	0.0
	#B213822	97.3	--	0.0	0.0	0.6	0.1	0.9	1.1	0.0
	#B213823	97.3	--	0.1	0.0	0.6	0.1	0.9	1.0	0.0
	#B234003	97.4	--	0.0	0.0	0.6	0.1	0.7	1.1	0.0
	#B234004	97.3	--	0.0	0.0	0.5	0.1	0.8	1.3	0.0
	#B234005	97.1	--	0.1	0.0	0.6	0.1	0.8	1.2	0.0
Drug product	#CS2951	96.4	--	0.3	0.0	0.9	0.1	1.1	1.2	0.0
	#DR0917	97.3	--	0.1	0.0	0.7	0.1	0.8	0.9	0.0
	#VB50B1	97.0	--	0.4	0.0	0.6	0.1	0.6	1.0	0.0
	#VB50B2	97.3	--	0.2	0.0	0.7	0.1	0.7	1.0	0.0
	#VB50B3	97.3	--	0.3	0.0	0.6	0.1	0.7	0.9	0.0
	#VB25B1	97.1	--	0.3	0.0	0.6	0.1	0.8	0.9	0.0
	#VB25B2	97.1	--	0.5	0.0	0.6	0.1	0.7	0.9	0.0
	#VB25B3	97.0	--	0.5	0.0	0.6	0.1	0.8	0.9	0.0
Enbrel®	#G75422	90.3	1.2	0.7	1.1	3.5	0.7	1.6	0.9	0.1
	#H76640	89.6	0.6	1.1	1.7	4.0	0.6	1.6	0.8	0.1
	#H50892	86.6	1.7	1.6	2.2	4.6	0.7	1.6	0.9	0.1
	#1035224	89.5	0.9	1.1	1.5	4.0	0.5	1.6	0.8	0.1
	#1040542	90.7	1.3	0.7	1.1	3.2	0.5	1.7	0.8	0.1
	#1042402	90.1	1.6	0.9	1.2	3.4	0.5	1.5	0.7	0.1

Non-reduced Capillary Electrophoresis (CE): There are minor differences in the level of the main peak purity where US-licensed Enbrel and EU-approved Enbrel lots are lower (96.2-97.7%) compared to the GP2015 lots (96.9-98.9), Table 4-34, not copied. High molecular weight peaks were present in the US-licensed Enbrel and EU-approved Enbrel (1.1-2.1%), while the levels in GP2105 lots were less than the limit of quantitation. Low molecular weight variants are similar among GP2015, US-licensed Enbrel and EU-approved Enbrel.

SDS-PAGE (non-reduced): US-licensed Enbrel and EU-approved Enbrel lots contain a higher molecular weight band (290kDa) that is also present at a reduced amount in two of the older GP2015 lots (#CS2951 and #DR0917), Figure 4-84, not copied in review. The rest of the banding pattern is similar among all lots.

SDS-PAGE (reduced): No differences are observed among the GP2015 lots and the US-licensed Enbrel and EU-approved Enbrel lots, Figure 4-85, not copied.

Reviewer Comment: *The main band in GP2015 DP lot DR0917 under reducing conditions may have an additional higher molecular band that is not observed in other lots. However, this appears as a smear above the main band rather than a distinct band in the gel. Data from orthogonal analytical methods for size variants do not show significant differences between the lots.*

Analytical ultracentrifugation (AUC): No major differences were observed in either the monomer (%) or oligomer (%); however, US-licensed Enbrel and EU-approved Enbrel lots contain slightly higher levels of dimer (2.5-4.3%) compared to the GP2015 lots (1.1-2.1%), Table 4-35, not copied.

Asymmetric-field flow field fractionation: Figure 4-88, not copied shows representative FFF chromatogram where the peaks are labeled as monomer, shoulder, and oligomer. The overall percentage and molecular weight of monomer peak is consistent among GP2015 (70-73.6%; 121.6-122.6kDa), US-licensed Enbrel (72.4-73.3%; 121.7-123.3kDa) and EU-approved Enbrel (72-72.7%; 121.5-122.2) lots. The relative amounts and molecular weight of the shoulder are also relatively consistent among all lots. The relative amounts of peak 3 are similar among the lots, however the molecular weight of peak 3 is higher in US-licensed Enbrel (9.8 – 11.1%; 108.6 – 133.6 kDa) and EU-approved Enbrel (10.6 – 11.1%; 118.2 – 128.6 kDa) relative to GP2015 DS and DP (9.4 – 11.6%; 101.5 – 120.1 kDa), although there is overlap among the lots, Table 4-36, not copied.

Reviewer Comment: *A series of analytical methods were used to assess size heterogeneity and analytical similarity. A consistent trend was that the GP2015 lots had lower levels of the higher molecular weight component than the EU-approved Enbrel and US-licensed Enbrel lots. This may be due to differences in the age of the lots at the time of testing.*

Overall, the results show that GP2015 contains lower levels of aggregates and degradation products. The units for molecular mass given in Table 4-36 are incorrectly stated as Da, but they should be stated as kDa.

An IR (#1) was sent to Sandoz on 11/20/2015 that contained the following question:

We believe there is a typographical error in Table 4-36, where the units of measurement are given as [Da] instead of kDa. Update the 351(k) BLA to include a correct table.

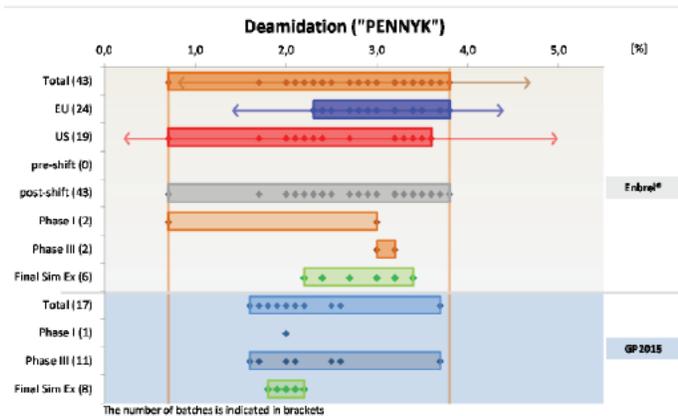
In the response (12/10/2015), Sandoz acknowledged the error and updated the table.

4.1.8 Heterogeneity amino acid modifications

Deamidation and oxidation are common post-translational modifications, which were assessed by mass spectroscopy. Although post-translational modifications are assessed on all peptides, the peptides that contain the highest levels of deamidation or oxidation are used as surrogates representing total deamidation or oxidation in the molecules. Both attributes were assigned to Tier 2 for statistical analysis.

Deamidation: The level of deamidation is stability indicating. A sequence motif (PENNYK, peptide L20) in the Fc region is used as a surrogate for total deamidation. There are slightly higher levels of deamidated variants in US-licensed Enbrel and EU-approved Enbrel lots (2.2-3.4%) compared to the GP2015 DP lots (1.8-2.2-%), Table 4-37, not copied. Figure 4-90 shows the results for all tested lots, which shows Phase 1 and Phase 3 GP2015 lots with a broader range of deamidation.

Figure 4-90 Relative abundances of deamidated variant L20 for GP2015 drug product and Enbrel



	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (%) /(lots)	1.85 (13)	2.6 (19)	2.9 (24)
range (+/- 3SD)	1.2-1.5	0.2-5	1.4-4.4

Table prepared by reviewer

Reviewer Comment: *In general, GP2015 has slightly lower levels of the deamidated PENNYK peptide compared to US-Enbrel and EU-Enbrel, and is within the range of values for US-Enbrel. These differences could be due to the age of the US-Enbrel and EU-Enbrel lots at the time they were tested. It is acceptable that GP2015 has slightly lower levels of these impurities.*

Oxidation: Differences in oxidized variants in the L1 peptide (1-34) among GP2015, US-licensed Enbrel and EU-approved Enbrel lots are minimal, Table 4-38 (not copied)

	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (%)/ lots	2.5 (17)	2.4 (8)	2.6 (15)
range (+/- 3SD)	0.8-4.2	0.3-4.6	1.5-3.7

Table prepared by reviewer

Reviewer Comment: *There are no significant differences between GP2015, US-licensed Enbrel and EU-approved. The rationale for using the L1 peptide as a surrogate for overall oxidation is based on experimental data showing that the L1 peptide is the most susceptible to oxidation when compared to four other peptides (L9, L18, L17+L18 and L23).*

4.1.9 Heterogeneity Charge

Capillary zone electrophoresis (CZE): The levels of basic variants are higher in US-licensed Enbrel and EU-approved Enbrel lots than in the GP2015 lots. Similarly, the level of the main peak is higher in GP2105 lots than in US-licensed Enbrel and EU-approved Enbrel lots, Table 4-39. The source of the observed differences is attributed, in part, to differences in the levels of C-terminal lysine. Following treatment with carboxypeptidase B the differences in the distribution of the basic peaks between US-licensed Enbrel and EU-approved Enbrel lots (22.8 – 24.5% peaks) is reduced significantly and is closer to the levels seen in GP2015 DP (15.7 – 20.6%), Table 4-40, not copied. The increased levels of the basic peak remaining even after digestion with carboxypeptidase B is due to elevated levels of the wrongly bridged disulfide variants. This is discussed in the greater detail in the section 4.1.1.5.

Table 4-39 Acidic and basic variants of GP2015 and Enbrel®

	Batch	Acidic variants	Basic variants	Main peak
		[%]		
Drug substance	#B213820	16.6	12.8	70.6
	#B213822	18.2	12.8	69.0
	#B213823	16.7	12.5	70.8
	#B234003	16.9	13.6	69.5
	#B234004	17.2	13.3	69.6
	#B234005	17.2	13.9	68.9
Drug product	#CS2951	15.9	20.4	63.7
	#DR0917	15.3	18.5	66.3
	#VB50B1	17.4	15.6	67.0
	#VB50B2	16.8	15.8	67.4
	#VB50B3	17.3	15.6	67.2
	#VB25B1	17.2	15.4	67.4
	#VB25B2	16.6	15.6	67.8
#VB25B3	17.4	15.5	67.0	
Enbrel®	#G75422	13.5	39.4	47.1
	#H76640	13.3	39.0	49.7
	#H50892	14.1	36.1	49.7
	#1035224	12.6	41.1	46.3
	#1040542	13.5	39.8	46.6
	#1042402	13.2	39.5	47.3

Reviewer Comment: Basic variants in GP2015 DP lots treated with CpB range from 15.7 – 20.6% (Table 4-40, not copied), which is consistent with the results before treatment. The experimental evidence is consistent with the explanation that the presence or absence of C-terminal lysine makes significant contribution to the observed differences in charge variants. C-terminal lysine does not affect the function of etanercept and is known to be cleaved rapidly in vivo upon administration to patient. The Sponsor has also shown that the misfolded peak present in the sample is detectable as a fraction designated 'main a'. Differences in the amount of misfolded peak present in the sample therefore may impact the level of the basic variants.

Capillary isoelectric focusing (cIEF): Figure 4-98 shows an electropherogram of GP2015 and the relative abundances of the individual peak groups in GP2015, US-licensed Enbrel and EU-approved Enbrel are shown in Table 4-41, not copied and Figure 4-99. The observed differences between among the lots are attributed to the presence or absence of the C-terminal lysine and sialylation.

Figure 4-98 Exemplary electropherogram of a GP2015 sample separated by cIEF

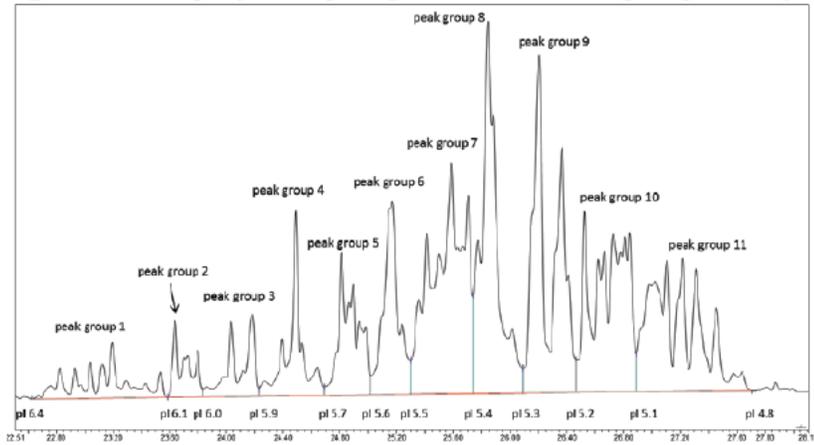
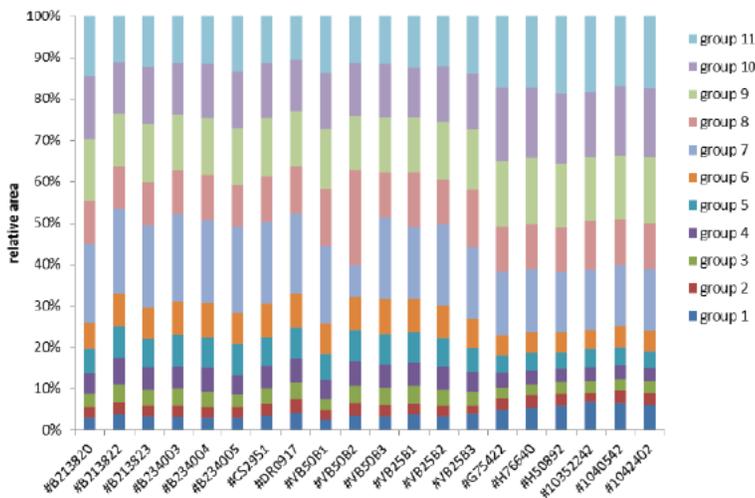


Figure 4-99 Relative abundances of group 1 – group 11 (cIEF) for GP2015 and Enbrel®



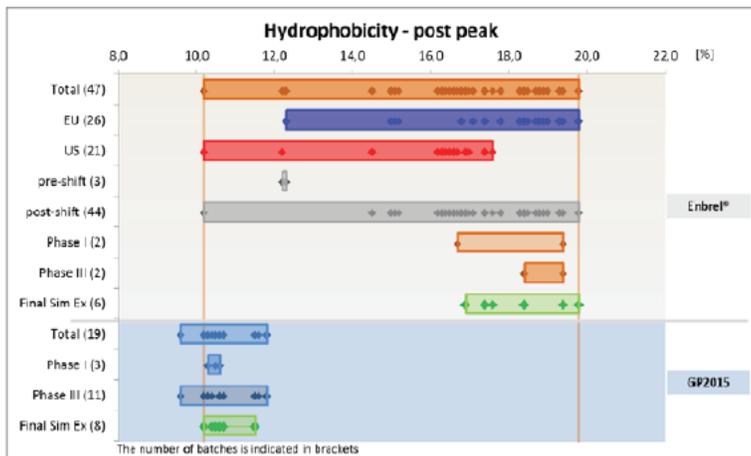
Reviewer Comment: There is slightly increased variability within the GP2015 lots compared to US-licensed Enbrel and EU-approved Enbrel, particularly in the region of groups 7, 8 and 9. This may be due to differences in the levels of basic variants and degradation products, such as the wrongly bridged variant. Analysis of charge heterogeneity using CZE and cIEF demonstrated that there are some relatively minor differences between GP2015, US-licensed and

EU-approved Enbrel. In the context of the analytical similarity assessment, the observed differences are relatively minor and are supportive of a finding that GP2015 is highly similar to US-licensed Enbrel.

4.1.10 Hydrophobicity

Reverse Phase Chromatography (RPC): Sialic acids are removed prior to analysis hydrophobic variants. Figures 4-100 to 4-102, not copied show chromatograms of GP2015, US-licensed Enbrel and EU-approved Enbrel and the levels of sum of pre-peaks, main peak and sum of post-peaks are shown in Table 4-42, not copied. Figures 4-103 and 4-104 summarize the relative abundance of the post peaks and main peak, respectively. The post-peak variants contain wrongly bridged variants. GP2015 lots contain 10.0 – 11.5% post peaks while US-licensed Enbrel and EU-approved Enbrel lots have 17.4 – 19.8% post peaks..

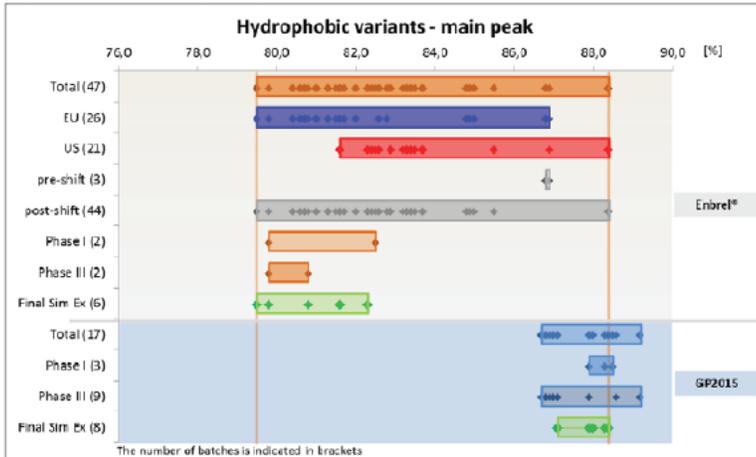
Figure 4-103 Relative abundance of post peaks for GP2015 drug product and Enbrel® batches



	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (%)/ lots	10.7 (19)	16.2 (21)	17.5 (26)
range (+/- 3SD)	8.9-12.6	10.4-21.9	11.5-20.6

Table prepared by reviewer

Figure 4-104 Main peak purities for GP2015 drug product and Enbrel® batches



	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (%) / lots	88.5 (17)	83.5 (21)	82.1 (26)
range (+/- 3SD)	79.7 – 97.3	78.6 – 88.4	76.2 – 88.1

Table prepared by reviewer

Reviewer Comment: Differences in the distribution of the pre, main and post peaks are due to increased levels of post peak present in US-licensed Enbrel and EU-approved Enbrel lots compared to the GP2015 lots. GP2015 contains lower levels of the post peak, which is consistent with an increase in GP2015 potency, determined by TNF- α reporter gene assay,

The relationship between the wrongly bridged disulfide bond variants in the post-peak and the TNF- α neutralization assay was the subject of several information requests and a teleconference with Sandoz.

