

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761071Orig1s000

PRODUCT QUALITY REVIEW(S)



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

LABELS AND LABELING REVIEW

Date of review:	October 30, 2018
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Chih-Jung (CJ) Hsu, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research II
Application:	BLA 761071
Applicant:	Sandoz Inc.
Submission Date:	October 30, 2017
Product:	Hyrimoz (adalimumab-adaz)
Dosage form(s):	Injection
Strength and Container-Closure:	40 mg/0.8 mL single-dose prefilled syringe and single-dose prefilled pen
Background and Summary Description:	The Applicant submitted a biologics license application for Agency review.
Recommendations:	The prescribing information, medication guide, instructions for use, quick reference guides, container labels, and carton labeling submitted on October 29, 2018 are acceptable from an OBP labeling perspective.

Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Other	B (n/a)
Evaluation Tables	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

DISCUSSION and CONCLUSION

We evaluated the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations (21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100) and evaluated against recommendations in FDA Guidance and United States Pharmacopeia (USP) standards (see Appendix C).

The prescribing information, medication guide, instructions for use, quick reference guides, container labels, and carton labeling submitted on October 29, 2018 were reviewed and found to be acceptable (see Appendix D) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted on October 30, 2017

<\\cdsesub1\evsprod\bla761071\0005\m1\us\114-labeling\draft\labeling\prescribing-information-pdf.pdf>)

Medication Guide/Instructions for Use (submitted on October 30, 2017

<\\cdsesub1\evsprod\bla761071\0005\m1\us\114-labeling\draft\labeling\medication-guide-and-ifu-pdf.pdf>)

Quick reference guides (submitted October 30, 2017

<\\cdsesub1\evsprod\bla761071\0005\m1\us\114-labeling\draft\labeling\gp2017-qrg-ai.pdf> and <\\cdsesub1\evsprod\bla761071\0005\m1\us\114-labeling\draft\labeling\gp2017-qrg-pfs.pdf>)

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

Appendix B: Other (n/a)

Appendix C: Evaluation Tables (Label^{1,2} and Labeling³ Standards)

Container⁴ Label Evaluation

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Regulations, FDA Guidance, USP	Conforms
Proper Name 21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10 <i>for container of a product capable of bearing a full label</i>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Manufacturer name, address, and license number 21 CFR 610.60 <i>for container of a product capable of bearing a full label</i> Comment/ Recommendation: Revise the manufacturer statement using the following qualifying statement "Manufactured by:" (see 21 CFR 610.64) <i>The applicant revised as requested</i>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
Lot number or other lot identification 21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Expiration date 21 CFR 610.60, 21 CFR 201.17	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.60	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24 Comment/ Recommendation: <i>see carton</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
No Package for container 21 CFR 610.60	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Partial label 21 CFR 610.60 21 CFR 201.10	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A

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

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

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

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

No container label 21 CFR 610.60	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Ferrule and cap overseal	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Visual inspection 21 CFR 610.60	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<i>NDC numbers</i> 21 CFR 201.2 21 CFR 207.35	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Route of administration 21 CFR 201.5 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Preparation instructions 21 CFR 201.5	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Package type term 21 CFR 201.5	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Drugs Misleading statements 21 CFR 201.6	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Strength 21 CFR 201.10 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Drugs Prominence of required label statements 21 CFR 201.15	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Spanish-language (Drugs) 21 CFR 201.16	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Sulfites; required warning statements 21 CFR 201.22	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Bar code label requirements 21 CFR 201.25 21 CFR 610.67	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68. 21 CFR 201.26	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Net quantity 21 CFR 201.51	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Inactive ingredients 21 CFR 201.100	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Comment/Recommendation: <i>see carton</i>	
Storage requirements	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Dispensing container 21 CFR 201.100	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A

Prefilled syringe

Regulations, FDA Guidance, USP	Conforms
Proper Name 21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10 <i>for container of a product capable of bearing a full label</i> Comment/Recommendation: <i>partial label</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Manufacturer name, address, and license number 21 CFR 610.60 <i>for container of a product capable of bearing a full label</i> Comment/Recommendation: <i>partial label</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Lot number or other lot identification 21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100 Comment/Recommendation: <i>partial label</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Expiration date 21 CFR 610.60, 21 CFR 201.17 Comment/Recommendation: <i>partial label</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.60	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A

Comment/Recommendation: <i>partial label see carton</i>	
No Package for container 21 CFR 610.60	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Partial label 21 CFR 610.60 21 CFR 201.10	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
No container label 21 CFR 610.60	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Ferrule and cap overseal	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Visual inspection 21 CFR 610.60	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
NDC numbers 21 CFR 201.2 21 CFR 207.35	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Route of administration 21 CFR 201.5 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Preparation instructions 21 CFR 201.5	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Comment/Recommendation: <i>partial label</i>	
Package type term 21 CFR 201.5	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Comment/Recommendation: <i>partial label</i>	
Drugs Misleading statements 21 CFR 201.6	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Strength 21 CFR 201.10 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Drugs Prominence of required label statements 21 CFR 201.15	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Spanish-language (Drugs) 21 CFR 201.16	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A

<p>Phenylalanine as a component of aspartame 21 CFR 201.21</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p>Sulfites; required warning statements 21 CFR 201.22</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p>Bar code label requirements 21 CFR 201.25 21 CFR 610.67</p> <p>Comment/Recommendation: Ensure the linear bar code appears on the label. Ensure there is adequate white space around the linear bar code to facilitate scanning. Any 2D barcodes the appear on the label should appear away from the linear bar code on a side or back panel, away from the linear bar code in a size that does not compete with, distract from the presentation of other required or recommended information on the label. 2D barcodes cannot replace the linear barcodes because not all healthcare institutions have upgraded equipment to scan 2D barcodes.</p> <p><i>Applicant's response: In a letter dated September 19, 2018, (b) (4)</i></p> <div style="background-color: #cccccc; height: 400px; width: 100%; margin-top: 10px;"> (b) (4) </div> <p><i>Applicant's response: Applicant (b) (4) revised other components of the label to allow for the linear barcode to be applied. OBP labeling finds the revisions to accommodate the linear barcode acceptable.</i></p>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<p>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A

Net quantity 21 CFR 201.51	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100 Comment/ Recommendation: <i>partial label</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Inactive ingredients 21 CFR 201.100 Comment/ Recommendation: <i>partial label</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Storage requirements Comment/ Recommendation: <i>partial label</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Dispensing container 21 CFR 201.100	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A

Package Label⁵ Evaluation

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Regulations, Guidance, and USP	Conforms
Proper name 21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Manufacturer name, address, and license number 21 CFR 610.61 Comment/ Recommendation: Revise the manufacturer statement using the following qualifying statement "Manufactured by:" (see 21 CFR 610.64) <i>The Applicant revised as requested</i>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
Lot number or other lot identification 21 CFR 610.61	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Expiration date 21 CFR 610.61 21 CFR 201.17	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Preservative 21 CFR 610.61	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Number of containers 21 CFR 610.61	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A

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

Strength/volume 21 CFR 610.61 21 CFR 201.10, 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Storage temperature/requirements 21 CFR 610.61	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Handling: "Do Not Shake", "Do not Freeze" or equivalent 21 CFR 610.61	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.61	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Route of administration 21 CFR 610.61 21 CFR 201.5, 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Known sensitizing substances 21 CFR 610.61	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Comment/Recommendation: <i>carton has statement: "Caution: Contains Natural Rubber Latex Which May Cause Allergic Reactions"</i>	
Inactive ingredients 21 CFR 610.61 21 CFR 201.100	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
Comment/Recommendation: list all inactive ingredients in alphabetical order (see USP General Chapters <1091>) <i>The Applicant revised as requested</i> Add the suffix to the proper name in the ingredient list and revise the water for injection to USP nomenclature (Water for Injection, USP) <i>The Applicant revised as requested</i>	
Source of the product 21 CFR 610.61	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Minimum potency of product 21 CFR 610.61	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Rx only 21 CFR 610.61 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Divided manufacturing 21 CFR 610.63	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Distributor 21 CFR 610.64	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Bar code 21 CFR 610.67	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes

21 CFR 201.25	<input type="checkbox"/> N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68, 21 CFR 201.26	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
NDC numbers 21 CFR 201.2 21 CFR 207.35	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Preparation instructions 21 CFR 201.5	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Package type term 21 CFR 201.5	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Drugs Misleading statements 21 CFR 201.6	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Drugs Prominence of required label statements 21 CFR 201.15	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Spanish-language (Drugs) 21 CFR 201.16	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Sulfites; required warning statements 21 CFR 201.22	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Net quantity 21 CFR 201.51	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100 Comment/Recommendation: Revise the statement " (b) (4) " to read " <i>Usual Dosage: See prescribing information</i> " (see 21 CFR 201.55) <i>The Applicant revised as requested</i>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
Dispensing container 21 CFR 201.100	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24 Comment/Recommendation: Increase the prominence of the medication guide statement	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A