An IR (#1) was communicated to Sandoz on 12/11/2015 that contained the following question: Reference is made to the post peak fractions of GP2015 that can be separated from the main active peak by reverse phase chromatography (RPC) and consist mainly of inactive wrongly disulfide variants. Provide data showing the potency and TNF binding activity associated with this fraction compared with the main peak and unseparated product for both GP2015 and US-licensed Enbrel. You should assess the level of purity of each isolated peak for interpreting the results.

In the response (1/15/2016), Sandoz provided the following information:

Separation of the hydrophobic variants using RPC involves the use of acetonitrile which is denaturing. Therefore it is not possible to assess the potency of the individual fractions eluting from the RPC.

Additional data were presented showing the correlation between levels of the T7 peptide containing one of the wrongly bridged disulfide variants. Furthermore, a correlation was established between levels of the post-peak and potency using data from G2015 DS lots and process intermediates, (b) (4). This allowed an assessment of the contribution of WBV, low molecular variants (LMV) and aggregation products to potency. The contribution of the aggregation products is not significant. The relationship between potency and presence of the WBV and LMV is described using regression ANOVA analysis.

The GP2015 HIC post-peak has relatively high T7 levels and low TNF-alpha RGA activity, see Figures 6-2 and 6-3 from response to IR. (b) (4)

Figure 6-2 Small scale HIC – increase of wrongly bridged variants towards post-peak

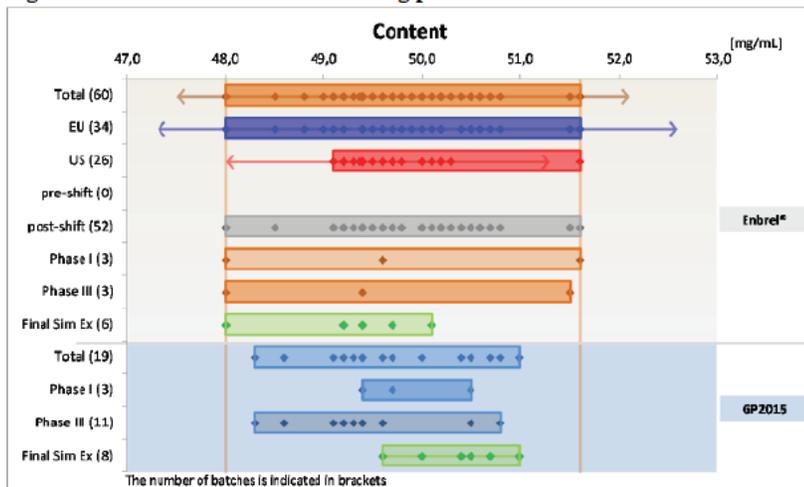


Figure 6-3 Small scale HIC – level of HMWs and LMWs towards post-peak

(b) (4)

**4.1.11 Content**

Protein content is determined by using specific absorption of UV light and applying the Beer-Lambert law. The extinction coefficient was determined using the Beer-Lambert law and the declared protein concentration of the US-licensed Enbrel and EU-approved Enbrel lots. The protein content in GP2015 DP (49.6 – 51.0 mg/mL) is slightly higher than that of US-licensed Enbrel and EU-approved Enbrel (49.4 – 50.1 mg/mL). Table 4-43, not copied, and Figure 4-102.

Figure 4-105 Content for GP2015 drug product batches and Enbrel®

	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (mg) / lots	49.8	49.6	50
range (+/- 2SD)	48.2-51.3	48.9-50.3	48.3 – 51.6.4

Table prepared by reviewer

Reviewer Comment: *The GP2015 protein content is within the range of the US-licensed Enbrel and EU-approved Enbrel. These data are supportive of a finding that GP2015 is highly similar to US-licensed Enbrel.*

An IR (#1) was communicated to Sandoz on 11/20/2015 that contained the following question:

Section 4.1.11 describes protein content of GP2015, which was determined using an extinction coefficient based on the declared content of batches of EU-approved Enbrel, US- licensed Enbrel and GP2015. The extinction coefficient should be experimentally determined using an analytical approach that is independent of the label claims of the originator. (see Q+A #I.12 in Guidance for Industry “ Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009” (April 2015), available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm444661.pdf>).

In the response (12/11/2015), Sandoz provided the following information:

The extinction coefficient was experimentally determined by UV/Vis spectroscopy according to the Lambert-Beer’s law by analyzing US-licensed and EU-approved Enbrel lots and using the labeled content. Consequently, this experimentally determined extinction coefficient was used for content evaluations of GP2015 drug substance and drug product. The extinction coefficient was further proven to be correct by analyzing 60 batches of reference product with expiry dates covering more than five years and resulting in an average content of 49.7 mg/ml across all batches, Table 6-1 not copied, that matches Enbrel’s labeled content of 50 mg/mL.

4.1.12 Compendial methods

Color of Solution: Color of the solution of GP2015 drug product lots were graded as >B9 (colorless), with one lot at >Y5. US-licensed Enbrel and EU-approved Enbrel lots were graded as >Y6 and >Y7 (slightly yellowish), Table 4-44, not copied.

Clarity: Ratio turbidimetry was used to calculate the opalescence of the solution. GP2015 drug product lots had slightly lower values (7-8 NTU) compared to US-licensed Enbrel and EU-approved Enbrel lots (7-9 NTU), Table 4-45, not copied .

pH: GP2015 drug substance and drug product lots had slightly higher values (pH 6.3-6.4) compared to the EU-approved Enbrel and US-licensed Enbrel lots (pH 6.2), Table 4-46, not copied .

Extractable volume: Values obtained for extractable volume are consistent between GP2015 lots (0.5 – 1.0 mL, US-licensed Enbrel, and EU-approved Enbrel lots (0.5 – 1.0 mL), Table 4-47, not copied.

Visible particles: GP2015 drug product lots were graded as either 'free of visible particles' or practically free of extraneous particles, while the EU-approved Enbrel and US-licensed Enbrel lots varied from 3-30 particles, Tables 4-48 and 4-49, not copied.

Subvisible particles (SVP): The presence of SVP was assessed by microflow imaging and the results are shown in Table 4-50, not copied. On **average, GP2015 has higher levels of SVP ≤ 10 μm while US-licensed Enbrel and EU-approved Enbrel lots have slightly higher levels of SVP ≥ 10 μm .**

Reviewer Comment: *The average values for each size of SVP show that there is not a significant difference between the GP2015 lots, US-licensed Enbrel and EU-approved Enbrel. If anything, there are slightly lower values in GP2015 lots. This could be related to the age of the GP2015 DP lots, if they are not as far into the shelf life as the EU-approved and US-licensed Enbrel lots.*

Osmolality: The osmolality was assessed and the results for 3 lots of EU-approved and US-licensed Enbrel and 8 lots of the GP2015 DP are provided in Table 4-51, not copied. Due to the differences in the excipients an assessment of analytical similarity was not undertaken.

Reviewer Comment: *Overall, the slight differences in each of these compendial methods could be due to differences in the formulation or age of the products at the time of testing. These do not preclude a determination of highly similar.*

Process Related Impurities: DNA levels and protein A levels were provided only for GP2015 lots, while host cell proteins (HCP) were assessed in GP2015, US-licensed and EU-approved Enbrel lots. DNA levels in 6 lots of GP2015 DS are <0.2 ppb, Table 4-52, not copied, which is below the LOQ of the method. Similarly, protein A levels present in the GP2015 DS lots are below the LOQ of the assay, 0.1 ppm, Table 4-53, not copied.

Reviewer Comment: *The values obtained are below the LOQ in both cases and meet typical industry standards.*

HCP levels were higher in GP2015 drug substance lots (149-268 ppm) compared to the US-licensed and EU-approved Enbrel lots (74-94ppm), Table 4-54 and Figure 4-108, not copied.

Table 4-54 Quantitation of HCPs in GP2015 drug substance and Enbrel®

	Sample	HCPs [ppm]
Drug substance	#B213820	208
	#B213822	183
	#B213823	149
	#B234003	268
	#B234004	231
	#B234005	244
Enbrel®	#G75422	94
	#H76640	76
	#H50892	90
	#1035224	74
	#1040542	68
	#1042402	88

Reviewers comment: It is not unexpected that HCP levels are higher in GP2015 using reagents developed specifically for the GP2015 expression system. Although the values are slightly higher in GP2015, they are within the range normally encountered for other products using reagents developed specifically for those products. A direct comparison of HCPs is problematic due to differences in the specificity of the antibody that is generated for specific expression systems. Additional information was provided identifying by mass spectrometry the HCPs present GP2015, US-licensed Enbrel and EU-approved Enbrel. See section 3.2.S.3.2.5.2.1. Most HCPs were seen in all three products, but there were some HCPs specific to GP2015 or US-licensed Enbrel and EU-approved Enbrel.

4.2 Functional characterization

Results of all the functional methods, TNF- α and TNF- β reporter gene assays, apoptosis (TNF- α neutralization) and TNF- α binding, are shown in Table 4-55.

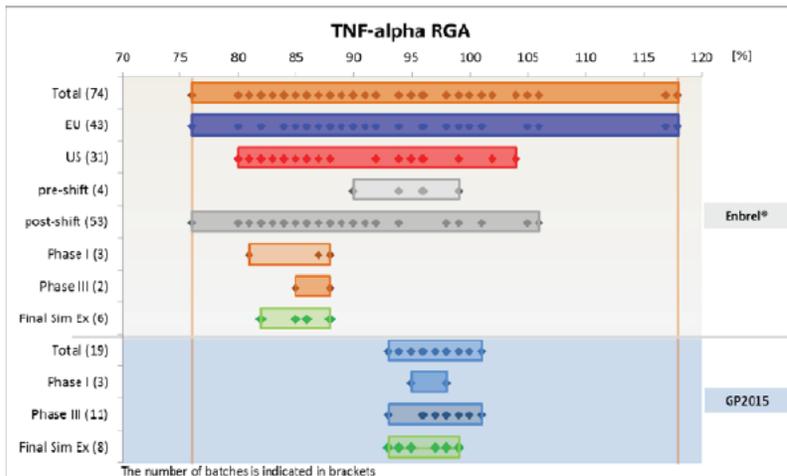
Table 4-55 Functional bioassays

	Sample	RGA (TNF- α neutralization)	RGA (TNF- β neutralization)	Apoptosis (TNF- α neutralization)	Binding to TNF- α
[% potency relative to GP2015.02REF]					
Drug substance	#B213820	103	95	120	98
	#B213822	99	93	114	94
	#B213823	98	91	103	92
	#B234003	102	99	113	92
	#B234004	100	92	108	96
	#B234005	98	91	100	98
Drug product	#CS2951	97	96	109	100
	#DR0917	98	96	101	89
	#VB50B1	94	94	97	101
	#VB50B2	93	95	102	97
	#VB50B3	94	90	106	91
	#VB25B1	95	93	92	98
	#VB25B2	99	94	97	95
	#VB25B3	99	93	104	96
Enbrel [®]	#G75422	85	87	101	95
	#H76640	88	84	98	85
	#H50892	88	87	120	95
	#1035224	86	79	122	99
	#1040542	82	78	122	98
	#1042402	85	83	128	92

4.2.1 Mode of action: TNF- α and TNF- β neutralization and TNF- α binding

TNF- α reporter gene assay (RGA): The neutralization of TNF- α is assessed using HEK293 cells containing a NF- κ B dependent luciferase reporter gene. The results are reported as % potency relative to the GP2015.02REF standard. GP2015 drug product lots are more potent than the US-licensed Enbrel and EU-approved lots used in the final analytical similarity exercise. However when all the lots are included, the GP2015 DS and DP lots are within the range of values obtained for the total US-licensed Enbrel and EU-approved Enbrel lots tested, Figure 4-109.

Figure 4-109 Potency determination (TNF-alpha RGA) for GP2015 drug product and Enbrel



Brown vertical lines: min-max range for the overall Enbrel® range

Reviewer Comment: GP2015 drug product has higher potency when compared to US-licensed reference product. Sandoz indicates that a potential reason for this is the presence of higher levels of misfolded protein present in the US-licensed Enbrel and EU-approved Enbrel. Given that the potency of the GP2015 drug product is within the range of values obtained for historical values obtained for lots of US-licensed Enbrel, this difference does not preclude a finding that GP2015 is highly similar to US-licensed Enbrel. However, the statistical analysis by Meiyu Shen, OTS, OB, using the equivalency method indicates that there is statistically significant difference between the means of GP2015 drug product and US-licensed Enbrel.

Several IR's were sent to the Sandoz to address this issue.

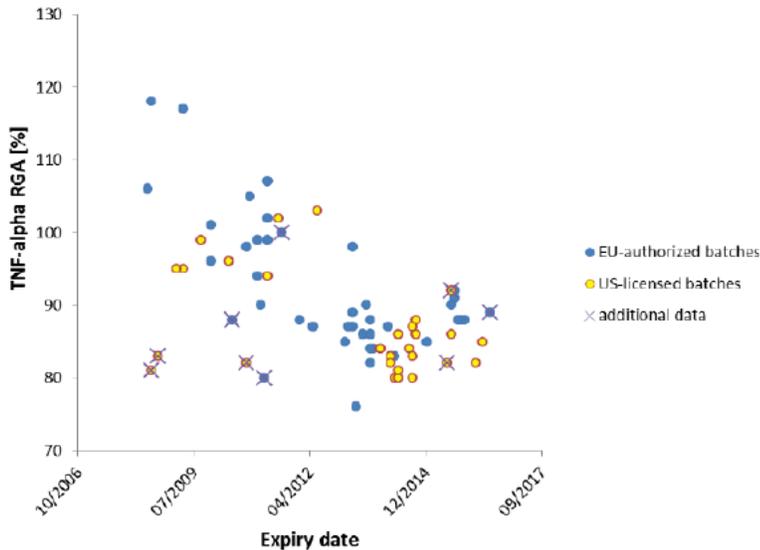
An IR (#1) was communicated to Sandoz on 11/20/2015 with the following question:

For TNF-alpha neutralization using the Reporter Gene Assay (RGA), you provided data for 8 GP2015 drug product lots and 25 lots of US-licensed Enbrel. This is a sufficient number of US-licensed Enbrel lots; however, we note that most of the US-licensed Enbrel lots have lower potency relative to the GP2015 lots. We also note that most of the US-licensed Enbrel lots with lower potency have expiration dates ranging from 2014 through 2015, suggesting that many may have been manufactured during (b) (4). If available, provide data from additional US-licensed Enbrel lots that were more likely to have been manufactured during (b) (4).

In the response (12/11/2015), Sandoz provided additional data from 5 lots of US-licensed Enbrel and 4 lots of EU-approved Enbrel. The data for potency versus expiry date shows the change in

potency over time, Figure 2-1, from the IR response. The lots with expiration dates in 2014 – 2016 period are restricted to ~80 and ~95%, while the earlier lots had a wider distribution, 80% - 118%.

Figure 2-1 TNF-alpha neutralization of Enbrel® – variation over time



An IR (#2) was communicated to Sandoz on 12/11/2015 that contained the following question:

We recommend that you perform studies on both GP2015 and US-licensed Enbrel to assess if the wrongly bridged disulfide bonds are reversible in human serum. We recommend a time course experiment at 37°C to establish if the wrongly bridged disulfide bonds are modified in the presence of oxidoreductases present in serum and could convert to the active form found in the RPC main peak.

Sandoz responded on 1/15/16 and 1/29/16.

In the initial response (1/15/2016) Sandoz provided published examples demonstrating that isomerization of disulfide bonds occurs in vivo for other proteins, such as IgG4 half antibody exchange (van der Neut Kolfschoten et al 2007) and IgG2 antibodies (Dillon et al 2008, Pristatsky et al 2009). In addition, experimental studies involving human serum were initiated.

In the subsequent response (1/29/2016), Sandoz outlined an experimental approach that was based on data generated from in vivo and in vitro studies (Liu 2013) that assessed disulfide isomerization in an IgG2 antibody.

Three samples containing low (GP2015 DS), medium (GP2105 CAP.E) and high (GP2015 HICPOST.E^(b)₍₄₎) levels of T7 peptide were tested. Samples were diluted in the redox buffer and incubated at 2-8°C for 48 hours and dialyzed prior to analysis. The redox buffer and control buffers components were:

Redox buffer: 0.83 mM cysteine, 0.17 mM cystamine in 200 mM TRIS HCl pH 8.0.
 Control: 200 mM TRIS HCl pH 8.0

The results demonstrate that exposure to the redox buffer leads to a reduction in the T7 peptide, Table 2-1 from the response to the 1/29/16 IR.

Table 2-1 WBV levels prior and after incubation in a redox-system

Batch	Experiment 1		Experiment 2	
	untreated sample	Redox	Control	Redox
	T7 [% related to a standard peptide]			
GP2015 CAP.E	4.0	1.6	3.8	1.8*
GP2015 DS	1.5	1.1	1.3	1.4
GP2015 HIC POST.E ^(b) ₍₄₎	5.1	2.1*	4.3	2.3

* SST criterion not met. However, the same trend can be observed for both experiments and, therefore, the results are considered to be reliable.

In a subsequent response, Sandoz provided additional data from the same samples analyzed using the TNF-RGA assay, Table 2-2, from 3/2/16 submission. In addition, these data maintain the relationship that was shown between the T7 peptide levels and potency, Figure 2-1 from 3/2/16 submission, not copied.

Table 2-2 TNF-alpha neutralization prior and after incubation in a redox systemsam

Batch	Experiment 1		Experiment 2	
	untreated sample	Redox	Control	Redox
	TNF-alpha neutralization [%]			
GP2015 DS	97	102	104	103
GP2015 CAP.E	66	97	70	92
GP2015 HIC POST.E ^(b) ₍₄₎	52	84	65	90

The 3/2/2016 submission also included data from experiments that were undertaken to establish if isomerization of disulfide bonds could be demonstrated by incubation in human serum. Enbrel and GP2015 DP (containing low amounts of WBV), GP2015 HIC fraction, (containing high amounts of WBV), were incubated at 37°C or 2-8°C in freshly prepared serum samples at three concentrations reflecting the concentrations observed in clinical studies of psoriasis patients and healthy volunteers (c1 = 5,000 ng/mL; c2 = 2,500 ng/mL; c3 = 1,250 ng/mL). The samples were analyzed on days 0, 1, 4, 5, 7 and 12.

The concentration of free (and functional) GP2015 and Enbrel was assessed by adapting the free drug assay used in preclinical studies., where functional Enbrel or GP2015 in the serum sample is captured by TNF coated on an ELISA plate. In addition, the samples were also tested using

the total drug assay developed for clinical samples, where a polyclonal anti-hTNFR2 antibody is used for capture and detection. The precision and accuracy of these assays is $\pm 20\%$, so recovery between 80-120 ng/mL is accepted for an expected concentration of 100 ng/mL.

The results for GP2015 and GP2015 HIC fraction in the free drug assay are shown in Table 2-3 and 2-5 and the total drug assay in Table 2-4 and 2-6. Tables 2-4 (free drug) and 2-7, not copied, show the results for Enbrel, which has the same trends as the GP2015. The initial trends showed that the sample recovery was within the 80-120% range and reflected differences in the amount of misfolded protein present in the GP2015 HIC fraction. The HIC fraction has ~50% activity in the TNF-RGA assay and ~50% was recovered in the free drug assay. However, all three samples degraded over the 12 day period and as a consequence, it was not possible to identify if refolding had occurred. The total drug assay showed similar levels of recovery for all three samples at all time points, except for the HIC fraction at day 12, which had much lower recovery than the other samples.

Table 2-3 Free drug assay results of GP2015 DP

GP2015 DP	Day 0	Day 1	Day 4	Day 5	Day 7	Day 12
Mean recovery c_1 [%]	94	76	44	29	20	16
Mean recovery c_2 [%]	92	72	52	35	25	16
Mean recovery c_3 [%]	87	76	52	38	29	23

$c_1 = 5,000$ ng/mL; $c_2 = 2,500$ ng/mL; $c_3 = 1,250$ ng/mL

Table 2-5 Free drug assay results GP2015 HIC fraction

GP2015 HIC fraction	Day 0	Day 1	Day 4	Day 5	Day 7	Day 12
Mean recovery c_1 [%]	49	36	21	16	10	6
Mean recovery c_2 [%]	50	36	18	17	12	4
Mean recovery c_3 [%]	50	37	17	17	14	10

$c_1 = 5,000$ ng/mL; $c_2 = 2,500$ ng/mL; $c_3 = 1,250$ ng/mL

Table 2-6 Total drug assay results of GP2015 DP

GP2015 DP	Day 0	Day 1	Day 4	Day 5	Day 7	Day 12
Mean recovery c_1 [%]	101	80	32	33	23	20
Mean recovery c_2 [%]	97	74	49	37	29	20
Mean recovery c_3 [%]	89	80	49	39	34	24

$c_1 = 5,000$ ng/mL; $c_2 = 2,500$ ng/mL; $c_3 = 1,250$ ng/mL

Table 2-8 Total drug assay results of GP2015 HIC fraction

GP2015 HIC fraction	Day 0	Day 1	Day 4	Day 5	Day 7	Day 12
Mean recovery c_1 [%]	102	75	39	33	21	8
Mean recovery c_2 [%]	101	77	36	36	25	7
Mean recovery c_3 [%]	97	74	37	36	28	18

$c_1 = 5,000$ ng/mL; $c_2 = 2,500$ ng/mL; $c_3 = 1,250$ ng/mL

Reviewer Comment: The results are consistent with the degradation of the samples over time, which was seen as early as day 1. Decreasing amounts (5000ng/mL to 1250ng/mL) of etanercept

did not impact the percentage recovery. The relatively low recovery values for the GP2015 HIC fractions is consistent with the presence of reduced levels of active GP2015 and reflect the differences in the amount of known active protein. It was observed previously that soluble TNFR2 is reasonably stable at 24°C in plasma for 20 days (Aziz N., et al, 6 89-95, Clin and Diag Lab Imm, 1999). Therefore degradation observed in the serum sample may be a reflection of the absence of protease inhibitors and the presence of proteases in the serum samples. Sandoz provided several publications describing technical challenges associated with these experiments that include sample recovery and maintaining the redox balance of the serum. The challenges described in the literature are consistent with the results of these experiments.

During a teleconference (4/7/2016) Sandoz provided the following information:

Additional data from the analysis of GP2015 potency used data from the TNF-RGA assay and T7 peptide levels to generate a model to derive an adjusted potency level to compensate for changes in WBV that are thought to occur in vivo. The results from the analysis of a single lot of EU-approved and US licensed Enbrel were used to demonstrate the validity of this approach. FDA requested that Sandoz use a minimum of three lots of US-licensed Enbrel to derive an adjusted potency calculation.

Additional data were submitted on 4/28/2016 that included four lots of US-licensed Enbrel and three lots of GP2015 DP in addition to the previous data, Table 1-3 from 4/28/16 submission.

Table 1-3 Experiment 3 + 4 (new data)

Sample	Control		Redox Incubation	
	T7 [% rel. to standard peptide]	Bioactivity [%]	T7 [% rel. to standard peptide]	Bioactivity [%]
GP2015 DS	1.0	99	1.2	103
GP2015 CAP.E	3.4	76	1.6	98
GP2015 HIC.E	5.5	58	2.0	93
GP2015 DP Batch 1	1.2	98	1.5	103
GP2015 DP Batch 2	1.8	97	1.3	101
GP2015 DP Batch 3	1.2	100	1.7	98
Enbrel/US #1040542	2.6	89	1.7	107
Enbrel/US #1062728	2.5	85	1.8	98
Enbrel/US #1034018	2.8	81	1.8	96
Enbrel/US #1034842	2.5	85	1.8	95
Enbrel/EU #J13793	2.3	92	1.6	100

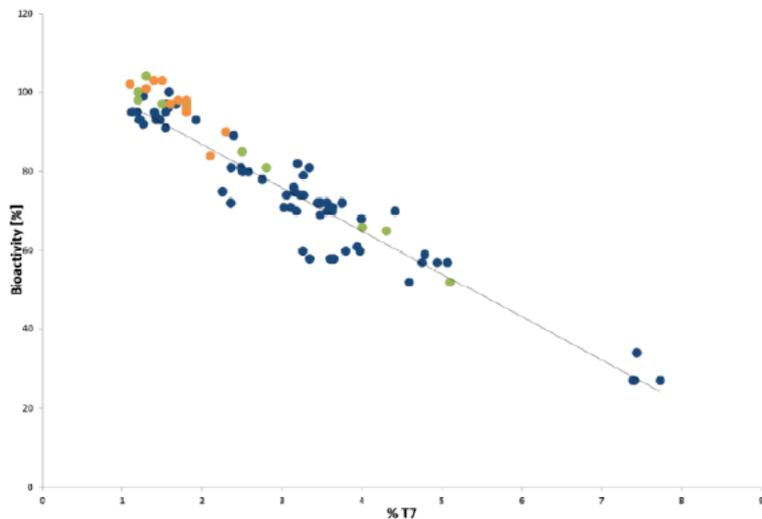
The linear relationship between T7 levels and TNF-RGA potency assay data that was established with the previous samples was maintained, R=0.9143, see IR S.4.1.1 Primary Structure – disulfide bridging

The accumulated experimental data were used to generate a computed potency model using the structure/function relationship shown below.

(b) (4)

The average value for the T7 peptide [%rel. to standard peptide] from the accumulated experimental data was 1.6%, Table 1-3. This value was used to generate the computed potency. The calculated values were compared to show that they remain within the established structure activity relationship, Figure 1-2 and Table 1-4, not copied.

Figure 1-2 Samples from the redox experiments fit the established structure function relationship



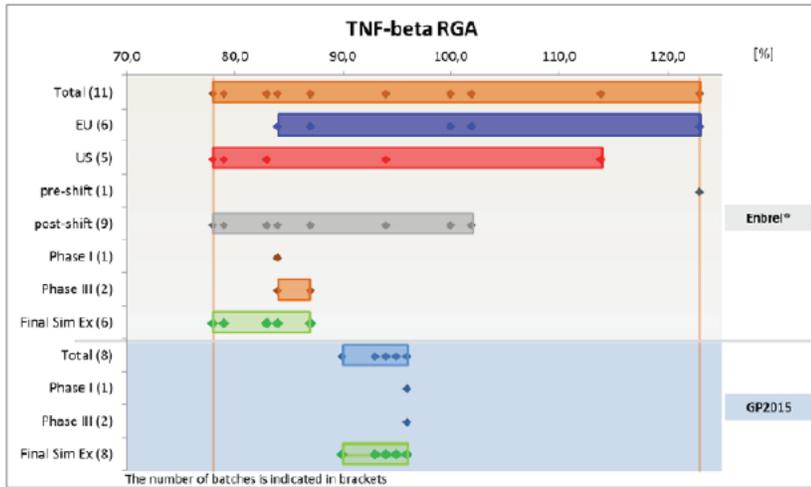
blue: data points generated during development to establish structure-function relationship; green: control samples of redox experiments; orange: sample after redox incubation

The computed potency was determined for 9 lots of GP2015 DP, 13 lots of US-licensed Enbrel and 11 lots of EU-approved Enbrel assuming 100% refold and 50% refold. The expiration dates of the US-licensed Enbrel lots were evenly distributed over the period from 2008 – 2016. The computed potency was increased for US-licensed Enbrel by an average of 5.5% and for EU-approved Enbrel by an average of 6.1%, while the computed potency for GP2015 was reduced by an average of 3.9%. Statistical analysis of the data was carried out by Meiyu Shen (OTS/OB) and demonstrated statistical equivalence..

The computed potency was also assessed using sensitivity analysis to show that normalization of the data did not impact the statistical analysis. Upper and lower normalization values ($1.6 \pm 0.4\%$), which covered the observed range of %T7 were used, Table 1-8, not copied. Statistical analysis showed that when the normalization values were applied that the computed potency passed equivalence testing.

TNF- β reporter gene assay (RGA): The ability to neutralize TNF- β was assessed using the same approach used for the analysis of TNF- α . The assay results and the statistical analysis are shown in Figure 4-114. The trends in the results are similar to TNF- α .

Figure 4-114 Potency determination (TNF-beta RGA) for GP2015 drug product and Enbrel



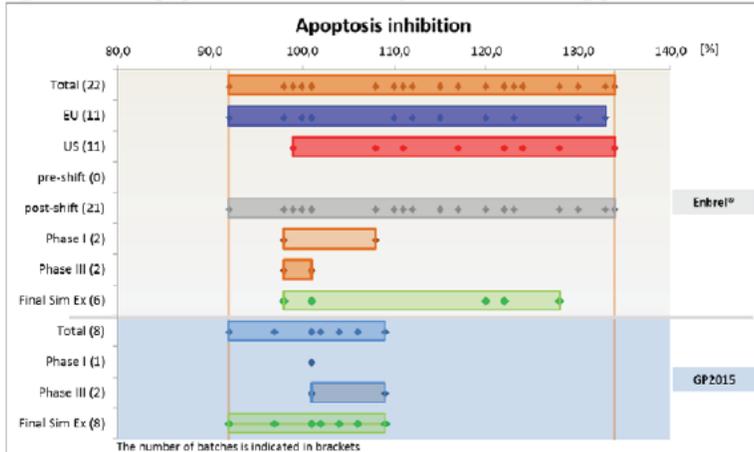
Reviewer Comment: The results of the analysis of TNF-β (lymphotoxin-alpha) are similar to those observed for TNF-α. It is not known if binding and neutralization of lymphotoxin alpha has a role in the mechanism of action of etanercept. TNF antagonists including adalimumab, golimumab and infliximab do not bind lymphotoxin alpha. Similarly, clinical trials with a lymphotoxin-alpha antagonist were not clinically effective for the treatment of rheumatoid arthritis (Kennedy W.P., et al. 16 467-476 Arthritis Research and Therapy). Therefore it is appropriate to exclude lymphotoxin-alpha from the Tier 1 statistical analysis. GP2015 lots were within the quality range of US-licensed Enbrel.

	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (%) lots	93.9 (8)	89.6 (5)	97.2 (6)
range (+/- 2SD)	90-97.8	59.5-119.7	67.8-126.5

Apoptosis (TNF-α neutralization): Neutralization of TNF-α was examined using a U937 cell line that undergoes apoptosis in response to being exposed to TNF-α. See results in Table 4-55 above. A statistical analysis of the results from this assay was performed.

Reviewer Comment: An analysis of the data shows that the GP2015 drug substance has 9% higher neutralization capacity (100-120%) compared to the GP2015 drug product (92-109%). Both are within the range of results for US-licensed and EU-approved Enbrel (98-128%). Given the variability in these data compared to the TNF-a RGA and the different trend of the data (that is, the US-licensed Enbrel and EU-approved Enbrel have increased potency compared to the GP2015 drug substance and product lots),

Figure 4-120 Apoptosis inhibition assay for GP2015 drug product and Enbrel®



Brown vertical lines: min-max range for the overall Enbrel® range

	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (%) lots	101 (8)	117.7 (11)	112 (11)
range (+/- 2SD)	90-112	97-138	85-139

Table prepared by reviewer

An IR (#1) was communicated to Sandoz on 11/20/2015 that contained the following question: Data were presented in Table 4-57 that include apoptosis (TNF-neutralization), but these data were not evaluated in the same way that was performed for the TNF-alpha and TNF-beta RGAs (Figures 4-108 and 4-109). We note that the trends for the apoptosis assay (higher potency for US-licensed Enbrel) contradict those observed in the TNF-alpha RGA (lower potency for US-licensed Enbrel). Provide an explanation for why the trends in the data are different.

In the response (12/11/2015), Sandoz stated that (b) (4). In addition, method variability and the relatively lower number of samples analyzed were cited as an explanation for the trend differences.

TNF-α Binding: TNF-α binding was assessed using surface plasmon resonance (SPR). In the final similarity exercise, there were no major differences in the binding of US-licensed Enbrel and EU-approved Enbrel lots (92-99%) compared to GP2015 drug substance (92-98%) and product lots (89-101%).

Reviewer Comment: TNF-α binding is considered a highly critical quality attribute assigned to Tier 1 for equivalence testing. However in the initial BLA submission, data were analyzed only for the final similarity study which used only 3 lots each of US-licensed Enbrel and EU-approved

Enbrel. Therefore additional lots should be analyzed. In contrast to the TNF- α RGA assay the absence of a major difference in binding suggests that the presence of the misfolded protein in US-licensed and EU-approved Enbrel lots is not sufficient to cause a measurable change in binding. The reason for this difference between assays is not clear.

An IR (#1) was communicated to Sandoz on 11/20/2015 that contained the following question:

TNF binding should be analyzed using the equivalence method. For TNF binding, you provided data for 8 GP2015 drug product lots, but only three lots of US-licensed Enbrel. Provide an updated analysis using additional lots of US-licensed Enbrel. In the response (12/11/2015) Sandoz indicated that [REDACTED] (b) (4) and undertook to provide data from 3 additional lots.

In their response on 12/11/2015, Sandoz indicated that additional data would be submitted by the end of January 2016.

An additional IR (#2) was communicated to Sandoz on 12/11/2015 that contained the following question:

Regarding the TNF α binding assay, we acknowledge that you will provide data for at least 3 additional batches of US-licensed Enbrel in January 2016. However, we do not agree with your assertion that [REDACTED] (b) (4). In order to more fully support the totality of the evidence and to meet the established criteria for equivalence testing, you should submit data from a minimum of 10 lots, which can include the three lots submitted in the original BLA (See November 20, 2015 IR Question #3). In addition, for both the TNF α binding and TNF α neutralization assays, you should also provide data for a minimum of 10 lots of EU-Enbrel to support the analytical bridge.

In the response (1/15/2016), Sandoz provided data from 11 batches of US-licensed Enbrel, (7 lots expired), 12 batches of EU-approved Enbrel (7 lots expired) and 8 batches of GP2015, Table 11-16, not copied. Some of the lots were assessed after the expiration date.

An IR (#3) was communicated to Sandoz on 2/26/2016 that contained the following question:

Response to information request submitted January 15th, 2016. We acknowledge your response to Question 15 in the Information Request from the Agency dated December 11th, 2015. Your analysis of TNF-binding and apoptosis included 7 lots each of US-licensed Enbrel and EU-approval Enbrel lots that were beyond their expiration dates at the time of testing. Analytical testing of product lots should be performed prior to their expiration dates. Therefore, provide data for additional lots using US-licensed Enbrel and EU-approved Enbrel that are within their expiration dates.

In the response (3/10/2016) Sandoz indicated that [REDACTED] (b) (4) The expired

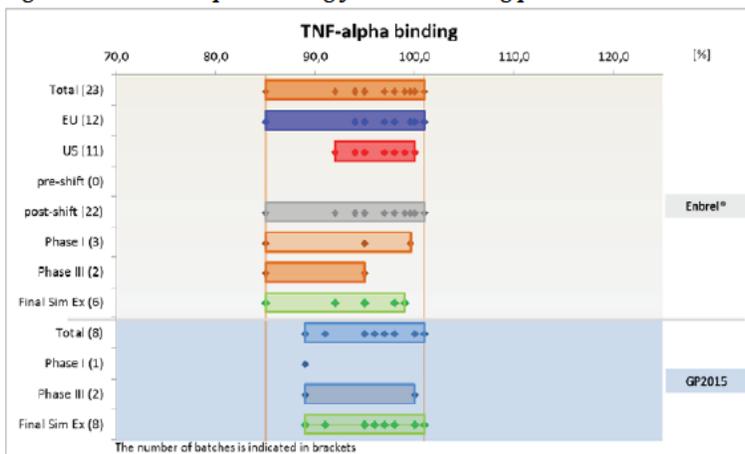
lots had been stored at ^{(b) (4)} C prior to expiry and 4 lots were stored at 2-8 °C beyond their expiry date. Storage at 2-8°C could be considered a worst case scenario in terms of possible adverse impact on activity. Table 3-1 from the 3/10/16 submission, shows that the lots stored at 2-8°C post-expiry did not lose activity in the TNF-α potency assay. Therefore, we accepted the data from the expired lots.