(see 21 CFR 610.60(a)(7). Consider revising it to read as follows: "ATTENTION: Dispense the enclosed Medication Guide to each patient"
The Applicant revised as requested

Prefilled Syringe foil and carton

Regulations, Guidance, and USP	Conforms
Proper name 21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Manufacturer name, address, and license number 21 CFR 610.61	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
Comment/Recommendation: Revise the manufacturer statement using the following qualifying statement "Manufactured by:" (see 21 CFR 610.64) <i>The applicant revised as requested</i>	
Lot number or other lot identification 21 CFR 610.61	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Expiration date 21 CFR 610.61 21 CFR 201.17	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Preservative 21 CFR 610.61	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Number of containers 21 CFR 610.61	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Strength/volume 21 CFR 610.61 21 CFR 201.10, 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Storage temperature/requirements 21 CFR 610.61	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Handling: "Do Not Shake", "Do not Freeze" or equivalent 21 CFR 610.61	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.61	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Route of administration 21 CFR 610.61 21 CFR 201.5, 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Known sensitizing substances 21 CFR 610.61	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Comment/Recommendation: <i>foil and carton have statement: "Caution: Contains Natural</i>	

Rubber Latex Which May Cause Allergic Reactions"

<p>Inactive ingredients 21 CFR 610.61 21 CFR 201.100</p> <p>Comment/Recommendation: list all inactive ingredients in alphabetical order (see USP General Chapters <1091>) <i>The applicant revised as requested</i></p> <p>Add the suffix to the proper name in the ingredient list and revise the water for injection to USP nomenclature (Water for Injection, USP) <i>The Applicant revised as requested</i></p>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<p>Source of the product 21 CFR 610.61</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p>Minimum potency of product 21 CFR 610.61</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p>Rx only 21CFR 610.61 21 CFR 201.100</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p>Divided manufacturing 21 CFR 610.63</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p>Distributor 21 CFR 610.64</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p>Bar code 21 CFR 610.67 21 CFR 201.25</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68, 21 CFR 201.26</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p>NDC numbers 21 CFR 201.2 21 CFR 207.35</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p>Preparation instructions 21 CFR 201.5</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p>Package type term 21 CFR 201.5</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p>Drugs Misleading statements 21 CFR 201.6</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p>Drugs Prominence of required label statements 21 CFR 201.15</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A

Spanish-language (Drugs) 21 CFR 201.16	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Sulfites; required warning statements 21 CFR 201.22	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Net quantity 21 CFR 201.51	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100 Comment/Recommendation: Revise the statement " (b) (4) " to read "Usual Dosage: See prescribing information" (see 21 CFR 201.55) <i>The applicant revised as requested</i>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
Dispensing container 21 CFR 201.100	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24 Comment/Recommendation: Increase the prominence of the medication guide statement (see 21 CFR 610.60(a)(7). Consider revising it to read as follows: "ATTENTION: Dispense the enclosed Medication Guide to each patient" <i>The applicant revised as requested</i>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A

Prescribing Information Evaluation

Regulations	Conforms
PRESCRIBING INFORMATION	
Highlights of prescribing information	
PRODUCT TITLE 21 CFR 201.57(a)(2)	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
3 DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(c)(4)	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
Comment/Recommendation: We deleted this statement (b) (4) <div style="background-color: #cccccc; height: 15px; width: 100%;"></div> <div style="background-color: #cccccc; height: 15px; width: 100%;"></div> <div style="background-color: #cccccc; height: 15px; width: 100%;"></div> <p><i>The applicant revised as requested</i></p>	
11 DESCRIPTION (21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)) Comment/Recommendation: list all inactive ingredients in alphabetical order (see USP General Chapters <1091>) <i>The applicant revised as requested</i>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
16 HOW SUPPLIED/ STORAGE AND HANDLING 21 CFR 201.57(c)(17) Comment/Recommendation: we added identifying characteristics of the drug product per 21 CFR 201.57(c)(17) <i>The applicant revised as requested</i>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
MANUFACTURER INFORMATION 21 CFR 610.61, 21 CFR 610.64 Comment/Recommendation: Use the qualifying phrase "Manufactured by." (see 21 CFR 610.64) <i>The applicant revised as requested</i>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
MEDICATION GUIDE, INSTRUCTIONS FOR USE, QUICK REFERENCE GUIDES	
TITLE (NAMES AND DOSAGE FORM)	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A

<p>Comment/Recommendation: For the quick reference guides: Add the Proprietary name, proper name, and dosage form <i>The Applicant revised as requested</i></p>	
<p>STORAGE AND HANDLING</p>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<p>Comment/Recommendation: For the medication guide: we added storage instructions to not return to the refrigerator once reached room temperature for consistency with the carton labeling and IFU <i>The applicant revised as requested</i></p>	
<p>INGREDIENTS</p>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<p>Comment/Recommendation: For medication guide: list all inactive ingredients in alphabetical order (see USP General Chapters <1091>) <i>The applicant revised as requested</i></p>	
<p>MANUFACTURER INFORMATION 21 CFR 610.61, 21 CFR 610.64</p>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<p>Comment/Recommendation: For medication guide and IFU: Use the qualifying phrase "Manufactured by." (see 21 CFR 610.64) <i>The applicant revised as requested</i></p>	

APPENDIX D. Acceptable Labels and Labeling

- Prescribing Information (submitted on October 29, 2018
<\\cdsesub1\evsprod\bla761071\0059\m1\us\114-labeling\draft\labeling\pf-clean.pdf>)
- Medication Guide/Instructions for Use (submitted on October 29, 2018
<\\cdsesub1\evsprod\bla761071\0059\m1\us\114-labeling\draft\labeling\mg-ifu-pdf-clean.pdf>)
- Quick reference guides (submitted on October 29, 2018
<\\cdsesub1\evsprod\bla761071\0059\m1\us\114-labeling\draft\labeling\quick-reference-guide-ai-clean.pdf> and <\\cdsesub1\evsprod\bla761071\0059\m1\us\114-labeling\draft\labeling\quick-reference-guide-pfs-clean.pdf>)

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



Vicky
Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 10/30/2018 10:40:31AM
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Chih-Jung (CJ)
Hsu

Digitally signed by Chih-Jung (CJ) Hsu
Date: 10/30/2018 10:58:45AM
GUID: 57f29b1500707804ae9c0cb6ead3c77c

Recommendation: Approval

BLA Number: 761071

Review Number: 2

Review Date: 9/28/2018

Drug Name/Dosage Form	Hyrimoz - adalimumab- (b) (4) / Injection
Applicant/Sponsor	Sandoz Inc.

The CDRH consult reviews were not completed at the time of finalization of the original [OPQ Executive Summary](#). The current addendum provides a summary of the CDRH conclusions and recommendations. Refer to the original OPQ Executive Summary for the detailed recommendation and conclusion on approvability, approval action letter language, benefit/risk considerations, and post-marketing commitments for BLA 761071.

Consults:

Discipline/Topic	Date Requested	Recommendation	Reviewer
CDRH/ODE	11/9/2017	Approval	Kathleen Fitzgerald
CDRH/OC	11/9/2017	Approval	Philip Lafleur

ODE: Office of Device Evaluation; OC: Office of Compliance

The CDRH/ODE review covered the devices constituent's parts information and performance testing and evaluated the design verification and validation, and the commercial specifications of the prefilled syringe (PFS) and the autoinjector (AI). The CDRH/ODE reviewer requested a mechanical engineering sub-consult to review the AI. Several information request items were sent to the applicant to confirm that the devices constituent's parts will function as intended through the lifecycle of the combination product. The responses, received on April 1, 2018 (eCTD submission 0024), were acceptable.

The CDRH/ODE reviewer concluded that the information included in the BLA and in master file MAF (b) (4) is acceptable to ensure that the PFS and the AI meet their "essential performance requirements when delivering the GP2017 drug in its intended use environment."

The CDRH/OC review covered the manufacturing facilities compliance status and the quality system requirements applicable to the devices constituent's parts. An information request was sent to the applicant to provide documentation of the compliance of the firm's quality system with 21 CFR 820 regulations. The response, received on September 24, 2018 (eCTD submission 0052), was acceptable.

The CDRH/OC reviewer also concluded that device-specific inspections were not required because all the device-related facilities had recent NAI or VAI inspections.