Table 3-1 TNF-alpha RGA results of expired Enbrel® lots

Batch (Source)	Expiry date	TNF-alpha RGA [%] before expiry	TNF-alpha RGA [%] after expiry
1028232 (US)	08/14	84 (May 2012)	83 (Jan 2016)
1028722 (US)	09/14	83 (May 2012)	83 (Jan 2016)
1029715 (US)	10/14	88 (Sep 2012)	85 (Jan 2016)
1030768 (US)	09/14	87 (Sep 2012)	83 (Jan 2016)

The TNF-α binding data are summarized in Figure 4-117. Statistical analysis of the data using equivalency testing was carried out by Meiyu Shen (OTS/OB). GP2015 was found to be equivalent to US-licensed Enbrel and all two-way comparisons had equivalent mean values.

Figure 4-117 TNF-alpha binding for GP2015 drug product and Enbrel®



Brown vertical lines: min-max range for the overall Enbrel® range

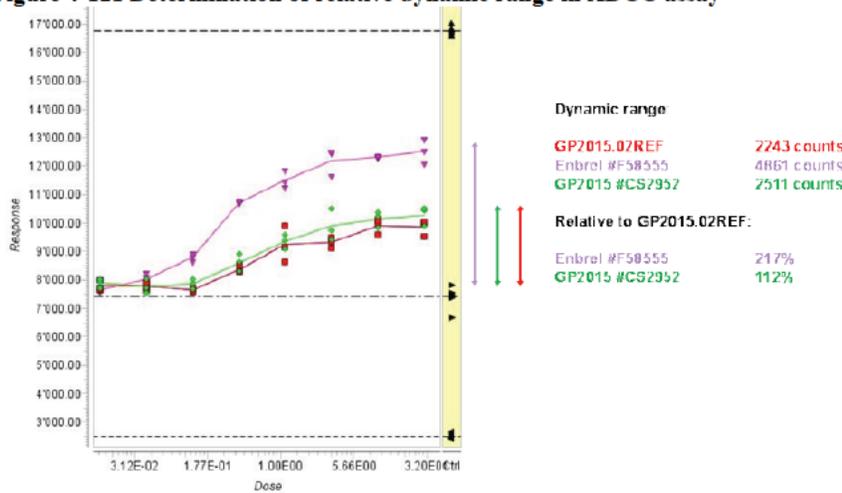
4.2.2 Additional cell based assays: ADCC and CDC

Antibody dependent cellular toxicity (ADCC): The assay consists of an immortalized natural killer cell line (NK3.3) and target HEK293 target cells that express mTNF-α. The mTNF-α is expressed constitutively with the cleavage site removed so that no soluble TNF-α is present. The HEK293 cells are labelled with a cytoplasmic fluorescent dye (calcein), which is released on cell death. Quantitation of the fluorophore released into the supernatant facilitates analysis.

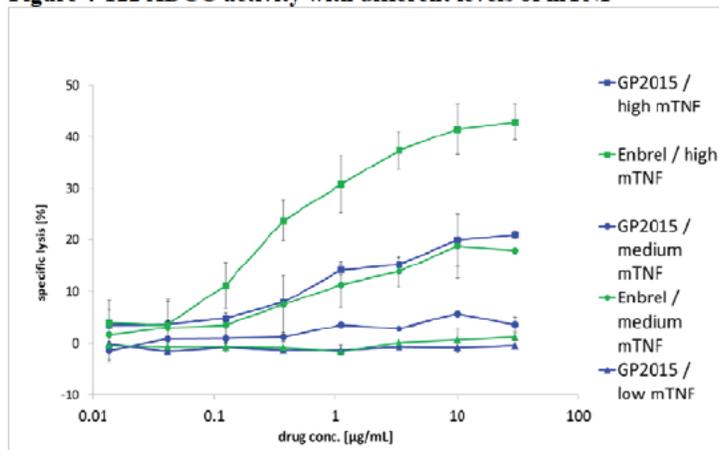
The results are given in Table 4-65, not copied, and are expressed as a percentage relative to the reference standard (GP2015.02REF), however data for US-licensed and EU-approved Enbrel

were not determined because the data have non parallelism in the dose response, as shown in Figure 4-121. Therefore, it is not possible to directly compare them to GP2015.

Figure 4-121 Determination of relative dynamic range in ADCC assay



US-licensed Enbrel and EU-approved Enbrel have relatively higher ADCC activity compared to GP2015, which is attributed to the higher level of afucosylated glycans in US-licensed Enbrel and EU-approved Enbrel compared to GP2015. Given the observed differences in ADCC activity, a rationale based on published data along with additional experimental data was provided, to demonstrate that ADCC activity is unlikely to contribute to the mechanism of action. First, the TNF antagonist certolizumab, which does not have an Fc region, is clinically effective in the treatment of the same diseases. Second, pharmacogenomic studies have been unable to show a link between phenotypic variants of the FcγRIIIa receptor clinical outcomes when treated with TNF antagonists. Third, experimental data demonstrate that the ADCC assay does not reflect *in vivo* conditions due to unusually high levels of membrane-bound TNF expression on the target cells. To demonstrate this, HEK293 cells with low, medium and high mTNF-α expression levels were tested for ADCC activity. The data presented in Figure 4-122 shows the relationship between ADCC activity and mTNF-α expression levels. Additional experimental data is described, but not included, outlining how the expression levels of a monocytic cell line (U937) stimulated with LPS has relatively lower expression levels of mTNF-α.

Figure 4-122 ADCC activity with different levels of mTNF

Reviewer Comment: The analytical data show that GP2015 has significantly lower ADCC activity compared to US-licensed or EU-approved Enbrel. The US licensed and EU-approved Enbrel are more highly afucosylated, which in turn effects binding the FcRγIIIa receptor present on NK cells. Glycan analysis data and FcRγIIIa receptor binding are consistent with these results. However, Sandoz contends that ADCC is not part of the mechanism of action and therefore, the differences are not clinically relevant. I agree that ADCC is not part of the mechanism of action for etanercept. The source of any potential risk for GP2015 is reduced activity, therefore, it would appropriate to use a heterogeneous cell population such as PBMC's that are more representative of the cellular milieu that would be encountered in vivo. Using PMBC's in the ADCC assay along with the appropriate positive and negative controls provide stronger support for the contention that the observed differences are not clinically relevant

The experimental data that underpins Sandoz's contention that mTNF is overexpressed on HEK293 cells were not included in the submission and should be provided. Sandoz should provide experimental data showing that mTNF-α levels on LPS stimulated U937 cells are lower than the HEK293 cells.

An IR (#1) was communicated to Sandoz on 11/20/2015 that contained the following question:

You contend that ADCC is not part of the mechanism of action (MOA) for US-licensed Enbrel. A comparison of ADCC activity which uses PBMCs may represent a more relevant model to support this claim. In addition, you can provide further justification that ADCC is not a MOA for US-licensed Enbrel by citing relevant literature.

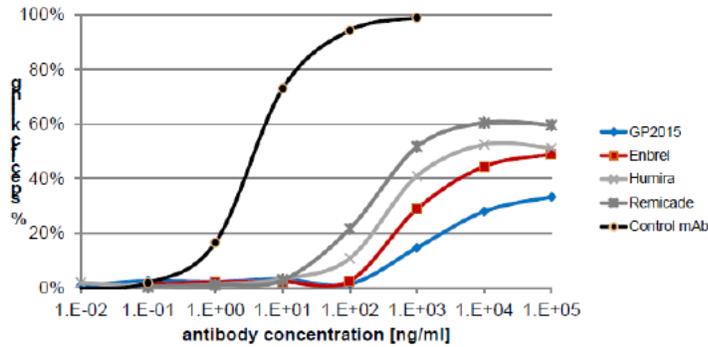
Submit experimental data, such as FACS analysis, that compare mTNF expression levels on LPS stimulated U937 cells and HEK293 cells transfected with mTNF. This type of

analysis will provide more direct evidence that the observed trends in figure 4-117 are due to differences in TNF expression.

In the response (12/11/2016): Sandoz provided both publically available information and experimental data. Publically available information includes the prescribing information for US-licensed Enbrel which does not mention ADCC and information that there is no association between Fc receptor CD16 / FcγRIIIa variants and clinical efficacy.

Experimental data showed that as a class, the TNF antagonists (GP2015, Enbrel, Humira, Remicade) are much less effective at inducing apoptosis compared to a control monoclonal antibody, Figure 7-1 from 12/11/2016 submission.

Figure 7-1 Comparison of different TNF antagonists



Additional evidence included experimental data using primary human monocytes isolated from peripheral blood that were treated with LPS to induce TNFα, shown in Figure 7-4.

Sandoz also provided data showing the results of the FACS analysis of the 3 cell lines that express high, medium and low levels of mTNF, Figure 7-2. The capacity of GP2015 and US-licensed and EU-approved Enbrel to induce ADCC was minimal compared with an anti-CD52 control antibody (Lentrada, alemtuzumab).

Figure 7-2 Comparison of different cell lines by FACS analysis

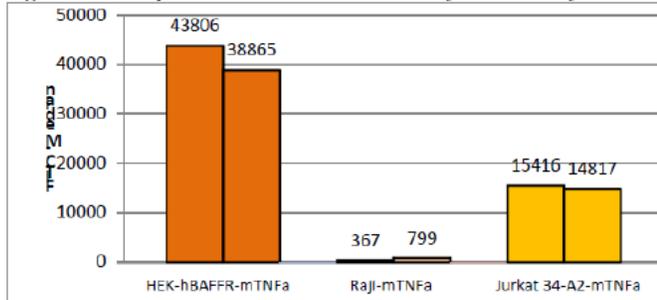
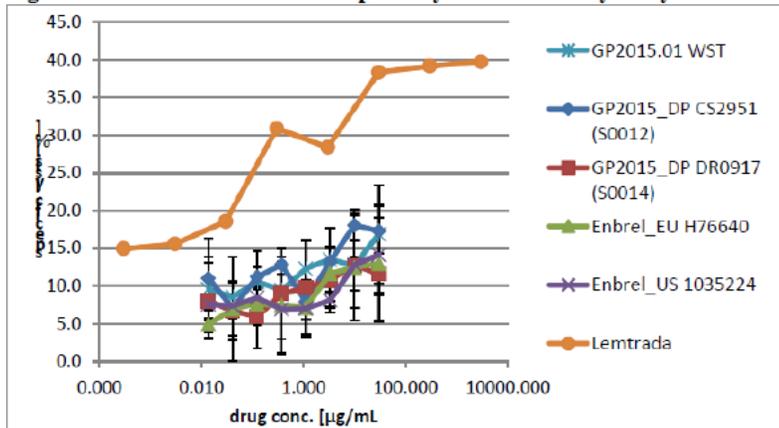


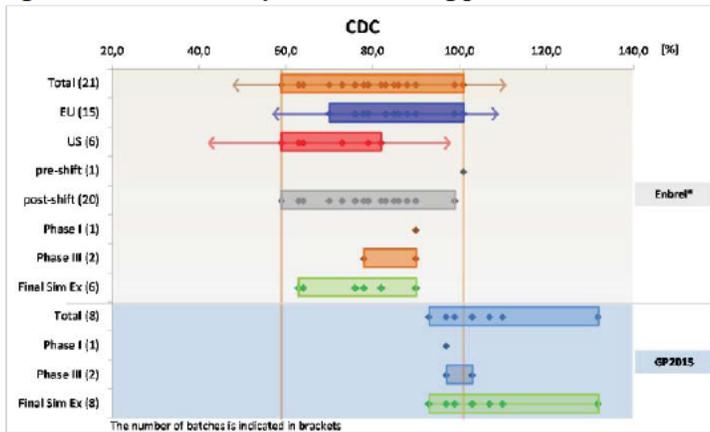
Figure 4-124 ADCC induction on primary human monocytes by NK cell line NK3.3

LPS-stimulated primary human monocytes were analysed in an ADCC assay using NK3.3 effector cells. The positive control Lemtrada (alemtuzumab) is directed against the CD52 antigen expressed on the monocyte cell surface and confirms the ability of NK3.3 cells to induce antibody-dependent apoptosis in this target cell population. Neither GP2015 nor Enbrel were seen to induce target cell lysis.

Complement dependent cellular cytotoxicity (CDC): This assay uses Jurkat cells transfected with mTNF- α , with the cleavage site removed, as target cells. The cells are co-incubated with human serum and the target protein. The depletion of the Jurkat cells is quantified by chemiluminescence. Based on the results of the CDC assay, GP2015 drug substance (90-111%) and drug product (97-132%) have an enhanced capacity to induce CDC compared to US-licensed and EU-approved Enbrel (63-90%). Differences are observed between the US licensed and the EU-approved Enbrel as well, Figure 4-125. Sandoz indicates that CDC is not clinically relevant as it is not expected to be part of the mechanism of action.

Reviewer's comment: *The data show that GP2015 is more effective at inducing CDC compared to US-licensed and EU-approved Enbrel. Published data comparing the C1q binding capacity of Enbrel and two monoclonal antibody TNF antagonists (infliximab and adalimumab) showed that Enbrel is not able to effectively bind C1q, which indicates that it is less effective at activating the classical pathway (Arora, T., et al. 45 124-31, 2009). Considering the binding data and the differences observed in the CDC assay, it is possible that CDC is being activated by a mechanism other than the classical pathway. In addition, the data show there is a difference between the US-licensed Enbrel and EU-approved Enbrel or potentially a difference in the level of error in the assay.*

Figure 4-125 CDC activity for GP2015 drug product and Enbrel



Brown horizontal arrows: Quality range (mean \pm 3 SD) for the overall Enbrel® range; blue horizontal arrows: Quality range (mean \pm 3 SD) for EU-authorized Enbrel® batches; red horizontal arrows: Quality range (mean \pm 3 SD) for US-licensed Enbrel® batches; brown vertical lines: min-max range for the overall Enbrel® range

	GP2015	US-Licensed Enbrel	EU-Approved Enbrel
mean (%)/ lots	101.7 (7)	70 (6)	82.9 (15)
range (+/- 3SD)	84.2-119.3	41.9-98.1	56.8-109.1

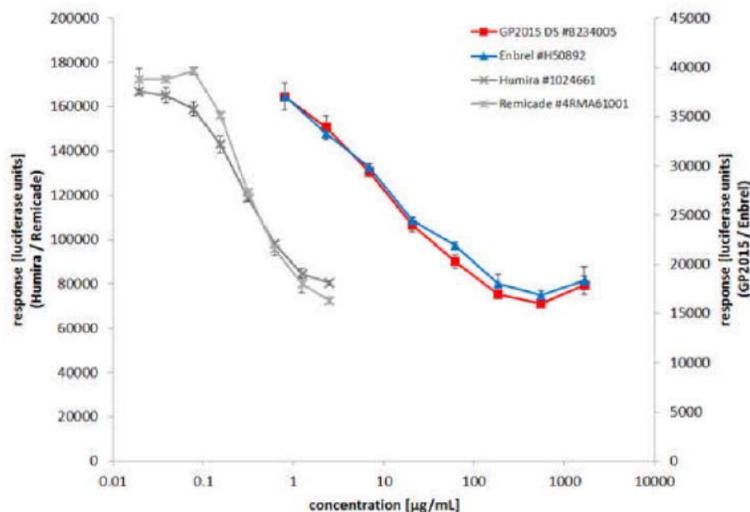
Table prepared by reviewer

An IR (#1) was communicated to Sandoz on 11/19/2015 that contained the following question:

GP2015 appears to be more effective at inducing a CDC response compared to US-licensed Enbrel and is inconsistent with the results of the C1q binding assay, which show similar binding between GP2015 drug product lots and US-licensed Enbrel lots, while GP2015 drug substance lots have higher C1q binding than US-licensed Enbrel. Submit figures of the actual curves showing the CDC results over a range of concentrations and calculate the EC50. We recommend that you compare GP2015 and US-licensed Enbrel to an anti-TNF mAb. Additional justifications for these differences and the mechanism(s) responsible for the elevated CDC may need to be identified and controlled.

In the response (12/11/2016): Sandoz provided dose response curves showing that infliximab and adalimumab induce CDC more effectively when compared to GP2015/Enbrel, Figure 7-5 from 12/11/16 submission. These data alleviate potential concerns regarding differences between GP2015 and Enbrel.

Figure 7-5 Dose-response curves of different anti-TNF proteins



4.2.3 Binding studies

C1q: The binding to C1q was assessed using surface plasmon resonance (SPR) and data reported as % potency relative to GP2015.02REF. GP2015 drug substance lots (125-141%) had relatively higher affinity compared to the GP2015 drug product lots (111-115%) and US-licensed and EU-approved Enbrel (113-115%) lots, Table 4-66, not shown.

Reviewer's comment: *The data for GP2015 DP, US-licensed Enbrel and EU-approved Enbrel are within the same range while the data for the GP2015 DS are comparatively higher. As many of the GP2015 DP lots are derived from these GP2015 DS lots, this indicates that the source of the difference is not related to inherent biochemical properties of GP2015 or US-licensed Enbrel.*

The binding affinities for FcγR receptors were determined using SPR. These assays were assigned as Tier 2 quality attributes by Sandoz, however, no statistical evaluation was performed due to variability of the method.

FcγRIa: The affinity data are shown in Table 4-67, not copied, and reported as on and off rates and a K_D . There are no significant differences between the GP2015 drug substance (35.1 – 42.5 nM) and drug product (32.9 – 57.3 nM) lots and US-licensed Enbrel (35.3 – 37.1 nM) and EU-approved Enbrel (34.7 – 41.7 nM) lots. The on and off rates are also similar.

FcγRIIa: The affinity data are shown in Table 4-68, not copied, and reported as a K_D . There are no significant differences between the GP2015 drug substance (10.8 – 14.0 µM) and drug product (11.6 – 13.8 µM) lots and US-licensed Enbrel (11.3 – 14.4 µM) and EU-approved Enbrel (10.1 – 14.3 µM) lots.

FcγRIIb: The affinity data are shown in Table 4-68, not copied, and reported as a K_D . There are no significant differences between the GP2015 drug substance (27.6 – 36.0 μM) and drug product (29.1 – 37.5 μM) lots and US-licensed Enbrel (25.8 – 36.2 μM) and EU-approved Enbrel (29.1 – 36.2 μM) lots.

FcγRIIIa: The affinity data are shown in Table 4-68, not copied for the F158 and V158 genotype and reported as a K_D . The GP2015 drug substance (16.4 – 25.5 μM) and drug product (19.3 – 29.8 μM) lots have a slightly lower K_D for F158 compared to US-licensed Enbrel (17.2-19.4 μM) and EU-approved Enbrel (18.5 – 21.0 μM) lots. In the case of V158, GP2015 drug substance (10.8 – 13.2 μM) and drug product (9.2 – 13.5 μM) lots also have a slightly lower K_D compared to the US-licensed Enbrel lots (8.4-10.6 μM) and EU-approved Enbrel (7.9 -9.6 μM) lots.

Reviewer's comment: *GP2015 lots have a relatively lower affinity interaction with FcγRIIIa (V158 and F158) compared the US-licensed and EU-approved Enbrel lots. This is consistent with the observed differences in afucosylation and ADCC.*

FcγRIIIb: The affinity data are shown in Table 4-68, not copied, and reported as a K_D . There overlap among the ranges for each of the products: GP2015 drug substance (25.7 – 33.0 μM) and drug product lots (20.4-35.7 μM) compared to the EU-approved (25.4-29.3 μM) and US-licensed Enbrel lots (20.8-29.4 μM).

Reviewer's comment: *These minor differences in the ranges are insignificant and likely reflect the low affinity interaction as well as the fact that only 3 lots each of US-licensed and EU-approved Enbrel were tested.*

FcRn: The FcRn binding affinity data are reported in Table 4-69, not copied, and there are no significant differences between the GP2015 drug substance lots (13.4 – 17.7 μM) and drug product lots (14.1 – 16.5 μM) when compared to US-licensed Enbrel (13.0 – 16.1 μM) and EU-approved Enbrel (13.6 – 15.1 μM) at pH 6.0.

Reviewer's comment: *It is known that the affinity between FcRn and US-licensed Enbrel is relatively lower than monoclonal antibodies such as adalimumab and infliximab. This may account for greater variability, but overall there are no differences in the affinity for FcRn among the products.*

5 Stability studies

Stability studies at long term and accelerated conditions were undertaken to demonstrate analytical similarity between GP2015, US-licensed Enbrel and EU-approved Enbrel. All GP2015 drug product validation batches were put on stability including 5 lots at 50mg/1mL and 3 lots at 25mg/0.5mL, Table 3-1 not copied. Two lots of US-licensed and 3 lots of EU-approved Enbrel were included in the stability studies, Table 5-1, not copied.

The stability study included an assessment of the degradation profiles for low molecular weight (LMWs), high molecular weight (HMWs), SEC-main peak purity, hydrophobic variants and acidic variants at 5°C, 25°C and 40°C. Stability data are available for the following lots and time

points for LMW, HMW, SEC main-peak purity and RPC. Data for the acidic charge variants that were stored under accelerated condition for 6 months were assessed at 25°C only.

- storage at 5°C for 12months: 3 lots of GP2015
1 lot of EU-approved Enbrel
1 lot of US-licensed Enbrel
- storage at 25°C 6 months 5 lots of GP2015
4 lots of EU-approved Enbrel
2 lots of US-licensed Enbrel
- storage at 40°C 1.5 months 5 lots of GP2015
4 lots of EU-approved Enbrel
2 lots of US-licensed Enbrel

A summary of the stability results at 5°C, 25°C and 40°C for GP2015 DP, US-licensed and EU-approved Enbrel lots is provided in Tables 5-2 to 5-14 and Figures 5-1 to 5-13, not copied in review.

i) LMW:

- Data to 12 months at 5°C: GP2015 (2.6-2.8%), US licensed Enbrel (3.5%), EU-approved Enbrel (3.2%). The slope (%/month) was consistent for GP2015 (0.05-0.07), US licensed Enbrel (0.07%) and EU-approved Enbrel (0.06%).
- Data to 6 months at 25°C: GP2015 (6.6-7.8%), US licensed Enbrel (7.2-9.3%) and EU-approved Enbrel (7.0-9.5%). The slope (%/month) was consistent for GP2015 (0.05-0.07), US licensed Enbrel (0.07%) and EU-approved Enbrel (0.06%).
- Data to 1.5 months at 40°C: fGP2015 (11.1-12.7%), US licensed Enbrel (11.4-12.2%) and EU-approved Enbrel (10.9-13.2%).

Reviewer Comment: *There are relatively lower levels of LMW species for GP2015 and the rate of change is similar for GP2015, US-licensed Enbrel and EU-approved Enbrel.*

ii) HMW

- Data to 12 months at 5°C: GP2015 (0.5%), US licensed Enbrel (2%) and EU-approved Enbrel (3.6%). The slope (%/month) was consistent for GP2015 (0.01-0.02), US licensed Enbrel (0.025%) and EU-approved Enbrel (0.015%).
- Data to 6 months at 25°C: GP2015 (2.0-2.2%), US licensed Enbrel (4.6%) and EU-approved Enbrel (4.0-5.6%). The slope (%/month) was consistent for GP2015 (0.3), US licensed Enbrel (0.3%) and EU-approved Enbrel (0.4%).

- Data to 1.5 months at 40°C: GP2015 (4.7-6.4%), US licensed Enbrel (10.7-12.2%) and EU-approved Enbrel (9.6-13.1%).

Reviewer Comment: *There are relatively lower levels of HMW species for GP2015 and the rate of change is similar for GP2015, US-licensed Enbrel and EU-approved Enbrel*

iii) SEC-main peak purity

- Data to 12 months at 5°C: GP2015 (96.7-96.8%), US licensed Enbrel (94.4%) and EU-approved Enbrel (93.2%). The slope (%/month) was consistent for GP2015 (0.01-0.02), US licensed Enbrel (0.025%) and EU-approved Enbrel (0.01%).
- Data to 6 months at 25°C: GP2015 (90.1-91.3%), US licensed Enbrel (86.1%) and EU-approved Enbrel (84.9-88.6%). The slope (%/month) was consistent for GP2015 (-1.4 to -1.0), US licensed Enbrel (-1.1 to -1.2%) and EU-approved Enbrel (-0.8 to -1.2%).
- Data to 1.5 months at 40°C: GP2015 (80.9-83.8%), US licensed Enbrel (75.5-76%) and EU-approved Enbrel (74.9-79.5%).

Reviewer Comment: *There are relatively higher levels of SEC-main peak for GP2015 and the rate of change is similar for GP2015, US-licensed Enbrel EU-approved.*

iv) Acidic Variants

- Data to 6 months at 25°C: GP2015- 2 lots (22.7-23%), US licensed Enbrel-1 lot (18.1%) and EU-approved Enbrel- 2 lots (18.3 – 20.3%). The slope (%/month) was consistent for GP2015 (1.4), US licensed Enbrel (0.9), and EU-approved Enbrel (1.0).

Reviewer Comment: *There are relatively higher levels of the acid variants for GP2015 compared to US-licensed and EU-approved Enbrel at the six month time point. The more significant change in acidic variants occurs between the 3 month and 6 month time points for GP2015, however this is within release specifications. This is acceptable.*

v) Hydrophobic Variants

The degradation profile for hydrophobic variants at 5°C shows minimal changes over time, although it appears there is more variability in the US-licensed and EU-approved Enbrel lots, Table 5-11. The relatively higher levels of hydrophobic variant (post peak) present in the US-licensed Enbrel lots is due higher levels present compared to GP2015.

Table 5-11 Degradation profile (hydrophobic variants) of GP2015 drug product and Enbrel® (5°C)

Time [months]	#CG6468	#CG6467	#BW6911	#F64618	#1026663
	GP2015 drug product [%]			EU-authorized Enbrel® [%]	US-licensed Enbrel® [%]
0	10.3	10.4	10.5	18.0	16.9
1	10.1	9.9	11.1	19.0	16.6
2	10.2	10.2	10.1	18.6	16.8
3	12.5	12.2	10.1	22.0	20.2
6	14.1	14.0	10.3	20.9	21.1
9	9.1	9.4	10.5		
12	10.8	10.8	10.5	19.3	17.4
18	11.1	11.2	10.5		
24	10.6	10.6	10.2		
30	10.9	10.8	10.9		
36			11.0		
EOS				19.1	18.2
Slope [%/month]	0.0	0.0	0.0	0.1	0.1
Average [%/month]			0.0	0.1	0.1

The degradation profile for hydrophobic variants at 25°C shows similar degradation rates over the 6 month time period for US-licensed and EU-approved Enbrel lots compared to GP2015, Table 5-12.

Table 5-12 Degradation profile (hydrophobic variants) of GP2015 drug product and Enbrel® (25°C, 6 months)

Time [months]	#DR0929	#DR0918	#CG6468	#CG6467	#BW6911	#F64618	#G75422	#H50892	#H76640	#1040542	#1026663
	GP2015 drug product [%]					EU-authorized Enbrel® [%]				US-licensed Enbrel® [%]	
0	11.8	11.8	10.3	10.4	10.5	18.0	18.5	20.1	20.2	18.2	16.9
1	12.2	12.2	10.9	10.7	11.3	18.6	16.9	18.5	18.8	16.7	17.1
2	n.t.	n.t.	11.4	11.5	11.7	19.6	18.5	20.9	20.2	18.3	17.6
3	13.3	13.5	13.5	13.2	12.2	21.7	18.9	20.7	19.3	18.2	21.8
6	15.0	15.1	15.1	16.8	14.0	23.4	20.6	22.7	21.9	20.1	23.1
Slope [%/month]	0.5	0.6	0.8	1.1	0.6	1.0	0.5	0.5	0.4	0.4	1.2
Average [%/month]					0.7				0.6		0.8

The degradation profile for hydrophobic variants at 40°C shows similar degradation rates over the 1.5 month time period for US-licensed and EU-approved Enbrel lots compared to GP2015, Table 5-13.

Table 5-13 Degradation profile (hydrophobic variants) of GP2015 drug product and Enbrel® (40°C, 1.5 months)

Time [months]	#DR0929	#DR0918	#CG6468	#CG6467	#BW6911	#F64618	#G75422	#H50892	#H76640	#1040542	#1026663
	GP2015 drug product [%]					EU-authorized Enbrel® [%]				US-licensed Enbrel® [%]	
0	11.8	11.8	10.3	10.4	10.5	18.0	18.5	20.1	20.2	18.2	16.9
0.5	n.t.	n.t.	12.9	13.1	14.2	21.8	20.6	22.9	22.9	20.4	19.7
1	16.7	16.8	17.5	16.3	16.7	26.0	23.3	25.2	25.1	24.3	23.9
1.5	19.3	19.3	20.2	19.8	20.2	29.0	25.5	31.6	32.1	30.7	26.8

Reviewer Comment: Sandoz assessed stability under three different storage conditions and used three analytical methods to demonstrate similar degradation profiles. The data support similarity in the degradation profiles between GP2015, US-licensed Enbrel and EU-approved Enbrel

Forced degradation Study

Forced degradation studies included lots of GP2015 drug substance and drug product, US-licensed and EU-approved Enbrel, Table 6-6. US-licensed Enbrel and EU-approved Enbrel were not directly compared and were assumed to be analytically similar based on the analytical data acquired to date. Stress conditions included oxidation, light exposure, pH and mechanical stress. The analytical methods assessed size, charge, hydrophobicity and potency.

Table 6-6 GP2015 and Enbrel® batches used for forced degradation study

	Batch	Manufacturing date / Expiry date	Intended use/Origin
GP2015 DS	B213820	06.11.2013	Validation (b) (4)
GP2015 DP	PVB50B3 ¹ 884968 / S0014 ² DR0917 ³	24.06.2013	Clinical studies: GP15-103, GP15-104, GP15-302 (DS B170047, B170075)
	CB50B1 ¹ 884968 / S0011 ² CS2938 ³	16.07.2012	Clinical study: GP15-302 (DS B098255, B100829)
	US-licensed #1034018	Expiry date 08/2015	--
Enbrel®	EU-authorized #G64164	Expiry date 11/2014	--

1) Technical development batch number, 2) Novartis Stein batch number, 3) Sandoz batch number

The specific forced degradation conditions were:

- Oxidation: Three H₂O₂ concentrations (0.3 %, 3 % and 10 %) for a maximum of 6 hours at 40 ± 2°C.
- pH value: Three pH values (pH 3.0 (GP2015 DP, US-licensed and EU-approved Enbrel) / 2.7 (GP2015 DS), 7.0 and 8.5) for a maximum of one week at 40 ± 2°C.
- Light: Artificial light: 1.2 Mio Lux h for 10.5 h; 2.4 Mio Lux h for 21 h
Day light (window sill): two weeks

- **Stirring:** Stir at 600 rpm for 1, 6 and 16 hours

Reviewer Comment: *The forced degradation studies included 1 lot of US-licensed Enbrel, 1 lot of EU-approved Enbrel and 3 lots of GP2015. There are several instances where the data for GP2015 lot D0917 are not available due to a sample mix-up and therefore, reduces the number of lots of GP2015 that are considered in the analytical similarity assessment.*

Oxidation: Amino acids including methionine, tryptophan, cysteine, tyrosine and histidine are susceptible to oxidation. Samples were incubated with increasing concentrations of H₂O₂ (0.3, 3 and 10%) to assess the impact of oxidation, Tables 6-8, to 6-10 and Figures 6-1 to 6-6, not copied. For HMW and LMW variants and % main peak, as the concentration of H₂O₂ increases, the main effect is an increase in the sum of LMW with a concomitant decrease in the % main peak. There are no differences observed in trends in the data between GP2015, US-licensed and EU-approved Enbrel and no new peaks were observed.

Size variants were also assessed using non-reduced CE-SDS. Table 6-11, not copied. There are no significant differences among the lots at the three treatment conditions.

Charge variants were assessed by CZE, Tables 6-12 to 6-14, not copied. Treatment at the three conditions increases acidic variants and reduces basic variants. The % main peak remains largely unchanged at 0.3% H₂O₂, but decreases when treated with 3% and 10% H₂O₂. There are no new peaks or trends in the data that differentiate the test articles from each other.

Hydrophobic variants were assessed using RPC, Tables 6-15 to 6-17 and Figures 6-7 to 6-12, not copied. At all three conditions, there is a decrease in the main peak and post-peak with a concomitant increase in the pre-peak area. There are no major differences among GP2015, US-licensed Enbrel and EU-approved Enbrel observed in the data with increasing amounts of H₂O₂.

TNF- α potency was assessed by the reporter gene assay, Table 6-18, not copied. The addition of H₂O₂ at all concentrations has a significant impact on potency that is common to all the test articles. There was no TNF-RGA activity observed following exposure to 3% or 10% H₂O₂. However in the case of the later this may have been due to sample mix-up or issues with the method.

Light Exposure (artificial light): In order to examine light sensitivity, the test articles were exposed to either artificial light for 21 hours and compared to a dark (control). A difference in the profile will reflect changes occurring in response exposure to artificial light. There is a decrease in the main peak with increases in both HMW LMW species after 10.5 and 21hr light exposure, Tables 6-19 and 6-20 and Figures 6-13 and 6-14, not copied.

Reviewer Comment: *For all samples, the levels of HMW and LMW species are higher after 10.5 hours than after 21 hours, but no explanation was provided.*

Using nrCE-SDS to assess size variants, there was an increase in HMW species, with a slight loss in main peak. There was no impact on LMW species, Tables 6-23 and 6-24, not copied.

The analysis of charge variants using CZE shows that exposure to artificial light results in a decrease in main peak with an increase in acidic peaks in GP2015 (14.5-16.5% to 44.1-32.9%), . US-licensed Enbrel and EU-approved Enbrel (12.4-12.6% to 21.1-21.2%). There is also a reduction in the levels of basic variants, Tables 6-27 and 6-28 not copied.

Using RPC, exposure to artificial light results in a decrease in the main peak with increases in the sum of pre-peaks (VP) and post-peaks (NP). The GP2015 main peak is reduced from 88.3 - 88.4% to 65.6 - 71.0%, the sum of VP from 1.2 - 1.1 to 17.6 - 14.1% the sum of NP from 10.0 - 10.5% to 14.9-16.8%. For US-licensed Enbrel and EU- approved Enbrel, the main peak is reduced from 82.1 - 88.9% to 65.1 - 65.7%, the sum of VP from <1.0 - 1.2% to 10 -12.3% and the sum of NP is increased from 17.1 -18.6 to 22.5 - 22.6%, Tables 6-31 and 6-32, not copied.

After 21 hour exposure, activity in the TNF- α RGA assay for GP2015 was reduced from 98 - 104% to 72 - 88%. For US-licensed Enbrel and EU- approved Enbrel, the potency was reduced from 84 - 86% to 68- 81%, Table 6-35, not copied.

Light Exposure (day light): In order to examine light sensitivity the test articles were exposed to either day light or dark (control) for two weeks. A difference in the profile will reflect changes occurring in response exposure to daylight. The SEC data show a decrease in the main peak and an increase in the sum HMW over the two week period, Tables 6-21 and 6-22 and Figures 6-15 and 6-16, not copied.

Analysis of size variants using CE-SDS shows no change in main peak, HMW or LMW species, Tables 6-25 and 6-26, not copied.

The analysis of the charge variants using CZE shows that exposure to day light results in minimal to no changes in main peak and a slight increase in acidic variants for GP2015 DP (14.5 and 16.5% to 20.3 and 19.7%) and US-licensed Enbrel and EU-approved Enbrel (12.4 and 12.6% to 14.4 and 15.3%). The results for basic variants also decrease slightly, except for GP2015 DS lot B213820, which has a slight increase in basic variants, Tables 6-29 Table 6-30, not copied.