Cristina
Ausin-Moreno

Digitally signed by Cristina Ausin-Moreno
Date: 10/01/2018 03:12:02PM
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Susan
Kirshner

Digitally signed by Susan Kirshner
Date: 10/01/2018 04:12:23PM
GUID: 508da6db000266b77da0ba4bfa620030

Recommendation: BLA Approval

BLA Number: 761071
Review Number: 1
Review Date: 7/12/2018

Drug Name/Dosage Form	Hyrimoz - adalimumab- ^{(b) (4)} / Injection
Strength/Potency	40 mg/0.8 mL
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, Crohn's Disease, Ulcerative Colitis, and Plaque Psoriasis
Applicant/Sponsor	Sandoz Inc.
US agent, if applicable	N/A

Product Overview

Hyrimoz is an anti-TNF α IgG1 human monoclonal antibody proposed as a biosimilar to US-licensed Humira. Hyrimoz is supplied as a prefilled syringe and an autoinjector as a sterile liquid solution for subcutaneous injection. Sandoz is seeking approval of Hyrimoz for the following indications: rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Yanming An	Division of Biotechnology Review and Research (DBRR) II
Drug Product	Chih-Jung Hsu	DBRR II
Immunogenicity	Chih-Jung Hsu	DBRR II
Analytical Similarity	Yanming An	DBRR II
Labeling	Vicky Borders-Hemphill	Office of Biotechnology Products
Facility	Michael Shanks	Division of Inspectional Assessment (DIA)
Facility Team Lead	Peter Qiu	DIA
Microbiology Drug Substance	Scott Norris	Division of Microbiology Assessment (DMA)
Microbiology Drug Product	Lindsey Brown	DMA
Microbiology Team Lead	Reyes Candau Chacon	DMA
Regulatory Business Process Manager	Keith Olin/ Anh-Thy Ly	Office of Program and Regulatory Operations
Application Team Lead	Cristina Ausin	DBRR IV
OBP Tertiary Reviewer	Susan Kirshner	DBRR III

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Nina Ton	OND/DPARP
Cross-disciplinary Team Lead	Nikolay Nikolov	OND/DPARP
Medical Officer	Mark Borigini	OND/DPARP
Pharm/Tox	Brett Jones / Andrew Goodwin	OND/DPARP
Clinical Pharmacology	Mohammad Absar / Anshu Marathe	OCP/DCP II
Statistics	Bob Abugov	OB/BD II
CMC Statistics	Tianhua Wang / Meiyu Shen	OB/ BD IV

1. Names:
 - a. Proprietary Name: Hyrimoz
 - b. Trade Name: Hyrimoz
 - c. Non-Proprietary Name/USAN: adalimumab- (b) (4)
 - d. INN Name: adalimumab- (b) (4)
 - e. Company Code: GP2017
 - f. OBP Systematic Name: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [GP2017]

Submissions Reviewed:

Submission(s) Reviewed	Document Date
STN 761071/0005 (resubmission)	10/30/2017
STN 761071/0007 (response to IR #1)	11/29/2017
STN 761071/0008 (response to IR #2 part 1)	12/11/2017
STN 761071/0010 (response to IR #3)	12/11/2017
STN 761071/0011 (response to IR #2 part 2)	12/13/2017
STN 761071/0012 (response to pharm/tox IR E+L)	12/19/2017
STN 761071/0014 (response to IR #4)	1/11/2018
STN 761071/0016 (corrections to analytical similarity and characterization sections)	1/31/2018
STN 761071/0018 (response to IR #5)	3/5/2018
STN 761071/0020 (part 1 of response to IR #6)	3/20/2018
STN 761071/0021 (part 2 of response to IR #6 and response to IR #7)	3/30/2018
STN 761071/0022 (error corrections to comparability (b) (4))	3/30/2018
STN 761071/0024 (part 1 of response to IR#10)	4/12/2018
STN 761071/0025 (response to IR #8)	4/23/2018
STN 761071/0026 (part 2 of response to IR #10)	4/26/2018
STN 761071/0027 (part 3 of response to IR #6)	4/27/2018
STN 761071/0028 (response to CMC stats IR)	5/9/2018
STN 761071/0029 (response to IR #11)	5/15/2018
STN 761071/0032 (response to IR #12 and 14)	6/8/2018
STN 761071/0033 (part 1 of response to IR #15)	6/13/2018
STN 761071/0034 (response to IR #13)	6/15/2018
STN 761071/0035 (part 1 of response to IR #16)	6/20/2018
STN 761071/0037 (part 2 of response to IR #15)	6/22/2018
STN 761071/0039 (response to IR #17)	6/25/2018
STN 761071/0040 (part 2 of response to IR #16)	6/29/2018
STN 761071/0041 (response to IR #18)	7/2/2018
STN 761071/0042 (response to IR #19)	7/3/2018

Quality Review Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code ¹	Status ²	Date Review Completed
(b) (4)	3	(b) (4)	(b) (4)	1	Adequate	6/29/2018
	3			3	Adequate	N/A
	3			3	Adequate	N/A
	N/A				Adequate	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, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	115732	Sandoz-sponsored under which GP2017 was developed and BPD meetings were held

3. Consults:

Discipline/Topic	Date Requested	Recommendation	Reviewer
CDRH/DAGRID	11/9/2017	Pending	Kathleen Fitzgerald
CDRH/OC	11/9/2017	Assembly site (b) (4) is acceptable, per DIA facilities memo .	Elijah Weisberg

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761071 for Hyrimoz manufactured by Sandoz Inc. The data submitted in this application, including the analytical similarity assessment, are adequate to support the conclusion that:

- The manufacture of Hyrimoz is well-controlled and leads to a product that is pure and potent;
- Hyrimoz is similar to US-licensed Humira notwithstanding minor differences in clinically inactive components,
- A sufficiently robust analytical bridge was established to support the use of EU-approved Humira as a comparator in non-clinical and clinical studies.

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

B. Approval Action Letter Language

- Manufacturing location:
 - Drug Substance:
 - § Sandoz GmbH Schaftebau: Biochemiestrasse 10, 6336 Langkampfen, Austria (FEI 3004828472)
 - § [REDACTED] (b) (4)
 - Drug Product:
 - [REDACTED] (b) (4)
- Fill size and dosage form: 40 mg/0.8 mL prefilled syringe and autoinjector
- Dating period:
 - Drug Product: 24 months at 2-8°C
 - Drug Substance: (b) (4) months at [REDACTED] (b) (4)
 - Stability Option:
 - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release
 - Yes
 - Rationale, if exempted: specified product

Note: Per FR notice 95-29960 well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products are exempted from 21 CFR 601.2a lot release requirements.

- Sandoz requested a categorical exclusion from the need to prepare an environmental assessment in accordance with 21 CFR 25.31. 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.

C. Benefit/Risk Considerations:

Adalimumab-(b) (4) is a proposed biosimilar to US-licensed Humira. Adalimumab-(b) (4) has the same dosage form and route of administration as US-licensed Humira. The reference product has several indications. However, the indications Juvenile Idiopathic Arthritis (JIA) in patients between 2 and 4 years old, pediatric Crohn's Disease, Hidradenitis Suppurativa, and Uveitis are covered by orphan exclusivity and are not claimed. Sandoz seeks licensure for the following indications:

- Rheumatoid Arthritis
- JIA in patients 4 years of age and older
- Psoriatic Arthritis
- Ankylosing Spondylitis
- Adult Crohn's Disease
- Ulcerative Colitis
- Plaque Psoriasis

The overall control strategy includes control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. The control strategy combined with in-process, release, and stability testing ensure process consistency and drug substance and drug product with appropriate quality attributes and free of adventitious agents.

The totality of the analytical similarity data support the conclusions that GP2017 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components. The non-clinical and clinical studies used US-licensed Humira and EU-approved Humira as comparators. Therefore, an analytical bridge was established to support the use of EU-approved adalimumab as a comparator.

The strength of U.S.-licensed Humira is labeled in mass per unit volume (40 mg/0.8 mL). U.S.-licensed Humira is filled into a single-use prefilled glass syringe with a volume of 0.8 mL¹. GP2017 is seeking approval for the same strength as U.S.-licensed Humira. Comparative protein concentration (mg/mL) reviewed as part of the analytical similarity assessment, and extractable volume (mL) and fill weight data reviewed as part of manufacturing process controls were used

¹ U.S. Prescribing Information, U.S. Licensed-Humira. Accessed June 21, 2018 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125057s4031bl.pdf

to inform the assessment of whether the proposed presentation of GP2017 has the same strength as the presentation of U.S.-licensed Humira. Based on the similarity and manufacturing data, the 40 mg/0.8 mL GP2017 prefilled syringe and autoinjector have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as the presentation of U.S.-licensed Humira. These presentations meet the statutory "same strength" requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.

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

1. To perform drug product shipping validation during summer by September 2018.
2. To implement an apoptosis inhibition assay to replace the current TNF- α neutralization reporter gene assay by March 2019.
3. To implement a control strategy for effector function by March 2019.
4. To qualify the bioburden test method for the (b) (4) at Sandoz Schafftenau using 10 mL test volumes. Submit the qualification report as a CBE in accordance with 21 CFR 601.12
5. To qualify the bioburden test for the (b) (4) using the (b) (4) and implement the new bioburden test method. Submit the qualification report as a CBE in accordance with 21 CFR 601.12

II. Analytical Similarity Assessment

As part of the demonstration of biosimilarity, the applicant performed analytical similarity studies. Sandoz evaluated twenty-two lots of GP2017 drug product, up to 35 lots of US-licensed Humira, and up to 42 lots of EU-approved adalimumab using the methods listed in **Table A** below. Of the twenty-two GP2017 drug product lots, several were manufactured using the same drug substance batch. Therefore, only eleven GP2017 drug product lots are considered independent lots.