Reviewer Comment: Although the trend in basic variants for the GP2015 DS lot was different compared with all other lots, this increase (12.2 – 14.6%) may be within the variability of the method. The slight decreases seen in the other lots ranged from 2.0 – 5.4%

The RPC analysis shows minimal changes in the main, peak VP and NP area following exposure to day light over two week time period, Tables 6-33 and 6-34, not copied.

After 2 weeks exposure to day light, activity in the TNF- α RGA assay for GP2015 was reduced slightly from 98 - 104% to 91 - 94%. For US-licensed Enbrel and EU- approved Enbrel , the potency was reduced from 84 - 86% to 78- 81%, Table 6-35, not copied.

Reviewer Comment: Table 6-35 includes data from a lot labelled CAN (1029710), which does not appear in the listing of lots in Table 6-6. A number of the Figures also include this lot (Figures 6-20 and 6-22). This lot is probably sourced from (b)(4).

An IR (#1) was communicated to Sandoz on 11/20/2015 that contained the following question:

Section 6.3.2.5, Forced Degradation Light Exposure: Table 6-35 “TNF-alpha RGA after light exposure” includes data from a lot labelled (b) (4) (1029710), which does not appear in the listing of lots in Table 6-6 “GP2015 and Enbrel batches used for forced degradation study”. A number of the figures also include data from this lot (e.g. Figures 6-20 and 6-22). Clarify if data from this lot is to be included in the submission and the country of origin of the lot.

In the response (12/11/2016) Sandoz indicated that Enbrel batch (b) (4) #1029710 was sourced from (b) (4) and was analyzed as an additional batch to US-licensed Enbrel and EU-authorized Enbrel in the head-to-head forced degradation study as presented in [Module 3.2.R Biosimilarity with reference product, Section 6] of the BLA. This batch was analyzed for information only and, therefore, data from this lot should not be included in the submission.

The updated “Biosimilarity with Reference Product” document submitted on 12/11/15 removed data from this lot in the Table and Figures. This is acceptable.

pH Stress: The test articles were incubated at pH 3.0, 7.0 and 8.5 for seven days. Results for SEC analysis are shown in Tables 6-36, 6-37 and 6-38, respectively, only Table 6-36 shown in review and Figures 6-17 – 6-22, not copied. For all samples there was a reduction in % main peak with increases in HMW and LMW species at pH 3.0 and pH 8.5. The trends at pH 7.0 were minor. However, at pH 3.0, the trends are not consistent for the GP2015 lots at pH 3.0, where the major changes for DP lot DR0917 occurred between day 0 and 1, Table 6-36. A possible explanation may be that fast aggregation and slow degradation is occurring.

Table 6-36 SEC results after pH 3.0 treatment

Parameter	Duration [d]	GP2015 DP		GP2015 DS	Enbrel®	
		CS2938	DR0917	B213820	#1034018 (US)	#G64164 (EU)
Area-%						
Main peak	0 ⁽¹⁾	95.7	96.7	97.5	90.6	92.5
	1	38.9	8.3	73.1	35.4	38.5
	2	34.7	6.4	54.0	30.2	32.6
	7	47.2	12.7	48.0	54.5	45.2
Sum HMW	0 ⁽¹⁾	0.7	0.5	0.3	2.7	3.1
	1	54.8	84.8	21.5	54.7	54.9
	2	58.0	86.0	40.0	61.9	61.1
	7	34.6	61.0	32.4	17.2	37.0
Sum LMW	0 ⁽¹⁾	3.6	2.8	2.3	6.7	4.3
	1	6.4	6.9	5.4	9.9	6.6
	2	7.2	7.6	6.0	7.9	6.3
	7	18.2	26.3	19.6	28.3 ⁽²⁾	17.8

Reviewer Comment: The trends observed for GP2015 DP lot CS2938 and DS lot B213820 were consistent with the US-licensed Enbrel and EU-approved Enbrel lots. The results from the SEC analysis of lot DR0917 indicate that this lot was more prone to aggregation given the rapid decline in the main peak after one day. This rapid aggregation rate was not seen at pH 8.5, although there was a reduction in main peak with increased in HMW and LMW peaks by day 7,

which was similar to all the other lots in the study. Taking the trends seen for the other lots and other pH conditions, the rates of degradation between GP2015, US-licensed Enbrel and EU-approved Enbrel are similar.

Using nr-CE-SDS to assess size variants, there were decreases seen in all lots for % main peak, with increases in HMW and LMW species at day 7 at pH 3.0 and 8.5, Table 6-39, not copied. There were no changes at pH 7.0. The increases in HMW species at pH 8.5 were greater for all 3 GP2015 lots than for the US-licensed Enbrel and EU-approved Enbrel lots.

The analysis of charge variants using CZE shows that all lots had a reduction in main peak and acidic variants, with an increase in basic variants when treated at pH 3.0. Data were not available for several time points for each lot due to sample mix-ups, Table 6-40, not copied. There were minor decreases in all lots for main peak and basic variants, with increases in acidic variants after 7 days when treated with pH 7.0, Table 6-41, not copied. After treatment for 7 days at pH 8.5, there were decreases in % main peak and increases in both acidic and basic variants for all lots, Table 6-42, not copied.

Using RPC, all lots had a decrease in main peak with increases in VP at pH 3.0. The GP2015 DP lots showed minor decreases in NP, while the GP2015 DS and US-licensed Enbrel and EU-approved Enbrel lots had decreases in NP, Table 6-43, not copied. At pH 7.0, there was little to no changes in any peak for any of the lots, Table 6-44, not copied. At pH 8.5 there were decreases in main peak with increases in NP among all lots. There were little to no changes in VP, Table 6-45, not copied.

Using the TNF- α RGA assay, there was negligible activity for any lot after treatment at pH 3.0 and 8.5 and minor losses in activity (but within specification) after 7 days at pH 7.0, Table 4-46, not copied.

Mechanical stirring: The test articles were stirred at 600 rpm for 1, 6, and 16 hours. There were minimal changes in size variants after 16 hours by SEC among all lots, Table 6-47, not copied and by nr-CE-SDS, Table 6-48, not copied. There were also minimal to no changes in charge variant by CZE, hydrophobic variants by RPC and bioactivity among all lots, Tables 6-48 to 6-51, not copied.

Reviewer Comment: *The forced degradation studies of GP2015, US-licensed Enbrel and EU-approved Enbrel examined the impact of oxidation, pH, light exposure and mechanical stirring on quality attributes. With a few exceptions that were not consistent and could be lot specific, there were no significant differences in the degradation profiles of the lots. These data contribute to demonstrating analytical similarity.*

Reviewer's Overall Assessment of Analytical Similarity

The three-way analytical similarity assessment between GP2015, US-licensed Enbrel and EU-approved Enbrel involved a range of orthogonal physicochemical and biochemical assays, as well as functional assays. In addition, the use of the EU-approved Enbrel in clinical trials required a three way bridge to support a demonstration of biosimilarity. Therefore, the analytical

similarity studies included GP2015 DP and DS lots, US-licensed Enbrel and EU-approved Enbrel lots. Based on the totality of the analytical data, including the statistical analyses, I conclude that for quality attributes including primary structure and tertiary structure, potency, charge and size variants, most glycoforms, binding assays and stability profiles, that the data support a demonstration that GP2015 is highly similar to US-licensed Enbrel. In addition pairwise comparisons of the US-licensed Enbrel with GP2015 and EU-approved Enbrel established the analytical portion of the scientific bridge. For quality attributes which did not meet the pre-specified acceptance criteria, the basis for the variability and the impact on the similarity assessment were adequately addressed. Quality attributes such as main peak purity, aggregation and degradation products demonstrated that GP2015 had slightly higher purity levels than US-licensed Enbrel. Similarly, product related impurities such as deamidated and oxidized variants were present in slightly lower levels in GP2015.

Regarding Fc-effector function, etanercept is reported to have low levels of CDC and ADCC activity. GP2015, US-license Enbrel and EU-approved Enbrel were similar for CDC activity. For ADCC, a structure function relationship was established between glycans, FcγRIIa binding and ADCC activity. GP2015 had lower ADCC activity relative to US-licensed Enbrel, which can be attributed to lower levels of afucosylation and to FcγRIIIa binding in GP2015. This structure function relationship between Fc afucosylation with binding to FcγRIIIa and resulting ADCC activity is well understood. Experimental data were presented showing that ADCC activity of etanercept is low relative to the anti-TNF mAbs and all TNF antagonist ADCC activity is low relative to a control mAb whose major mechanism is through Fc effector functions. Altogether, based on the experimental data and supporting information from the literature, ADCC is unlikely to be associated with Enbrel's mechanism of action. Therefore, the lower ADCC activity of GP2015 does not preclude a determination of highly similar to US-licensed Enbrel.

Differences in misfolded variants that have reduced potency were identified as the reason for the observed differences in potency using the TNF-α RGA assay between GP2015 and US-licensed Enbrel, although the GP2015 lots were within the min/max range of the US-licensed Enbrel lots. A scenario in which the misfolded variants regain activity in vitro and could regain activity in vivo was presented. A computed potency model was applied to the potency data to facilitate a comparison and the statistical analysis showed that GP2015 and US-licensed Enbrel met equivalence criteria. Therefore, the differences observed for hydrophobic variants do not preclude a demonstration that GP2015 is highly similar to US-licensed Enbrel.

In conclusion, based on the totality of the analytical data, I conclude that GP2015 is highly similar to US-licensed Enbrel and that a 3-way analytical bridge among GP2015, US-licensed Enbrel and EU-approved Enbrel was established.



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

Date: July 25, 2016
To: Administrative File, STN 761042/0
From: Candace Gomez-Broughton, Ph.D., Reviewer CDER/OPQ/OPF/DMA/ Branch IV
Endorsed: Patricia Hughes, Ph.D. Acting Branch Chief CDER/OPQ/OPF/DMA/Branch IV
Subject: Original Biologics License Application (BLA)
US License: 2003
Applicant: Sandoz, Inc.
Facilities: Novartis Pharma Stein AG, Stein, Switzerland
Product: GP2015 (etanercept)
Dosage: solution for subcutaneous injection (50 mg/mL and 25 mg/mL)
Indication: Treatment for rheumatoid, polyarticular juvenile, idiopathic, and psoriatic arthritis; ankylosing spondylitis, plaque psoriasis
Due date: August 30, 2016

Recommendation: The BLA, as amended, is recommended for approval from a microbiology product quality perspective with the following Post-Marketing Commitment:

Repeat the microbial retention study using a more suitable surrogate solution. Attributes of the surrogate solution that are known to affect microbial retention (surface tension, viscosity, ionic strength, etc.) should model the drug product as closely as possible while preserving viability of the challenge organism. Alternatively, use of a reduced exposure time or modified process conditions (e.g., temperature) may be appropriate. Provide the summary data, the associated report, and justification for any modifications to the study. If any filtration parameters are changed as a result of the study, update the BLA file accordingly. The final report will be submitted as a CBE30 by September 30, 2017.

INTRODUCTION

Sandoz, Inc. has submitted Biologic License Application (BLA) 761042 in eCTD format for the approval of GP2015 (etanercept) as a biosimilar product to the reference biologic product Enbrel® (licensed under BLA 103795 by Amgen Inc.). The drug product is filled in either single-use pre-filled syringe or single-use pre-filled autoinjector. The drug substance is manufactured at Sandoz GmbH in Langkamfen, Austria (FEI: 3004828473).

This report covers the drug product sections of the BLA. Drug substance is covered in a separate review completed by Reyes Candau-Chacon, Ph.D.

Amendments Reviewed for Drug Product Quality Microbiology

Sequence	Date	Comments
0008	1/15/2016	Response to Information Request sent 12/11/2015
0029	6/3/2016	Response to Information Request sent 05/26/2016
0031	6/24/2016	Response to Information Request sent 06/17/2016
0032	7/7/2016	Response to Information Request sent 05/19/2016

ASSESSMENT

P Drug Product

P.1 Description and Composition of the Drug Product

GP2015 drug product is a liquid for injection filled into syringes at two different dosage concentrations, 25 mg/0.5 mL and 50 mg/1.0 mL. The formulation includes GP2015 drug substance, sodium citrate, sodium chloride, sucrose, L-lysine, and water for injection.

The container closure system consists of a colorless syringe barrel made of (b) (4) glass, class I. The syringe is equipped with a staked stainless steel needle and a rigid needle shield in (b) (4) rubber formulation. The syringes also contain (b) (4) rubber stoppers (b) (4). There are no diluents supplied with the drug product.

P.2 Pharmaceutical Development

P.2.4 Manufacturing Process Development



In their response submitted on June 24, 2016 (Sequence #0031), the sponsor has agreed to repeat the bacterial retention study using a surrogate fluid that resembles the drug product more closely. The study will include the following three components:



The sponsor has agreed to provide the results of the repeated bacterial retention study that are expected to be available in Q3/2017 and communicated in the first Annual Report in 2017.

P.2.6 Microbiological Attributes

P.2.6.2 Container Closure Integrity Test

P.2.6.2.1 Microbiological Integrity

P.2.6.2.1.1 Testing Procedure and Results

In order to test container closure integrity, the sponsor performed a microbial ingress test. Each test consisted of 40 units filled with sterile media (soybean casein digest medium). The units were submerged in a suspension of *Brevundimonas diminuta* (ATCC 19146) for one hour under negative pressure (650 mbar). Pressure is then brought to 1300 mbar. The units are removed from the suspension and incubated for 5 to 7 days at 29-31°C and then checked for turbidity.

The units must remain clear. The study included two controls in which (b) (4) µm capillary tubes were used to breach the units. Growth promotion properties of the medium was confirmed by inoculating two of the incubated test units with *B. diminuta* and incubated again. The limit of detection was determined to be (b) (4) µm.

Results from the study show no visible growth in the test units. Growth was observed in the 2 positive controls and 2 breach controls. No growth was observed in the two negative control units.

The following information request was sent to the applicant:

The description of the microbial ingress test in Section 3.2.P.2 Pharmaceutical Development states that the two controls included in the study were breached with (b) (4) µm capillary tubes. In addition, it states the limit of detection (LOD) was determined to be (b) (4) µm.

A breach size of (b) (4) µm is relatively large, therefore the test is inadequate. Please repeat the study using a smaller breach size in the positive control. Include a description of how the limit of detection is determined in this study and how it correlates with the LOD of the dye ingress test used to test drug product placed on stability.

In their response (amendment 0008 dated January 11, 2016); the applicant stated that the CCIT using a (b) (4) µm was completed in 2012. The test was revalidated in 2014 by an improved validation program. These studies demonstrated suitability of the ingress test down to (b) (4) µm by

applying pressure conditions lower than 700 mbar for under pressure conditions and higher than 1,250 mbar for over pressure condition. The (b) (4) μm breach control is used to the test drug product placed on stability.

SATISFACTORY

P.2.6.2.1.2 Stability Program

Potential growth promoting effects of GP2015 were evaluated. Sterile nutrient medium was filled into syringes and stored horizontally for 6 months, 1, 2, 3, 4 and 5 years at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$. Another group of syringes were stored at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. 40 syringes were tested at each time point using the microbial ingress test described in the previous section however; syringes tested at the 5 year time point was subjected to 650 mbar and 1500 mbar pressure conditions. The results are summarized in the table below. Large scale studies are discussed in Section P.3.5.

Table 6-4 Stability program, CCIT requirements and results

Test article	Storage condition [°C]	Storage time before CCIT	Requirement	Result	Passed?
40 test syringes	25 ± 2	6m, 1y, 2y, 3y, 4y, 5y	No visible growth	No visible growth	Yes
2 positive controls	25 ± 2	6m, 1y, 2y, 3y, 4y, 5y	Visible growth	Visible growth	Yes
2 breach controls	25 ± 2	4y, 5y	Visible growth	Visible growth	Yes
2 negative controls	25 ± 2	6m, 1y, 2y, 3y, 4y, 5y	No visible growth	No visible growth	Yes
40 test syringes	5 ± 3	6m, 1y, 2y, 3y, 4y, 5y	No visible growth	No visible growth	Yes
2 positive controls	5 ± 3	6m, 1y, 2y, 3y, 4y, 5y	Visible growth	Visible growth	Yes
2 breach controls	5 ± 3	4y, 5y	Visible growth	Visible growth	Yes
2 negative controls	5 ± 3	6m, 1y, 2y, 3y, 4y, 5y	No visible growth	No visible growth	Yes

Based on this growth promotion data, (b) (4)

P.2.6.2.2 Dye Ingress Testing

The dye ingress test for container closure integrity was used during process validation. Results are presented in Section 3.2.P.3.5. This method will be performed on drug product placed on stability (Section 3.2.P.8.2).

P.2.6.3 Rabbit Pyrogen Test

Three lots of drug product (VB50B1 (50 mg/1.0 mL), VB50B2 (50 mg/1.0 mL), and VB25B1 (25 mg/0.5 mL)) were subjected to the rabbit pyrogen test on February 26, 2015. The test was completed according to 21CFR610.13 (b) and USP <151>. Results show that all three batches passed and are summarized in the following table.

Table 6-5 Results of rabbit pyrogen test

GP2015 batch number	Dosage	RPT result [°C]	RPT conclusion
VB50B1	0.75 mg/kg	Rabbit 1: 0.1 Rabbit 2: 0.0 Rabbit 3: 0.0	Passed
VB50B2	0.75 mg/kg	Rabbit 1: 0.0 Rabbit 2: 0.0 Rabbit 3: 0.1	Passed
VB25B1	1.5 mg/kg	Rabbit 1: 0.2 Rabbit 2: 0.0 Rabbit 3: 0.0	Passed

Results show that the GP2015 drug product is non-pyrogenic.

Reviewer comment: The rabbit pyrogen test report was requested and submitted to the BLA under Sequence #0008.

P.3 Manufacture

P.3.1 Manufacturer(s)

The GP2015 drug product is manufactured by Novartis Pharma Stein AG in Stein, Switzerland (FEI: 3002653483) in Building (b)(4). Pre-filled syringes are assembled with the (b)(4) autoinjector by (b)(4). Release and stability testing (endotoxin, CCIT, and sterility) is performed by Sandoz GmbH in Kundl and Langkampfen Austria and Novartis Pharma Stein AG.