The analytical similarity studies included US-licensed Humira lots with expiry dates between August 2009 and July 2018 and the establishment of the analytical part of the 3-way scientific bridge included EU-approved adalimumab lots with expiry dates between October 2008 and July 2018. In addition, most of the testing took place in a range of 20 to 80 weeks before expiry. These wide ranges of expiry and testing dates ensure proper evaluation of the variability within US-licensed Humira and EU-approved adalimumab.

To support the use of non-clinical and clinical comparative data from studies that used EU-approved adalimumab, Sandoz established a 3-way scientific bridge. The applicant performed a 3-way evaluation of analytical similarity between GP2017, US-licensed Humira, and EU-approved adalimumab. Sandoz assessed the analytical similarity of GP2017 and US-licensed Humira using a comprehensive set of assays, as listed below.

Table A. Analytical Similarity Assessment

Quality Attribute	Analytical Methods
Primary structure (Tier 3)	Amino acid sequence by peptide mapping with mass spectrometry detection Post-translational modifications by RP-HPLC-UV peptide mapping (met oxidation, deamidation, N-terminal and C-terminal modifications) Disulfide bonds by non-reducing peptide mapping and LC-MS Free thiols by Ellman's assay Met256 oxidation by RP-HPLC-UV reducing peptide mapping Molecular weight by ESI-qTOF MS Thioethers by reducing CE-SDS Aspartate isomerization by ISOQUANT kit
Higher order structure (Tier 3)	FT-IR CD spectroscopy Differential scanning calorimetry H/D exchange X-ray crystallography 1D ¹ H-NMR and 2D ¹ H- ¹ H NOESY NMR
High molecular weight variants/aggregates	Size exclusion chromatography (SEC) (Tier 2) AUC (Tier 3) SEC-MALLS (Tier 3)

Charge heterogeneity	CEX (Tier 2) pI variants by iCE (Tier 3) Charge and charge distribution by 2D-DIGE (difference gel electrophoresis) (Tier 3)
Intact protein purity	SEC (Tier 2) Non-reduced CE-SDS (Tier 2) Hydrophobicity by HIC (Tier 3)
Carbohydrate structure	N-glycan galactosylated, non-fucosylated, high mannose (HILIC) (Tier 2) Site-occupancy Fc N-glycan by peptide mapping and reducing CE-SDS (Tier 3) Glycation by boronate affinity chromatography (Tier 3)
Bioactivity	Inhibition of TNF α -induced apoptosis (bioassay) (Tier 1) s-TNF α binding (SPR) (Tier 1) Apoptosis induction (reverse signaling, flow cytometry) (Tier 2) m-TNF α binding (flow cytometry) (Tier 2) Antibody-dependent cell-mediated cytotoxicity (ADCC) assay with primary NK cells (Tier 2) Complement-dependent cytotoxicity (CDC) with Jurkat cells (Tier 2) C1q binding (ELISA) (Tier 2) TNF α neutralization (reporter gene assay) (Tier 2) Induction or regulatory macrophages (Tier 3) Off-target binding of cytokines (Tier 3)
Fc receptor binding	Fc γ RIIIa V158 binding by surface plasmon resonance (SPR) (Tier 2) Fc γ RIIIa F158 binding by SPR (Tier 2) FcRn binding by SPR (Tier 2) Fc γ RI, RIIa, and RIIIb by SPR (Tier 3)
Protein content	UV Absorbance (Tier 2)
Particles (Tier 3)	Visible particles Sub-visible particles by MFI and resonant mass measurement
General properties	Extractable volume (Tier 2)

The tier assignment proposed by Sandoz agrees with FDA's current thinking for adalimumab. The analytical similarity assessment includes lots from both GP2017 drug substance manufacturing sites, including process performance qualification lots, and the lots used in the clinical studies. The applicant proposes to market two presentations, a prefilled syringe and an autoinjector. Only prefilled syringe lots were included in the analytical similarity assessment. However, the only difference between the two presentations is the final assembly into the secondary container closure system and Sandoz provided adequate information to demonstrate that the assembly into the autoinjector does not have an effect on product quality. Therefore, it is acceptable not to include GP2017 lots assembled in the autoinjector.

TNF α binding and neutralization of TNF α -induced apoptosis are generally considered as the main mechanism of action of adalimumab products. These two assays were assigned to Tier 1 and results analyzed by equivalence testing. Sandoz tested 14 independent GP2017 (10 DP and 4 DS lots), 18 US-licensed Humira and 18 EU-approved adalimumab lots by the TNF α binding assay and 15 independent GP2017 (9 DP and 6 DS lots), 16 US-licensed Humira and 21 EU-approved adalimumab lots by the apoptosis inhibition assay. According to the CMC statistics reviewer, the data met the equivalence margins for all three pairwise comparison for both assays.

Assays that are orthogonal to the two Tier 1 assays, assays that evaluate additional potential mechanisms of action proposed for adalimumab, and assays that evaluate purity, protein content, and other general properties of adalimumab were assigned to Tier 2 and analyzed using quality ranges.

Regarding the Tier 2 attributes, 90% of GP2017 lots were within the quality ranges calculated for US-licensed and EU-approved Humira with the following exceptions:

- All GP2017 lots have higher galactosylation than US-licensed and EU-approved Humira (23.7-37.4% vs. 14.7-23.1%). However, this difference does not result in differences in CDC or C1q binding.
- All GP2017 lots have higher afucosylation (2.4-3.2% vs. 0.5-0.9%) and lower high mannose content (0.9-1.3% vs. 3.9-6.6%) than US-licensed and EU-approved Humira. However, these differences do not result in differences in ADCC activity or Fc γ RIIIa binding.
- Several GP2017 lots have slightly lower acidic variants content than US-licensed and EU-approved Humira (6.8-10.7% vs. 9.2-13.9%). The main acidic variants are the result of deamidation and iso-Asp formation. Sandoz evaluated the bioactivity of these variants with the TNF α binding assay and the TNF α neutralization reporter gene assay and showed comparable potency to the unmodified moiety. Therefore, these acidic variants have low risk of impact in vivo.
- All GP2017 lots have lower basic variants content than US-licensed and EU-approved Humira (12.9-17.7% vs. >20.3%). This difference is caused by differences in the presence of C-terminal lysine and proline amide variant, which is a C-terminal modification following the clipping of lysine and glycine. It is a well-known fact that C-terminal lysine is enzymatically removed in serum. Therefore, these basic variants have a low risk of impact in vivo.
- Some GP2017 lots have slightly higher levels of HMW variants than US-licensed and EU-approved Humira. However, in all cases the amount is \leq 0.5% which is very low and it is not expected to have an effect in terms of safety or efficacy.

The residual uncertainty raised by these results is mitigated by the totality of the analytical similarity evidence.

The analytical similarity analysis also included an evaluation of the stability of GP2017, US-licensed Humira, and EU-approved adalimumab under long-term, accelerated, and stressed storage conditions. The analytical testing results indicated that the long-term stability of GP2017 DP and US-licensed and EU-approved Humira are similar.

There were no differences in clinical studies regarding pharmacokinetics, pharmacodynamics, safety, efficacy, and immunogenicity.

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

- GP2017 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components.
- For attributes where differences between GP2017 and US-licensed Humira are noted, the totality of the analytical data support that there is no impact on function, activity, or stability in vitro. Specifically, the differences noted in glycosylation were not reflected in functional assays such as ADCC, CDC, and the corresponding binding assays. Therefore, these differences are not expected to affect the mechanism of action of the product.
- A 3-way analytical bridge was established to support the use of EU-approved adalimumab as a comparator in non-clinical and clinical studies.