P.3.2 Batch Formula

(b)(4)

P.3.2.2 Manufacturing formula

(b)(4)

30 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

P.8 Stability

Storage conditions covered in the stability studies included long term storage at $5\pm 3^{\circ}\text{C}$ for up to 42 months or at Condition A. Condition A includes an initial temperature excursion to $25 \pm 2^{\circ}\text{C}$, then applied shaking stress, followed by storage at $5\pm 3^{\circ}\text{C}$ and another temperature excursion at $25\pm 2^{\circ}\text{C}$ prior to analysis.

Studies were also done using accelerated and stress storage conditions at $25\pm 2^{\circ}\text{C}/60\pm 5\%$ RH or at $40\pm 2^{\circ}\text{C}$. Data was collected for 6 or 1.5 months, respectively. The stability studies completed at summarized in the following table.

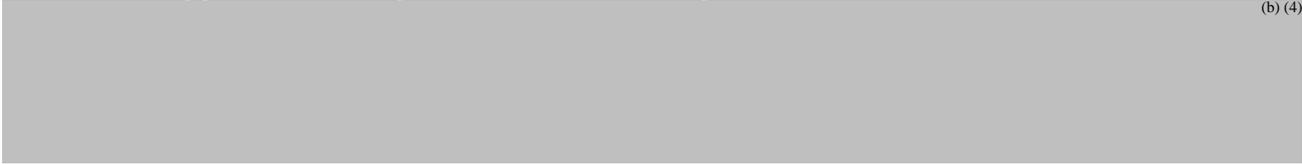
Table 2-1 Summary of conditions and available data

Condition		Data available [months]	
		GP2015 25 mg/0.5 mL	GP2015 50 mg/1.0 mL
$5 \pm 3^{\circ}\text{C}$	Long term storage	30	36
Condition A*	Long term storage	30	36
$25 \pm 2^{\circ}\text{C}/60 \pm 5\%$ RH	Accelerated	6	6
$40 \pm 2^{\circ}\text{C}$	Stress	1.5	1.5

*Condition A refers to a set of similar condition (see [Table 3-2](#))

The proposed shelf-life for both DP strengths is 24 months. All results for sterility and endotoxin met the specifications.

P.8.2 Post-Approval Stability Protocol and Stability Commitment



(b) (4) GP2015_50 Combination Product

The GP2015 50/mg/1.0 mL prefilled syringe preassembled into an autoinjector device to form a single integral unit which is not to be separated.

The autoinjector consists of the following components:



A diagram of the device is provided in the figure below (copied from Section 3.2.R Technical Summary (b) (4) Device of the submission)

Figure 4-4 Graphical depiction of the ^{(b) (4)}GP2015_50 and its key components ^{(b) (4)}



The assembly, labeling, and packaging of the AI take place at ^{(b) (4)}
^{(b) (4)}. Assembly and packaging is completed in building ^{(b) (4)}
^{(b) (4)} for final packaging, both located in building ^{(b) (4)}.

Assembly consists of ^{(b) (4)}

^{(b) (4)}

Reviewer comment: The AI and its assembly have been adequately described. The autoinjector does not come into contact with the drug product. Please refer to the CDRH review for assembly and functionality of the assembled product.

Assembly Process Qualification and Validation

The assembly process of the ^{(b) (4)}GP2015_50 autoinjector was validated with three consecutive batches with batch sizes ranging from ^{(b) (4)} pieces. A description of the batches is provided in the following table.

These studies were done to confirm the performance and reproducibility of the assembly process and to verify the product quality after assembly. Acceptance criteria and results from the visual inspection and functionality testing were discussed in the submission and should be reviewed by CDRH.

A risk assessment on the assembly process was completed to evaluate the possible impact of the assembly process on the prefilled syringe, the drug product, and the interface between the (b) (4) AI and the PFS. The results showed that the assembly process for the (b) (4) AI is not expected to have an influence on the product quality.

In addition, samples of all three batches were kept for stability testing to provide evidence that the assembly process does not have any impact on the product quality of the drug product. The stability testing includes both sterility testing and container closure integrity.

Table 13-4 Overview on validation batches

Combination Product (b) (4) GP2015_50	Quantity	GP2015 50mg / 1.0mL PFS	(b) (4)
[Batch No.]	[pieces]	[SDZ Batch No]	(b) (4) [Batch Number]
10041403	(b) (4)	30949725	14143006 / 14143005
07041401		30949721	14133002 / 14128001
08041402		30949722	14139004 / 14139003

Shipping Validation

A Transport Validation Master Plan has been submitted to the BLA. The plan covers validation (b) (4)



Results from the transport studies met acceptance criteria for temperature and container closure integrity as assessed using the dye ingress test previously described.

Reviewer comment: The results from the transport validation studies have been reviewed by CDRH in its entirety. The results are adequate from a microbiology product quality perspective.

SATISFACTORY

CONCLUSION

- I. The drug product section of the BLA, as amended, is recommended for approval from a sterility assurance and microbiology product quality perspective with the following Post-Marketing Commitment:

Repeat the microbial retention study using a more suitable surrogate solution. Attributes of the surrogate solution that are known to affect microbial retention (surface tension, viscosity, ionic strength, etc.) should model the drug product as closely as possible while preserving viability of the challenge organism. Alternatively, use of a reduced exposure time or modified process conditions (e.g., temperature) may be appropriate. Provide the summary data, the associated report, and justification for any modifications to the study. If any filtration parameters are changed as a result of the study, update the BLA file accordingly. The final report will be submitted as a CBE30 by September 30, 2017.

- II. CMC product specific information and data should be reviewed by the OBP reviewer.
- III. No additional inspectional follow-up items were identified.

Information Requested During Review Cycle

Information Request Sent 09 December 2015

P.2 Pharmaceutical Development

1. Provide study reports for bacterial retention studies and integrity test (bubble point and forward flow) validation studies for the sterilizing filters.
2. Submit the Rabbit Pyrogen Test report to the BLA.
3. This section states that filter integrity testing is (b) (4) using either the forward flow or bubble point test. What factors determine which test is used?

P.3.3 Description of Manufacturing Process and Process Controls

1. Indicate if the formulation buffer is monitored for bioburden and endotoxin prior to formulation. Indicate the established limits for the buffer solution and if the buffers are filtered prior to use.
2. Confirm that bioburden samples are collected (b) (4) sample points.

P.3.4 Control of Critical Steps and Intermediates

4. [REDACTED] (b) (4)
5. [REDACTED]
6. [REDACTED]

P.3.5 Process Validation and/or Evaluation

1. The [REDACTED] (b) (4) of NMT [REDACTED] (b) (4) hours was established based on growth promotion studies. However, the duration of the validation studies was only 8 hours and 24 minutes.
2. Provide the number of rejected vials from each media fill run [REDACTED] (b) (4).
3. Provide data from the most recent requalification of the [REDACTED] (b) (4) relevant for GP2015 PFS.
4. With regard to [REDACTED] (b) (4) qualification studies, provide a description and/or diagram of the locations of the [REDACTED] (b) (4).
5. Provide and update on the progress of the transport validation studies currently in progress.

Information Request Sent 19 May 2016

P.5 Control of Drug Product

1. Both the rapid sterility test and compendial test have been validated to test the sterility of GP2015. Specify when the rapid sterility test would be used as opposed to the compendial test.
2. Provide descriptions of the [REDACTED] (b) (4) bioburden test, compendial sterility test, and bacterial endotoxins (LAL) test.
3. Please move container closure integrity method validation section from Section R. Regional Information to Section P.5.3 Validation of Analytical Procedures.
4. Bacterial retention studies completed to validate the sterilizing filter were not adequately performed. The use of [REDACTED] (b) (4) in place of the product for the challenge organism preparation is not acceptable. A surrogate fluid which matches the product as much as possible in terms of its physical and chemical characteristics should be used for the

challenge study. Alternatively, the bactericidal effect of the formulated drug product may be overcome by performing the study at a reduced exposure time, or using modified process or using a modified product, etc. Propose a strategy and timeframe for repeating the study with more relevant challenge conditions.

5. With regard to the two sterility test methods proposed for release testing, the BLA states that the rapid sterility test is (b) (4) and that the compendial sterility test method (b) (4). The Applicant should test for sterility using one method.

In addition, the rapid test has not been adequately validated. A full validation study supporting the use of this method should be submitted. More robust studies are necessary to determine the limit of detection. In addition, the bioluminescent background test should be performed using the appropriate controls.

6. The description of the microbial ingress test in Section 3.2.P.2 Pharmaceutical Development states that the two controls included in the study were breached with (b) (4) µm capillary tubes. In addition, it states the limit of detection (LOD) was determined to be (b) (4) µm.

A breach size of (b) (4) µm is relatively large, therefore the test is inadequate. Please repeat the study using a smaller breach size in the positive control. Include a description of how the limit of detection is determined in this study and how it correlates with the LOD of the dye ingress test used to test drug product placed on stability.

7. With regard to the proposed in-process controls, please implement in-process endotoxin testing with appropriate limits to your microbial control strategy.
8. Provide the purpose of the container closure integrity test (b) (4) during process validation. No description was provided in the BLA.
9. With regard to the endotoxin test method, the effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin standard (CSE or RSE) into undiluted drug product and then testing for recoverable endotoxin over time. Please complete this study to demonstrate that drug product does not interfere with endotoxin recoverability and submit the study report to the BLA.

Information Request Sent 17 Jun 2016

1. With regard to the bacterial retention studies, PDA Technical Report No. 26, Chapter 6.8.3 suggests removing the bactericidal component or using a surrogate fluid, however, it does not suggest the use (b) (4). We maintain that the use of (b) (4) in place of the product for the challenge organism preparation is not acceptable. A surrogate fluid which matches the drug product as much as possible in terms of its physical and chemical characteristics should be used for the challenge study. Please repeat the bacterial retention study using a surrogate fluid that more closely resembles the composition of GP2015 drug product. Also, please inform the Agency when you expect

to complete the study. If necessary, the study may be completed as a Post-Marketing commitment.

2. As part of the validation of the Rapid Sterility Test, a bioluminescent background test was completed and results from the test using GP2015 DP without spiking were provided. However, the results from the positive control, verifying that the bioluminescence reaction is not inhibited by the DP were not provided. Please provide results from the positive control (described in section 3.2.P.5.3.2.2.4.3 Verification That Bioluminescence Reaction Is Not Inhibited).
3. Please provide the specific conditions under which the alternative sterility test method would be used and amend the BLA accordingly. Also, please confirm that the alternative test method will not be used in response to a sterility test failure

SIGNATURES

Candace Y. Gomez-
broughton -A

Digitally signed by Candace Y. Gomez-broughton -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=2000640207,
cn=Candace Y. Gomez-broughton -A
Date: 2016.08.04.11.08.56 -04'00'

Patricia F.
Hughestroost
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Hughestroost -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
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6547, cn=Patricia F. Hughestroost -
S
Date: 2016.08.04.11.23:25 -04'00'



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

Date: July 21, 2015
To: Administrative File, STN 761042/0
From: Reyes Candau-Chacon, PhD. Reviewer

Maria D. Candauchacon -S
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0.9.2342.19200300.100.1.1=2000639745, cn=Maria D. Candauchacon -S
Date: 2016.07.25 13:22:12 -04'00'

Through: Patricia Hughes, Ph.D., Acting Branch Chief

Patricia F. Hughestroost -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1200096547, cn=Patricia F.
Hughestroost -S
Date: 2016.07.26 07:27:37 -04'00'

Subject: New Biologic License Application (BLA)
US License: 2003
Applicant: Sandoz Inc.
Facilities: Sandoz GmbH, Biochemiestrasse 10, Langkampfen, A-6336 Austria (FEI 3004828473)
Product: (b) (4) (proposed biosimilar to US approved etanercept, GP2015)
Dosage: 50 mg/mL and 25 mg/0.5 mL sterile solution for subcutaneous injection in a prefilled syringe (PFS) with a needle safety device (NSD) or an autoinjector (AI) device.
Indication: Rheumatoid Arthritis; Polyarticular Juvenile Idiopathic Arthritis; Psoriatic Arthritis; Ankylosing Spondylitis; Plaque Psoriasis
Due date: August 30, 2016

Recommendation for Approvability: The drug substance part of BLA 761042 is recommended for approval from a microbial control and microbiology product quality perspective

Review Summary

Sandoz Inc. has submitted BLA 761042 to license (b) (4) drug substance and drug product and their manufacturing processes.

BLA 761042 was submitted in eCTD on December 22, 2014 and contained modules 1, 2, and 4; modules 3 and 5 were submitted on July 30, 2015. This review contains the assessment of the manufacturing process GP2015 bulk drug substance from a microbiological quality perspective. For review of drug product aspects of the application, please see the review by Dr. Candace Gomez-Broughton.

Amendments Reviewed for Drug Substance Quality

Information Request date	Question numbers	Amendment sequence	Amendment date
November 20, 2015	1 to 8	0007	December 11, 2015
February 26, 2016	1, 2, 4, 5	0018	March 22, 2016
April 7, 2016	1, 2, 4, 5,	0024	April 22, 2016
April 22, 2016	4, 5	0027	May 4, 2016

Detailed review of the sponsor's responses is included at the end of this memo (pages 26-40)

Review Narrative

S DRUG SUBSTANCE

S.1 General Information

GP2015 is a dimeric fusion protein that binds to the tumor necrosis factor (TNF) to reduce systemic inflammation. The glycoprotein is produced in Chinese Hamster Ovary (CHO) cells.

The description is satisfactory

S.2 Manufacture

S.2.1 Manufacturer(s)

The following facilities are used for the manufacture, release testing, and stability testing of GP2015 drug substance:

- Sandoz GmbH, Biochemiestrasse 10, 6336 Langkampfen, Austria; DS manufacture, release, stability, and IPC testing, storage of WCB and MCB FEI 3004828473
- Sandoz GmbH, Biochemiestrasse 10, 6250 Kundl, Austria; DS release, stability, and IPC testing, storage of WCB and MCB FEI 3002806523
- [REDACTED] (b) (4)
[REDACTED] release testing
FEI (b) (4)
- [REDACTED] (b) (4)
[REDACTED] DS release testing
FEI (b) (4) 7
- [REDACTED] (b) (4)
[REDACTED]; DS release and stability testing
FEI (b) (4) 8
- Novartis Pharma AG, Lichtstraße 35, 4056 Basel, Switzerland; DS release and stability testing
FEI 3002807772
- [REDACTED] (b) (4) DS release and stability testing, preparation and storage of WCB, storage of MCB
FEI: [REDACTED] (b) (4)

Reviewer comments:

Bioburden and endotoxin IPC and release testing is conducted in the Kundl facility, approximately 17 Km from the DS manufacturing facility in Langkampfen (Refer to Section P.3.1, Table 2-4 of the BLA. Refer to Panorama for the compliance status of the manufacturing and testing facilities.

S.2.2 Description of the Manufacturing Process and Process Controls

S.2.2.1 Batches and Scale Definition

(b) (4)

S.2.2.2



S.7.2 Stability Data

Bioburden samples were taken from (b) (4) °C, (b) (4) mL stability batches (b) (4); endotoxin samples were taken (b) (4) for some batches. All results met specifications.

Bioburden and endotoxin samples from (b) (4) mL containers stored at (b) (4) °C were taken for batches B089976, B098255, and B100829 at (b) (4) up to (b) (4) months; all results met specifications. Bioburden and endotoxin samples from (b) (4) mL containers stored at (b) (4) °C were taken for batches B166648, B170047, and B170075 at (b) (4) months; all results met specifications.

Reviewer Comments:

Microbial quality results of stability samples are not necessarily representative of microbial quality of drug substance stored in different containers. Bioburden and endotoxin results from (b) (4) mL containers stored at (b) (4) °C met specifications.

SATISFACTORY

Conclusion

- I. The Drug Substance section of the BLA is recommended for approval from a product quality microbiology perspective.
- II. Information and data not related to microbial control of the drug substance should be reviewed by an OBP reviewer.
- III. Refer to Panorama for GMP status of the relevant facilities.

15 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



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

Date: June 10, 2016
To: Administrative File, STN 761042/0
From: Zhong Li, Ph.D., Chemist, CDER/OPQ/OPF/DIA
Endorsement: Zhihao Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
US License: 2003
Applicant: Sandoz, Inc.
Mfg. Facilities: Drug Substance: *Sandoz GmbH*, Langkampfen, Austria
FEI 3004828473
Drug Product: *Novartis Pharma Stein AG*, Stein, Switzerland
FEI 3002653483
Combination Product: (b) (4)
Product: GP2015, Solution for Injection
Dosage: 25 mg/0.5 mL and 50 mg/1.0 mL
Indication: Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis
Goal Date: 8/30/2016

RECOMMENDATION:

Approval: This submission is recommended for approval from a facilities assessment perspective.

SUMMARY

BLA STN 761042/0 was submitted by Sandoz Inc., which provided information and data to support the manufacture of GP2015, solution for injection. GP2015 is a genetically-engineered dimeric fusion protein, which binds to tumor necrosis factor (TNF) to reduce systemic inflammation. GP2015 binds TNF via the extracellular ligand-binding portion of the human 75 kilodalton tumor necrosis factor receptor (TNFR), which is linked to the Fc portion of human immunoglobulin G (IgG1). The glycoprotein is produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) mammalian cell expression system. GP2015 drug product (DP), 25 mg/0.5 mL and 50 mg/1.0 mL solution for injection, is a colorless to slightly yellowish solution comprising GP2015 as drug substance (DS), sodium citrate as buffer, sodium chloride (b) (4), sucrose

and L-lysine (b)(4) and water for injection (b)(4) GP2015 drug product is supplied in pre-filled syringes (clear glass barrel with fixed needle) closed with a plunger stopper and is intended for subcutaneous (*s.c.*) administration.