III. Summary of Quality Assessments:

A. COA Identification, Risk and Lifecycle Knowledge Management

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

CQA (type)	Risk	Origin	Control Strategy (b) (4)	Other
Potency	Directly linked to efficacy	Intrinsic to molecule		PMC to replace the current cell based assay with the inhibition of apoptosis induction assay
ADCC (potency)	Directly linked to efficacy	Intrinsic to molecule		PMC to establish control strategy for effector function
CDC (potency)	Directly linked to efficacy	Intrinsic to molecule		
Charge variants (product related variants)	Efficacy and safety	Intrinsic to molecule		
HMW	Efficacy and safety	Introduced during manufacturing process and storage		No or reduced activity in TNF- α reporter gene assay
LMW	Efficacy and safety	Introduced during manufacturing process and storage		No or reduced activity in TNF- α reporter gene assay
Fragments (product related impurities)	Safety	Introduced during manufacturing process and storage		
Oxidation (product related variants)	Efficacy and safety	Introduced during manufacturing process and storage		Consistently low amount of M ₂₅₆ oxidation ((b) (4) %)
Deamidation	Efficacy and safety	Introduced during manufacturing process and storage		

			(b) (4)
Higher Order Structure (potency)	Directly linked to efficacy and MOA	Intrinsic to molecule	
Glycosylation (potency and product related impurities)	Directly linked to efficacy and safety	Introduced during manufacturing process	

B. Drug Substance [adalimumab- (b) (4)] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA (type)	Risk	Origin	Control Strategy (b) (4)	Other
Bioburden (Contaminant)	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process.		PMC for bioburden test qualification
Endotoxin (Contaminant)	Safety and purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process		N/A
Host Cell Proteins (Process related impurity)	Safety and immunogenicity	Process; (b) (4)		
Host cell DNA (Process related impurity)	Safety	Process; (b) (4)		
Viruses (Process related impurity)	Safety	Contamination during manufacture		
(b) (4) (Process related impurity)	Safety	(b) (4)		
Leachables and extractables	Safety	Entire process		

(Process related impurity)			(b) (4)
(b) (4)	Safety	(b) (4)	
(b) (4)	Safety	(b) (4)	
Heavy metals	Safety	Entire process	

- Description:**
GP2017 is an IgG1 human monoclonal antibody that binds and neutralizes the activity of soluble and cell surface TNF α . The antibody is composed of two heavy chains (451 amino acid residues each) and two light chains (214 amino acid residues each). The N-linked oligosaccharide at Asn301 includes galactosylated, high mannose, and afucosylated species. Forced degradation studies show that deamidation and oxidation do not occur in the CDR region.
- Mechanism of Action (MoA):**
GP2017 binds specifically to soluble and transmembrane TNF α blocking its interaction with p55 and p75 cell surface receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF α are found in the synovial fluid of patients with RA, JIA, PSA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. In addition, antibody dependent cell mediated cytotoxicity, complement dependent cytotoxicity, antibody mediated reverse signaling, and induction of regulatory macrophages have been identified in the scientific literature as potential mechanisms of action for anti-TNF monoclonal products.
- Potency Assay:**
Sandoz uses a TNF- α neutralization reporter gene assay to assess the biological activity of GP2017. The assay measures the *in vitro* neutralization of soluble TNF- α by GP2017. A HEK293 cell line transfected with a firefly luciferase is used in the assay. The cells express luciferase while responding to the TNF- α and endogenous TNF receptors interactions. The luciferase assists oxidation of luciferin which then emits light. The luminescence is measured and it is inversely proportional to TNF- α neutralization. The activity of test samples is determined against a reference standard tested at the same time.

The applicant will implement an apoptosis inhibition assay as a replacement for the reporter gene assay as a PMC.

Sandoz indirectly controls GP2017 effector function through (b) (4)

- Reference Materials:

The applicant established a two-tiered reference material system. Both primary (GP2017.02REF) and working reference standard (GP2017.01WST) are stored at (b) (4) °C and derived from drug substance batch B153820, used in clinical studies. A protocol is provided for the qualification of future working reference materials. The protocol contains adequate testing and acceptance criteria. If a new primary reference material needs to be qualified, the applicant will submit a protocol for approval. Both primary and working reference materials are re-tested (b) (4).

- Critical starting materials or intermediates:

Cell bank system: The parental host cell line was CHO cell line (b) (4)

(b) (4)

For additional information see the [OBP Product Quality Review](#).

- Manufacturing process summary:

(b) (4)



For additional information see the [OBP Product Quality Review](#) and the [DMA Microbiology Drug Substance Review](#).

- Container closure:



- Dating period and storage conditions: (b) (4) months: (b) (4) °C
The proposed (b) (4) -month DS expiry when stored at (b) (4) °C is supported by the following data: 48 months of stability results for three batches manufactured at Schaftenau (b) (4) and three batches manufactured at (b) (4). In addition, the submission includes 24 months of stability results for three process validation batches for Schaftenau (b) (4), three process validation batches for Schaftenau (b) (4) three batches manufactured at (b) (4), two of which are process validation batches, and 18 months for the third (b) (4) process validation batches. The applicant committed to placing one batch of GP2017 on stability at (b) (4) °C and at (b) (4) °C each year that the product is manufactured. The stability testing program is adequate and consistent with ICH Q5C recommendations.

C. Drug Product [Hyrimoz] Quality Summary:

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

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

COA (type)	Risk	Origin	Control Strategy	Other
Sterility (contaminant)	Safety, purity and efficacy (degradation or modification of the product by contaminating microorganisms)	Contaminants could be introduced throughout DP manufacturing.	(b) (4)	
Endotoxins (contaminant)	Safety and purity and immunogenicity	Contaminants could be introduced throughout DP manufacturing.		
Container Closure Integrity (contaminant)	Safety	Container closure breaches during storage		
Identity (general)	Safety and efficacy	Intrinsic to molecule		
pH (general)	Safety and efficacy	Formulation		
Osmolality (general)	Safety	Formulation		
Polysorbate 80	Safety	Formulation		
Extractable volume (general)	Essential for dosing	Manufacturing Process		
Protein concentration (general)	Variable protein concentration causes variable dosage of the drug and may affect efficacy	(b) (4)		

Clarity and color (general)	Safety and efficacy	Clarity may be impacted by the number of particles in solution; differences in color are indicative of contamination or degradation	(b) (4)
Particulate matter (Sub-visible particles (SVP)) (product or process related impurities)	Immunogenicity, patient safety	Container closure system (CCS) and process	
Foreign matter (visible particles) (product and process related impurities)	Immunogenicity, patient safety	Manufacturing material and CCS	
Leachables/ extractables (Process related impurities)	Safety	Manufacturing equipment and CCS	

- Potency and Strength:
Hyrimoz is supplied as a 40 mg/0.8 mL solution of adalimumab- (b) (4)
- Summary of Product Design:
Hyrimoz is supplied in single-dose 1 mL prefilled syringes and autoinjectors.
- List of Excipients (amounts per PFS, 0.8 mL):
2.69 mg adipic acid, 0.206 mg citric acid monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80, 4.93 mg sodium chloride
- Reference Materials:
The same reference material is used for drug substance and drug product.
- Manufacturing process summary:

(b) (4)

(b) (4)

Bioburden and endotoxin are tested during manufacture, and sterility and endotoxin are tested at release. Container closure integrity testing using a validated dye ingress test is included in the stability program.

The applicant will validate shipping during summer as a PMC.

- Container closure:
 The primary container closure system is a 1 mL prefilled syringe with the following components: a glass syringe barrel with staked needle, a rubber plunger stopper, and a rigid needle shield.
 The secondary packaging components are either a plunger rod and a needle safety device with an add-on finger flange or an autoinjector.
 Appropriate compatibility studies were performed for the container closure systems.
- Dating period and storage conditions:
 24 months at 2-8 °C (with a 14-days temperature excursion to 25 ^{(b) (4)} °C ^{(b) (4)}
^{(b) (4)}).
 The applicant provided 30 months of stability results for fourteen lots and 24 months for the three process validation lots filled into prefilled syringes. In addition, the submission includes 14 months for a lot filled in an autoinjector. The applicant committed to placing one lot of GP2017 on stability at 2-8°C and at 25°C each year that the product is manufactured. The stability testing program is adequate and consistent with ICH Q5C recommendations.

For additional information see the [OBP Product Quality Review](#) and the [DMA Microbiology Drug Product Review](#).

D. Novel Approaches/Precedents:
 None

E. Any Special Product Quality Labeling Recommendations:
 None

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS manufacturing, in-process, release and stability testing, WCB storage	Sandoz GMBH – Schaftenau; Langkampfen, Austria	301698247/3004828473	VAI	1. Microbial hold times not adequately supported 2. Lack of controls to prevent changes to ^{(b) (4)} ^{(b) (4)} testing programs 3. Inadequate SOP for overdue deviations or unapproved modifications to batch records 4. Inadequate method for determination of	Approve

				material conformance to written specifications	
DS manufacturing, in-process, release and stability testing, WCB storage, (b) (4)	(b) (4)	(b) (4)	VAI	1. (b) (4) 2. 3. 4. 5.	Approve
DS in-process, release, and stability testing, MCB and WCB storage, (b) (4)	Sandoz GMBH – Kundl; Kundl, Austria	300220969/ 3002806523	---	---	Approve based on profile
DS in-process, release, and stability testing, WBC preparation, MCB and WCB release testing and storage	(b) (4)	(b) (4)	---	---	Approve based on profile
DS release and stability testing	Novartis Pharma AG; Basel, Switzerland	482347168/ 3002807772	NAI	---	Approve
DS release and stability testing	(b) (4)	(b) (4)	---	---	Approve based on profile
DS release and stability testing	(b) (4)	(b) (4)	---	---	Approve based on profile
DS release and stability testing	(b) (4)	(b) (4)	---	---	Approve based on profile
MCB and WCB release testing	(b) (4)	(b) (4)	---	---	Approve based on profile
MCB and WCB release testing, (b) (4)	(b) (4)	(b) (4)	---	---	Approve based on profile
(b) (4)	(b) (4)	(b) (4)	---	---	Approve based on profile
(b) (4)	(b) (4)	(b) (4)	---	---	Approve based on profile
DS in-process testing	(b) (4)	(b) (4)	---	---	Approve based on profile
Analytical similarity	Hexal AG, Oberhaching, Germany	312985647/ 3011617743	NAI	---	Approve

DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacturing, primary packaging, in-process and release testing	(b) (4)		---	---	Approve
Assembly and packaging of PFS and AI; DP release and stability testing	(b) (4)		VAI	See drug substance section	Approve
Bulk PFS, PFS, and AI release and stability testing	Sandoz GMBH – Schaftenau; Langkampfen, Austria	301698247/3004828473	VAI	See drug substance section	Approve
Bulk PFS release and stability testing	Sandoz GMBH - Kundl; Kundl, Austria	300220969/3002806523	---	---	Approve based on profile
Bulk PFS release and stability testing	(b) (4)		---	---	Approve based on profile
Bulk PFS release and stability testing	Novartis Pharma AG; Basel, Switzerland	482347168/3002807772	NAI	---	Approve
Bulk PFS release and stability testing	(b) (4)		---	---	Approve based on profile
Bulk PFS release and stability testing	(b) (4)		---	---	Approve based on profile
Bulk PFS release and stability testing	(b) (4)		---	---	Approve based on profile

G. Facilities:

A pre-license inspection for (b) (4) and GP2017 Drug Substance was conducted on 02/14-20/2018 at Sandoz GmbH (Langkampfen, Austria). A 4-item FDA Form 483 was issued and the initial recommendation is approval for this BLA. The firm’s corrective action plan was deemed appropriate to correct the deficiencies. The final classification of the Sandoz GmbH pre-license inspection was acceptable.

A pre-license inspection for GP2017 drug substance was conducted on (b) (4) at (b) (4). A 5-item FDA Form 483 was issued and the initial recommendation is approval for this BLA. The final classification of the (b) (4) pre-license inspection was acceptable.

The pre-approval inspection of the drug product site, (b) (4) was waived because of the site’s compliance status and its recent surveillance inspection (b) (4).

As part of the analytical similarity assessment, the review team inspected Hexal AG on 04/16-17/2018 and Novartis Pharma on 4/19-20/2018. The inspection outcome was NAI for both sites and the recommendation was approval.

For additional information refer to the [DIA Facility Review](#).

H. Lifecycle Knowledge Management:

a. Drug Substance:

- i. Protocols approved: shelf-life extension, (b) (4) at Schaftenau and (b) (4) qualification of WCB, stability protocols for MCB and WCB, qualification of working reference standard

eCTD Section	Protocol	Brief Summary	Reporting category

3.2.S.2.3	Production of a replacement working cell bank (WCB) and stability testing for master cell bank (MCB) and WCB	The procedure to generate and test a new WCB from the master cell bank. Includes WCB testing, DS release, characterization, and stability testing and one DP lot placed on stability	The full-scale qualification data confirming the suitability of the replacement WCB for use in routine manufacturing will be submitted in the Annual Report .
3.2.S.2.5	Concurrent validation protocol for (b) (4) at Schaftenau	Procedure and acceptance criteria for verification of the (b) (4) at commercial scale	Results will be reported in Annual Report following study completion
3.2.S.2.5	Concurrent validation protocol for (b) (4)	Procedure and acceptance criteria for verification of the (b) (4) at commercial scale	Results will be reported in Annual Report following study completion
3.2.S.5	Qualification protocol for future working reference standard and annual stability testing for primary and working reference standards	Procedure and acceptance criteria to qualify the future working reference standard	Results will be reported in Annual Report following study completion
3.2.S.2.5	Concurrent validation of (b) (4) at manufacturing scale	Procedure and acceptance criteria to validate the number of (b) (4) proposed based on small scale studies	N/A
3.2.S.7.1	Stability protocol - drug substance (DS) shelf-life extension	Protocol to extend the DS storage period	Annual Report
3.2.S.7.2	Stability protocol for DS	At (b) (4) °C, at least one batch per year at initial, 6, 12, 18, 24, 36, and 48 month per the tests and acceptance criteria listed in 3.2.S.7.2	Stability updates will be provided annually as part of the Annual Report

- ii. Outstanding review issues/residual risk:
See PMCs in section I. Recommendations
- iii. Future inspection points to consider:
None

b. Drug Product

i. Protocols approved: shelf-life extension

eCTD Section	Protocol	Brief Summary	Reporting category
3.2.P.8.1	Stability protocol – drug product (DP) shelf-life extension	Protocol to extend the DP storage period	Annual Report
3.2.P.8.2	Stability protocol for DP	At 2-8°C, at least one batch per year at initial, 6, 12, 18, and 24 per the tests and acceptance criteria listed in 3.2.P.8.2	Stability updates will be provided annually as part of the Annual Report

- ii. Outstanding review issues/residual risk:
See PMCs in section I. Recommendations
- iii. Future inspection points to consider:
None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/source material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non-Primate Mammalian Cell Substrate/source material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal source		X	
9.	Transgenic Plant source		X	
10.	New Molecular Entity		X	
11.	PEPFAR drug		X	
12.	PET drug		X	
13.	Sterile Drug Product	X		
14.	Other: [fill in information]			X
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]		X	
16.	Comparability Protocol(s)	X		
17.	End of Phase II/Pre-NDA Agreements tem		X	
18.	SPOTS (special products on-line tracking system)		X	
19.	USAN assigned name		X	
20.	Other [fill in]			X
Quality Considerations				
21.	Drug Substance Overage		X	
22.	Design Space	Formulation		X
23.		Process		X
24.		Analytical Methods		X
25.		Other		X
26.	Other QbD Elements	X		
27.	Real Time release testing (RTRT)		X	
28.	Parametric release in lieu of Sterility testing		X	
29.	Alternative Microbiological test methods		X	
30.	Process Analytical Technology in Commercial Production		X	
31.	Non-compendial analytical procedures	Drug Product	X	
32.		Excipients		X
33.		Drug Substance	X	
34.	Excipients	Human or Animal Origin		X
35.		Novel		X
36.	Nanomaterials		X	
37.	Genotoxic Impurities or Structural Alerts		X	
38.	Continuous Manufacturing		X	
39.	Use of Models for Release		X	
40.	Other {fill-in}			X



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Ausin-Moreno

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Susan
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BLA STN 761071

Product GP2017
Proposed Trade Name Hyrimoz
Manufacturer Sandoz Inc., a Novartis Division

CMC Addendum

OBP CMC Review Data Sheet

1. BLA#: 761071
2. Review Date: July 9, 2018
3. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request (OBP X)	June 25, 2018
Information Request (OBP XI)	June 28, 2018

4. Submissions Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
761071/0041 (OBP IR X response)	July 2, 2018	Yes
761071/0042 (OBP IR XI response)	July 3, 2018	Yes

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation

We recommend approval of the BLA. We recommend approval of the proposed release and shelf-life specifications for GP2017 drug substance and drug product.

Reviewer note: The IR responses are reviewed and acceptable (see details in the following sections). Refer to the initial OBP BLA761071 CMC memo for complete recommendation language.

3.2.S. Drug Substance

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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Primary Reviewer: Lindsey Brown, Ph.D.

Secondary Reviewer: Reyes Candau-Chacon, Ph.D.

Date: 1/29/2018

To: Administrative File

STN:761071

Subject: To support manufacture of Adalimumab drug product at (b) (4)

Applicant: Sandoz Inc.

US License Number:

Facility: (b) (4)

(FEI: (b) (4))

Product: Adalimumab

Indication: Rheumatoid Arthritis; Juvenile Idiopathic Arthritis in patients 4 years of age and older; Psoriatic Arthritis; Ankylosing Spondylitis; Adult Crohn's Disease; Ulcerative Colitis; Plaque Psoriasis

Dosage Form: 40mg/0.8mL, subcutaneous injections

PDUFA Date: 7/2/2018

Recommendation for Approvability: BLA 761071 is recommended for approval from a sterility assurance and microbiology product quality perspective pending BLA update. DMF (b) (4) was reviewed in support of this application and was found to be adequate. The BLA will be updated on 6/29/2018 to include a reduced endotoxin limit.

The following DMF was reviewed in support of BLA 761071:

DMF	Status	Review dates
DMF (b) (4)	Adequate	2/2/2018 6/29/2018

Review Summary

The following amendments have been reviewed in support of 761071.

Sequence	Date	
0000	8/25/2017	Original Submission
0004	10/21/2017	Submission Withdrawal
0006	12/6/2017	Resubmission
0008	12/11/2017	Response to Information Request (IR)
0011	12/13/2017	Response to IR
0023	4/12/2018	Response to IR
0026	4/26/2018	Response to IR
0032	6/8/2018	Response to IR
0033	6/13/2018	Response to IR
0039	6/26/2018	Response to IR

DMF (b) (4) was reviewed in support of this application. DMF (b) (4) reviews dated 2/2/2018 and 6/29/2018 support the sterility assurance of the prefilled syringe.