The subject BLA proposes commercial manufacture of GP2105 DS and DP at Sandoz GmbH, Langkampfen, Austria (FEI 3004828473) and Novartis Pharma Stein AG, Stein, Switzerland (FEI 3002653483), respectively. Cell banking and testing operations will occur at (b)(4); Sandoz GmbH, Kundl, Austria (FEI 3002806523); and Sandoz GmbH, Langkampfen, Austria (FEI 3004828473). Testing operations will also occur at (b)(4); Novartis Pharma AG, Basel, Switzerland (FEI 3002807772); and (b)(4). Labeling, assembly with a needle safety device (NSD) or autoinjector (50 mg strength only) as well as final packaging are performed at (b)(4)

ASSESSMENT

DRUG SUBSTANCE FACILITIES

- 3.2.S.2.1 DS Manufacturers

The sites proposed for commercial manufacturing of GP2015 DS, cell banking operations, and testing are presented below in **Table 1**.

TABLE 1. Proposed Sites for GP2015 DS Manufacturing and Testing Operations

Site Name	Address	FEI Number	Responsibilities
Sandoz GmbH	Biochemiestrasse 10 6336 Langkampfen Austria	3004828473	Manufacturing of drug substance; Release testing, Stability testing, IPC testing; Storage of WCB and MCB;
		(b)(4)	DS Release testing, Stability testing; (Potency-primary); Preparation of WCB; Storage of WCB and MCB
Novartis Pharma AG	Lichtstraße 35 4056 Basel Switzerland	3002807772	DS Release testing, Stability testing; (Potency-alternative) HCP ELISA
Sandoz GmbH	Biochemiestrasse 10 6250 Kundl Austria	3002806523	Release testing of DS; Release testing, Stability testing, IPC testing; (Storage of WCB and MCB)
		(b)(4)	DS Release testing, Stability testing
		(b)(4)	Release testing of GP2015 (b)(4)
		(b)(4)	Release testing of GP2015 (b)(4)

Reviewer Comment 1: *The facilities for commercial manufacturing of GP2015 drug substance are adequately described.*

• **Prior Inspection History for DS Manufacturing and Testing Sites**

Sandoz GmbH Schaftenau (FEI 3004828473)

- The inspection from **3/10-18/2014** was a GMP surveillance inspection conducted in accordance with CP7356.002A and CP7356.002F and covered the Quality, Production, Laboratory Control, Materials, and Facility and Equipment systems. No FDA-483 was issued. The inspection was classified **NAI**.
- The inspection from **3/8-16/2012** was a GMP surveillance inspection conducted in accordance with PAC 56002A, PAC 560021B, 7356.002F, PAC 56002F, PAC 71005 and covered the Quality, Production, Facilities & Equipment, and Lab Control systems. A 9-item FDA-483 was issued. The firm response was deemed adequate in addressing the deficiencies. The inspection was downgraded from OAI to **VAI**.
- The inspection from **7/26-29/2010** was a GMP surveillance inspection conducted in accordance with CPs 7356.002, 7356.002A, 7356.002M, and 7356.002F, and ICH Q7A; and covered the quality, production, laboratory control systems, and facilities-and-equipment systems. A 4-item FDA-483 was issued. The firm provided a written response which included details for acceptable corrective actions. The inspection was classified **VAI**.

(b) (4)

- The inspection from (b) (4) was a pre-license inspection in support of BLA (b) (4) conducted in accordance with CP 7346.832 and ICH Q7, and covered Quality, Facilities and Equipment, Production, Materials, and Laboratory systems. No FDA-483 was issued. The inspection was classified **NAI**.
- The inspection from (b) (4) was a GMP surveillance inspection conducted in accordance with CP7356.002F and covered the Quality, Production, Laboratory Control, and Facility and Equipment systems. No FDA-483 was issued. The inspection was classified **NAI**.
- The inspection from (b) (4) was a GMP surveillance inspection conducted in accordance with CP7356.002F and covered the Quality, Facilities and Equipment, Materials, Production, and Laboratory Controls systems. No FDA-483 was issued. The inspection was classified **NAI**.

Novartis Pharma AG (FEI 3002807772)

- The inspection from **1/12-14/2015** was a pre-approval and GMP surveillance inspection conducted in accordance with CP7356.002 and CP7346.832 and covered the Quality and Lab Control systems. No FDA-483 was issued. The inspection was classified **NAI**.
- The inspection from **12/2-5/2013** was a pre-approval and GMP surveillance inspection conducted in accordance with CP7356.002 and CP7346.832 and covered the Quality and Lab Control systems. No FDA-483 was issued. The inspection was classified **NAI**.

- The inspection from **7/12-18/2012** was a pre-approval and GMP surveillance inspection conducted in accordance with CP7356.002 and CP7346.832 and covered the Quality and Lab Control systems. No FDA-483 was issued. The inspection was classified **NAI**.

Sandoz GmbH Kundl (FEI 3002806523)

- The inspection from **4/20-30/2015** was a GMP surveillance inspection conducted in accordance with CPs 7356.002F, 7356.002, 7356.002A and 7356.002M and covered the Quality, Facilities and Equipment, Production, and Laboratory Control systems. A 3-item FDA-483 was issued. The firm's corrective action plan was deemed appropriate to correct the deficiencies. The inspection was classified **VAI**.
- The inspection from **9/8-16/2014** was a pre-approval and GMP surveillance inspection conducted in accordance with CPs 7346.832, 7356.002F, 7356.002, 7356.002A and 7356.002M and covered all 6 systems. A 4-item FDA-483 was issued. The firm's response to 483 was deemed adequately addressing the deficiencies. The inspection was classified **VAI**.
- The inspection from **10/3-12/2012** was a GMP surveillance inspection conducted in accordance with CPs 7356.002F, 7356.002, 7356.002A and 7356.002M and covered the Quality, Production, and Laboratory Systems. A 10-item FDA-483 was issued. The firm's response to 483 was deemed adequately addressing the deficiencies. The inspection was classified **VAI**.

(b) (4)

- The inspection from (b) (4) was a pre-approval and GMP surveillance inspection conducted in accordance with CP7356.002 and CP7346.832 and covered the Quality and Lab Control systems. No FDA-483 was issued. The inspection was classified **NAI**.
- The inspection from (b) (4) was a pre-approval and GMP surveillance inspection conducted in accordance with CP7356.002 and CP7346.832 and covered the Quality and Laboratory Control systems. No FDA-483 was issued. A 1-item FDA-483 was issued. The firm's response to 483 was deemed adequately addressing the deficiency. The inspection was classified **VAI**.
- The inspection from (b) (4) was a pre-approval and GMP surveillance inspection conducted in accordance with CP7356.002 and CP7346.832 and covered the Quality and Lab Control systems. No FDA-483 was issued. The inspection was classified **NAI**.

(b) (4)

- The inspection from (b) (4) was a GMP surveillance inspection conducted in accordance with CP7356.002M and covered the Facility/Equipment, Quality, Lab and Material systems. No FDA-483 was issued. The inspection was classified **NAI**.
- The inspection from (b) (4) was a GMP surveillance inspection conducted in accordance with CP7356.002M and covered the Facility/Equipment, Quality, Material and Laboratory systems. A 2-item FDA-483 was issued. The inspection was classified **VAI**.
- The inspection from (b) (4) was a pre-approval and GMP surveillance inspection conducted in accordance with CP7356.002 and CP7346.832 and covered the Quality,

Laboratory and Materials, and Facilities/Equipment systems. No FDA-483 was issued. The inspection was classified **NAI**.

(b) (4)

- The facility had *not* been inspected by FDA prior to 1/2016.

- **Current Pre-approval Inspection Decisions**

Sandoz GmbH Schafstenu (FEI 3004828473)

A pre-license inspection (PLI) of Sandoz GmbH, *Plant Schafstenu*, in Austria was completed in support of BLA 761042/0 for GP2015. The inspection occurred from **03/7-11/2016** and was conducted in accordance with CP7346.832 and ICH Q7. A comprehensive review of facilities, utilities, equipment, processes and procedures was conducted to evaluate product quality, compliance to commitments in the BLA and compliance to CGMPs. The adequacy of the controls in place to support concurrent multi-product manufacturing from was also assessed. Contamination and cross-contamination controls were evaluated. A 2-item FDA-483 was issued at the conclusion of the inspection, citing that (1) no demonstration of microbial control of (b) (4) during storage; and (2) (b) (4) (b) (4) and (b) (4) hold time not adequately established with supporting microbial quality data. The inspection was initially classed **VAI**. The firm's responses to FDA-483 observations are deemed adequate. OPF/DIA concurs with the VAI recommendation and recommends approval for BLA 761042 (CMS WA #123711).

During the PLI, FDA investigators found that the following (2) contact labs had been also involved in the GP2105 DS and DP primary/registration stability studies in support of the BLA.

(b) (4)

- The firm was most recently inspected by FDA from (b) (4). This was a pre-approval and GMP surveillance inspection conducted in accordance with CP7356.002 and CP7346.832 and covered the Quality and Laboratory systems. No FDA-483 was issued. The inspection was classified **NAI**. Profile code CTL was updated in FACTS and acceptable. The previous inspection from (b) (4) was also classified as **NAI**.

(b) (4)

- The firm was inspected by FDA from (b) (4). This was an initial, pre-approval and GMP surveillance inspection conducted in accordance with CP7356.002 and CP7346.832 and covered the Quality and Lab systems. No FDA-483 was issued. The inspection was classified **NAI**. Profile code CTL was updated in FACTS and acceptable.

Sandoz GmbH Kundl (FEI 3004828473)

A pre-license inspection (PLI) of Sandoz GmbH, *Plant Kundl*, in Austria was completed in support of BLA 761042/0 for GP2015 in conjunction with the PLI at Sandoz GmbH, Plant Schafstenu (see above). The current inspection at the Kundl site only covered the microbial quality (bioburden and endotoxin) testing and sample shipping and handling and sample storage for GP2015 DS. A 2-item FDA-483 was issued for: (1) Bioburden test for GP2015 (b) (4) is not conducted adequately; and (2) Bioburden results are not reported adequately in the batch records. The inspection was initially classified as **VAI**. The firm's

responses to FDA-483 observations are deemed adequate. OPF/DIA concurs with the VAI recommendation and recommends approval for BLA 761042 (CMS Work # 123701).

(b) (4)

The inspection of the facility from (b) (4) was an initial GMP inspection and a pre-approval inspection (PAI) in support of BLA 761042/0 for GP2015. The inspection was performed in accordance with Compliance Programs 7346.832 Pre-Approval Inspection/Investigation and 7 356.002 Drug Process Inspections. The inspection focused on the testing of GP2015 (b) (4). The inspection covered the Quality and Lab Control system. No FDA-483 was issued. The inspection was initially classified NAI. OPF/DIA concurs with the NAI recommendation and recommends approval for BLA 761042 (CMS WA #119762).

The inspection revealed that the firm subcontracts Mycoplasma testing to (b) (4). The Quality Agreement between Sandoz GmbH and (b) (4) was reviewed and found satisfactory. (b) (4) was inspected by (b) (4) in (b) (4) and by Sandoz in (b) (4), respectively. (b) (4) currently does not have any FDA inspection history. The firm was most recently inspected by (b) (4). This was a routine GMP inspection. An (b) (4) inspection report dated (b) (4) was reviewed by OPF/DIA. The facility was found involved in microbiological and biological testing of biological products including mycoplasma testing. No critical or major deficiencies were noted during the inspection. The firm's response to other deficiencies found was deemed acceptable. A recommendation was made to the (b) (4) to support this laboratory being named on licenses for finished product testing, stability testing and environmental monitoring.

Reviewer Comment 2: *The production and testing facilities associated with the manufacture of GP2015 DS are acceptable from a facilities assessment standpoint.*

• **3.2.S.2.2. Overview of DS Manufacturing Operations**

(b) (4)

CONCLUSION

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Sandoz GmbH (FEI 3004828473) and Novartis Pharma Stein AG (FEI 3002653483) proposed for GP2015 DS and DP manufacture. All proposed manufacturing and testing facilities are acceptable based on the basis of their currently acceptable CGMP compliance status and recent relevant inspectional coverage.

This submission is recommended for approval from a facilities assessment perspective.

Zhong Li -
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Date: 2016.06.10 09:54:47 -04'00'

Zhong Li, Ph.D.
Chemist
OPF Division of Inspectional Assessment
Branch 1

Zhihao
Qiu -S

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

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

Application: BLA 761042 Submission Type: 351(k)

Established/Proper Name: To be determined

Applicant: Sandoz, Inc. Letter Date: May 27, 2016

OND Office: ODEII/DPARP

Chemical Type: Biologic; Stamp Date: July 30, 2015
Fc-Fusion protein

Strength: 25mg/0.5mL,
50mg/1.0mL

Original BLA Biosimilar

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	Yes		
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 (NA)
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?	Yes		Need details of compendial methods used for drug substance and drug product and drug product microbial controls, Need additional data from analytical similarity studies. These and other questions will be sent in IRs separate from the 74 day letter

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	<input type="checkbox"/>	X	
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	
13.	Solid dispersion product ¹	<input type="checkbox"/>	X	
14.	Oral disintegrating tablet ¹	<input type="checkbox"/>	X	
15.	Modified release product ¹	<input type="checkbox"/>	X	
16.	Liposome product ¹	<input type="checkbox"/>	X	
17.	Biosimilar product ¹	X	<input type="checkbox"/>	
18.	Combination Product	X	<input type="checkbox"/>	Pre-filled syringe and autoinjector
19.	Other	X	<input type="checkbox"/>	Fc-fusion protein

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B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
Regulatory Considerations				
20.	USAN Name Assigned	<input type="checkbox"/>	X	To be determined
21.	End of Phase II/Pre-NDA Agreements	<input type="checkbox"/>	X	NA
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	X	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	X	
24.	Comparability Protocol(s) ²	<input type="checkbox"/>	X	
25.	Other	<input type="checkbox"/>	X	
Quality Considerations				
26.	Drug Substance Overage	<input type="checkbox"/>	X	
27.	Design Space	<input type="checkbox"/>	X	
28.		<input type="checkbox"/>	X	
29.		<input type="checkbox"/>	X	
30.		<input type="checkbox"/>	X	
31.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	X	
32.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	X	
33.	Alternative Microbiological Test Methods	<input type="checkbox"/>	X	
34.	Process Analytical Technology ¹	<input type="checkbox"/>	X	
35.	Non-compendial Analytical Procedures and/or specifications	<input type="checkbox"/>	X	
36.		<input type="checkbox"/>	X	
37.		<input type="checkbox"/>	X	
38.	Unique analytical methodology ¹	<input type="checkbox"/>	X	
39.	Excipients of Human or Animal Origin	<input type="checkbox"/>	X	
40.	Novel Excipients	<input type="checkbox"/>	X	
41.	Nanomaterials ¹	<input type="checkbox"/>	X	
42.	Hold Times Exceeding 30 Days	<input type="checkbox"/>	X	
43.	Genotoxic Impurities or Structural Alerts	<input type="checkbox"/>	X	NA
44.	Continuous Manufacturing	<input type="checkbox"/>	X	
45.	Other unique manufacturing process ¹	<input type="checkbox"/>	X	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	X	NA
47.	New delivery system or dosage form ¹	<input type="checkbox"/>	X	
48.	Novel BE study designs	<input type="checkbox"/>	X	NA
49.	New product design ¹	<input type="checkbox"/>	X	
50.	Other	<input type="checkbox"/>	X	

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
Parameter	Yes	No	N/A	Comment	
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	X	<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	X	<input type="checkbox"/>	<input type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

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C. FILING CONSIDERATIONS				
	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 			
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: <ul style="list-style-type: none"> <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) 	X	<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: <ul style="list-style-type: none"> <input type="checkbox"/> Is a manufacturing schedule provided? <input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle? 	X	<input type="checkbox"/>	<input type="checkbox"/>
DRUG SUBSTANCE INFORMATION				
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.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a	X	<input type="checkbox"/>	<input type="checkbox"/>

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C. FILING CONSIDERATIONS				
	<p>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 			<p>Descriptions of compendial methods are not provided. This information will be requested.</p> <p>Immunogenicity Assay validation reports are in Module 5</p>
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 <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 	X	<input type="checkbox"/>	

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C. FILING CONSIDERATIONS					
	<p>submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter?</p> <ul style="list-style-type: none"> <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 				<p>Description of the bioburden method was not included. Information will be requested.</p>
BIOPHARMACEUTICS					
8.	<p>If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies:</p> <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"/>	X	
9.	<p>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></p>	X	<input type="checkbox"/>	<input type="checkbox"/>	<p>Data from several comparability studies are provided</p>

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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"/>	X	
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"/>	X	
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"/>	X	
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"/>	X	
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"/>	X	<input type="checkbox"/>	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	X	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <input type="checkbox"/> manufacturing flow; adjacent areas <input type="checkbox"/> other products in facility <input type="checkbox"/> equipment dedication, preparation, sterilization and storage <input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <input type="checkbox"/> avoidance and control procedures <input type="checkbox"/> cell line qualification <input type="checkbox"/> other materials of biological origin <input type="checkbox"/> viral testing of unprocessed bulk <input type="checkbox"/> viral clearance studies <input type="checkbox"/> testing at appropriate stages of production <input type="checkbox"/> novel excipients	X	<input type="checkbox"/>	<input type="checkbox"/>	
17.	Are the following information available for Biotech Products: <input 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 example: <ul style="list-style-type: none"> <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be	X	<input type="checkbox"/>	<input type="checkbox"/>	Rabbit pyrogen test was completed. The report will be requested during the review cycle.

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marketed with summaries of test results for those samples				

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Brian M. Janelins -S
(Affiliate)

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Maria D. Candauchaon -S

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Maria Candau-Chacon, Ph.D., Drug Substance Microbiology Reviewer, Division of Microbial Assessment, Office of Process and Facilities

Candace Y. Gomez-broughton -S

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Zhong Li -S

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Zhong Li, Ph.D., Facilities Reviewer, Division of Inspectional Assessment, Office of Process and Facilities

Marjorie A. Shapiro -S

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Marjorie Shapiro, Ph.D., ATL, Division of Review and Research 1, Office of Biotechnology Products