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Brown

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Reyes
Candau-Chacon

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

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Date: 27 June 2018
To: Administrative File, 761071/6
From: Scott Nichols, Ph.D., Reviewer
OPQ/OPF/DMA/BIV
Through: Reyes Candau-Chacon, Ph.D., Quality Assessment Lead
OPQ/OPF/DMA/BIV
Subject: New 351(k) Biosimilar Biologics License Application (BLA)
US License Number: 2003
Sponsor: Sandoz Inc.
Manufacturing Site: Sandoz Schaftenau
Biochemiestrasse 10, 6336 Langkampfen, Austria
(FEI: 3004828473)
(b) (4)

Product: GP2017, adalimumab
Dosage: Sterile liquid for subcutaneous injection (40 mg/0.8 mL)
Indication: Rheumatoid Arthritis; Juvenile Idiopathic Arthritis in patients 4 years of age and older; Psoriatic Arthritis; Ankylosing Spondylitis; Adult Crohn's Disease; Ulcerative Colitis; Plaque Psoriasis
Action Date: 30 October 2018

Conclusion and Approvability Recommendation:

The drug substance portion of BLA 761071/6, as amended, is recommended for approval from a microbial control and a microbiological product quality perspective. The following post-marketing commitments should be communicated to the applicant:

1. To qualify the bioburden test method for the (b) (4) at Sandoz Schaftenau using 10 mL test volumes. Submit the qualification report as a CBE in accordance with 21 CFR 601.12.

2. To qualify the bioburden test for the (b) (4) using the (b) (4) and implement the new bioburden test method. Submit the qualification report as a CBE in accordance with 21 CFR 601.12.

Please refer to the review memo from Dr. Lindsey Brown for an assessment of sterility assurance and microbiological product quality for the drug product (DP) portions of the BLA.

(b) (4)



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Nichols

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Reyes
Candau-Chacon

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BLA STN 761071
Product GP2017
Proposed Trade Name Hyrimoz
Manufacturer Sandoz Inc., a Novartis Division

OBP CMC Review Data Sheet

1. BLA#: 761071

2. Review Date: June 27, 2018

3. Primary Review Team:

- | | |
|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| a. Medical Officer | Mark Borigini/ Nikolay Nikolov |
| b. Pharm/Tox | Brett Jones/ Andrew Goodwin |
| c. Product Quality Team | Yanning An (DS quality, similarity)
Chih-Jung Hsu (DP quality, immunogenicity)
Cristina Ausin (Application Technical Lead)
Scott Nichols (DS microbiology)
Lindsey Brown (DP microbiology) |
| d. Facilities | Michael Shanks/ Peter Qiu |
| e. Clinical Pharmacology | Mohammad Absar/ Anshu Marathe |
| f. Statistics | Bob Abugov
Tianhua Wang/ Meiyu Shen (CMC Stat) |
| g. OBP Labeling | Vicky Borders-Hemphill |
| h. CDRH consult | Kathleen Fitzgerald |
| i. RPM/RBPM | Nina Ton
Ladan Jafara
Keith Olin / Anh-Thy Ly (OPQ) |

4. Major GRMP Deadlines:

- | | |
|-------------------------|--------------------|
| a. Filing Meeting | December 11, 2017 |
| b. Mid-cycle meeting | April 10, 2018 |
| c. Late-cycle meeting | August 7, 2018 |
| c. Wrap-up meeting | September 11, 2018 |
| d. Primary review due | June 29, 2018 |
| e. Secondary review due | July 6, 2018 |
| f. BsUFA action date. | October 30, 2018 |

5. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request (OBP I)	November 21, 2017
Application Orientation Meeting	December 05, 2017
Information Request (DIA)	December 07, 2017
OPQ Filing Review	December 15, 2017
Information Request (OBP II)	December 22, 2017
Information Request (OBP III)	February 16, 2018
Information Request (OBP IV)	March 06, 2018
Information Request (OBP V)	March 19, 2018
Midcycle Meeting	April 10, 2018



Midcycle Communication	April 24, 2018
Information Request (OBP VI)	May 7, 2018
Label Meeting	May 29, 2018
Information Request (OBP VII)	June 8, 2018
Information Request (OBP VIII)	June 12, 2018
Information Request (OBP IX, DMA)	June 20, 2018
Teleconference to discuss IR OBP VIII	June 20, 2018
Information Request (OBP X)	June 25, 2018

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
761071/0005	October 30, 2017	Yes
761071/0007 (OBP IR I response)	November 29, 2017	Yes
761071/0010 (DIA IR response)	December 11, 2017	Yes
761071/0013 (Meeting Minutes)	December 19, 2017	Yes
761071/0014 (OBP IR II response)	January 11, 2018	Yes
761071/0016 (CMC amendment)	January 31, 2018	Yes
761071/0018 (OBP IR III response)	March 05, 2018	Yes
761071/0020 (OBP IR IV response)	March 20, 2018	Yes
761071/0021 (OBP IR IV & V response)	March 30, 2018	Yes
761071/0022 (CMC amendment II)	March 30, 2018	Yes
761071/0027 (OBP IR IV response)	April 27, 2018	Yes
761071/0028 (CMC stats IR response)	May 09, 2018	Yes
761071/0029 (OBP IR VI response)	May 15, 2018	Yes
761071/0033 (OBP IR VII response)	June 13, 2018	Yes
761071/0035 (OBP IR VIII response)	June 20, 2018	Yes
761071/0037 (OBP IR VII response)	June 22, 2018	Yes
761071/0039 (OBP IR IX response)	June 25, 2018	Yes
761071/0040 (OBP IR VIII response)	June 26, 2018	Yes

7. Drug Product Name/Code/Type:

- a. Proprietary Name GP2017
- b. Trade Name Hyrimoz(proposed)
- c. Non-Proprietary Name/USAN/INN adalimumab
- d. CAS Name: 331731-18-1
- e. Common Name:
- g. Compendial Name not applicable
- h. OBP systematic name (refer to OPQ-SOP-OBP-3006)
 MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [GP2017]

8. Pharmacological Category: Therapeutic recombinant human monoclonal antibody



9. Dosage Form: Injection

10. Strength/Potency:

- (i): The concentration/strength of the Drug Product
- (ii): Type of potency assay(s) Cell-based bioassay

11. Route of Administration: Intravenous infusion

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			Yes	DMF is current and will comply with all statements made in it.
			Yes	
			Yes	
			Yes	

13. Inspectional Activities:

A PAI was conducted from February 14 through February 20, 2018. Information about the facility and FDA personnel involved is described below:

Firm: Sandoz GmbH, Schaffenau

Location: Biochemiestrasse 10, 6336 Langkampfen, Austria

FEI: 3004828473

Dates of inspection: February 14-20, 2018

Days in the facility: 5

FDA Participants:	Machael R. Shanks	CDER/OPQ/OPF/DIA
	Laura Fontan	CDER/OPQ/OPF/DIA
	Deborah Schmiel, Ph.D.	CDER/OPQ/OBP/DBRRI
	Marjorie A. Shapiro, Ph.D.	CDER/OPQ/OBP/DBRRI

This pre-license inspection of the drug substance manufacturing facility at Sandoz GmbH Schaffenau was conducted on 2/14-2/20/2018 following a request by the Division of Inspectional Assessment,

Office of Process and Facilities, Office of Pharmaceutical Quality, CDER. The inspection was conducted to support the approval of Sandoz's biosimilar BLA STN761071/5 for GP2017. This inspection covered a comprehensive scope of Quality, Facilities and Equipment, Materials, Production and Laboratory Controls. This inspection was limited to the manufacturing of GP2015 and GP2017 drug substance. No refusals were encountered during the inspection. No sample collection was needed.

A four-item FDA Form-483 was issued at the close of the inspection on February 20, 2018. The observations were for: (1) Microbial hold times for EP2006 and GP2015 Drug Products are not adequately supported by process data at commercial scale; (2) Appropriate controls are lacking for (b) (4) (b) (4) testing machines to assure that only authorized personnel institute changes in testing programs; (3) Standard operating procedures are not adequate; and (4) the method for determination of material conformance to written specifications are not adequate.

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

Firm: (b) (4)
Location: (b) (4)
FEI: (b) (4)
Dates of inspection: (b) (4)
Days in the facility: 7
FDA Participants: (b) (4)

CDER/OPQ/OPF/DMA-IV
ORA/OMPTO/OPQO/DPQOIII/PQIB
CDER/OPQ/OBP/DBRRIV
CDER/OPQ/OBP/DBRRII

This pre-license inspection of the drug substance manufacturing facility at (b) (4) was conducted on (b) (4) following a request by the Division of Microbiology Assessment, Office of Process and Facilities, Office of Pharmaceutical Quality, CDER. The inspection was conducted to support the approval of Sandoz's biosimilar BLA STN761071/5 for GP2017. This inspection covered a comprehensive scope of Quality, Facilities and Equipment, Materials, Production and Laboratory Controls. This inspection was limited to the manufacturing of GP2017 drug substance. No refusals were encountered during the inspection. No sample collection was needed.

A five-item FDA Form 483 was issued to the firm at the end of this inspection on (b) (4). The observations included (b) (4) (b) (4) (b) (4). Three verbal observations were made for (b) (4) (b) (4). Management was notified that a written response should be provided to the Division Director within fifteen business days.

A PAI was conducted from April 16 to April 17, 2018. Information about the facility and FDA personnel involved is described below:

Firm: Hexal Ag
Location: Keltenring 1+3, Oberhaching, Bavaria, 82041
FEI: 3011617743
Dates of inspection: April 16-17, 2018
Days in the facility: 2
FDA Participants: Stephen D Brown
Yanming An

ORA/OMPTO/OPQO/DPQOII/PQIB
CDER/OPQ/OBP/DBRRII

This pre-license inspection of the drug substance similarity assessment laboratory Hexal Ag, was conducted on 4/16-4/17/2018 following a request by the Pharmaceutical Quality Investigation Branch, Division of Pharmaceutical Quality Operations II, Office of Pharmaceutical Quality Operations, Office of Medical Products and Tobacco Operations, ORA. This inspection covered the similarity assessment studies. This inspection was limited to GP2017. No refusals were encountered during the inspection. No sample collection was needed. No observations were made to the firm.

A PAI was conducted from April 19 to April 20, 2018. Information about the facility and FDA personnel involved is described below:

Firm: Novartis Pharma AG
Location: Lichtstrasse 35, Basel, Basel Stadt, 4056
FEI: 3002807772
Dates of inspection: April 19-20, 2018
Days in the facility: 2
FDA Participants: Stephen D Brown
Yanming An

ORA/OMPTO/OPQO/DPQOII/PQIB
CDER/OPQ/OBP/DBRRII

This pre-license inspection of the drug substance similarity assessment laboratory Novartis Pharma, was conducted on 4/19-4/20/2018 following a request by the Pharmaceutical Quality Investigation Branch, Division of Pharmaceutical Quality Operations II, Office of Pharmaceutical Quality Operations, Office of Medical Products and Tobacco Operations, ORA. This inspection covered the similarity assessment studies. This inspection was limited to GP2017. No refusals were encountered during the inspection. No sample collection was needed. No observations were made to the firm.

Refer to the OBP Drug Product review by Chih-Jung Hsu for information regarding inspectional activities related to Drug Product.

14. Consults Requested by OBP:

Discipline/Topic	Date Requested	Recommendation	Reviewer
CDRH/DAGRID	11/9/2017	Pending	Kathleen Fitzgerald

15. Quality by Design Elements:

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

	Design Space
X	Design of Experiments

	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. Precedents: None

17. Administrative:

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation

We recommend approval of the BLA, pending review of outstanding information requests. The data submitted in this Biologics License Application support the conclusion that the manufacture of GP2017 is well controlled and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents and sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. It is recommended that GP2017 be approved for human use (under conditions specified in the package insert).

We recommend an expiration dating period of (b)(4) months for GP2017 drug substance when stored at (b)(4) °C in (b)(4). The proposed self-life of 24 months for GP2017 drug product (DP) in pre-filled syringe (PFS) is supported by the stability studies.

We recommend approval of the proposed release and shelf-life specifications for GP2017 drug substance and drug product, pending adequate response to the IR regarding the glycosylation specification.

The analytical similarity assessment performed supports that:

- GP2017 is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components:
- A sufficiently robust analytical bridge was established to support the use of EU-approved Humira as a comparator in the clinical study.

II. List of Deficiencies to be Communicated

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

III. List of Post-Marketing Commitments/Requirements

There are 3 Product Quality-related Post-Marketing Commitment, which will include due dates negotiated with the sponsor:

1. To perform PFS shipping validation during summer.
2. To implement an apoptosis inhibition assay to replace the current TNF- α neutralization reporter gene assay.
3. To implement a control strategy for effector function.

IV. Review of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion

Sandoz claims a categorical exclusion to the environmental assessment requirements in compliance with the categorical exclusion criteria 21 CFR Part 25.31. The estimated concentration of the drug substance at the point of entry into the aquatic environment will be below 1 part per billion. Sandoz Inc.. claims that to the best of our knowledge, no extraordinary circumstances exist that would warrant the preparation of an EA, and that the firm is in compliance with all Federal, State and Local environmental laws and regulations.

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

V. Primary Container Labeling Review

The primary container labeling was reviewed separately by Vicky Borders-Hemphill with concurrence by Chih-Jung Hsu and Cristina Ausin.

VI. Review of Common Technical Document- Quality Module 3.2

CTD Modules 3.2.S, 3.2.R, and 3.2.A are reviewed by Yanming An and Cristina Ausin. Modules 3.2.P, 3.2.S.4.3, were reviewed by Chih-Jung Hsu and Cristina Ausin.

VII. Review of Immunogenicity Assays- Module 5.3.1.4

The immunogenicity assays were reviewed by Chih-Jung Hsu and Cristina Ausin.

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

3.2.R Biosimilarity with Reference Product

ANALYTICAL SIMILARITY ASSESSMENT

Reviewer Comment:

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

- *GP2017 is analytically highly similar to US-licensed Humira.*
- *The data demonstrate an analytical bridge between US-licensed Humira and EU-Approved Humira.*
- *For attributes where minor potential differences between GP2017 and US-licensed Humira are noted, the totality of the analytical data support that there are no impacts on function, activity, or stability in vitro. Specifically, the differences noted in glycosylation were not reflected in functional assays, such as ADCC, CDC, and the corresponding binding assays. Therefore, these differences are not expected to affect the mechanism of action of the product.*
- *Method validation or qualification results for methods used in the analytical similarity assessment are adequate to support that the methods are scientifically sound and suitable to study the intended quality attributes.*
- *The sponsor's proposed quality ranges based on a 3-standard deviation range are appropriate acceptance criteria for each attribute evaluated with Tier 2 statistical test unless otherwise noted.*
- *Sandoz intends to license two different presentations of GP2017, a pre-filled syringe (PFS) and an autoinjector. The analytical similarity assessment was performed with the PFS. According to the drug product review by Chih-Jung Hsu, the assembly into the secondary packaging component of the autoinjector does not have an effect on product quality attributes (refer to DP review memo) and it is acceptable to analyze only PFS batches in the analytical similarity assessment.*
- *The strength of U.S.-licensed Humira is labeled in mass per unit volume (40 mg/0.8 mL). U.S.-licensed Humira is filled into a single-use prefilled glass syringe with a volume of 0.8 mL¹. GP2017 is seeking approval for the same strength as U.S.-licensed Humira. Comparative protein concentration (mg/mL) reviewed as part of the analytical similarity assessment, and extractable volume (mL) and fill weight data reviewed as part of manufacturing process controls were used to inform the assessment of whether the proposed presentation of GP2017 has the same strength as the presentation of U.S.-licensed Humira. Based on the similarity and manufacturing data, the 40 mg/0.8 mL GP2017 prefilled syringe and autoinjector have the same total content of drug substance*

¹ U.S. Prescribing Information, U.S. Licensed-Humira. Accessed June 21, 2018 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125057s403lbl.pdf

in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as the presentation of U.S.-licensed Humira. These presentations meet the statutory “same strength” requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.

- *GP2017 has the same route of administration and dosage form as US-licensed Humira.*

3.2.R.1 Overall Strategy

The analytical similarity assessment consisted of three comparisons: GP2017 drug product to US-licensed Humira, GP2017 drug product to EU-approved Humira, and EU-approved Humira to US-licensed Humira. With this approach, GP2017 drug product could be demonstrated to be highly similar to the Humira product approved in the US and EU, and support the use of EU-approved Humira as the comparator in the comparative non-clinical and clinical studies.

The comparative physicochemical and functional assessment includes:

- Comparative similarity characterization studies of the following quality attributes (QA).
 - Primary structure and post-translational modifications/sequence variants
 - N-linked glycosylation
 - Charge heterogeneity
 - Product purity
 - Product related attributes
 - Higher order structure
 - Biological activity
- Assessment of the similarity of the degradation mechanism resulting from forced degradation studies.
- Assessment of the similarity of the long-term stability behavior at the intended storage condition of 5 ± 3 °C for up to 30 months, and the accelerated and stressed conditions for 6 months.

The sponsor ranked quality attributes related to similarity per their potential impact on the mode of action, risk score and the type of read-out. The risk score is a criticality score plus/minus a risk adjustment for the quality attribute. Each QA is evaluated for criticality assessing the possible impact of each attribute on efficacy, PK/PD, and immunogenicity and safety. The risk adjustment is applicable to product variants, host cell-derived and bioactive components, raw materials, process-

related impurities and extractables and leachables. The risk adjustment is not applicable to attributes which are directly related to safety, potency, composition, strength, pH, appearance, and description. Risk score and criticality score both range from 0 to 140. QAs directly related to the mode of action and with a high risk score (>85) were assessed using Tier 1 Statistical assessments². Attributes having a high risk score (>85) but not directly impacting the mode of action or those with moderate risk scores (56-85) were evaluated using Tier 2 statistical assessments, and the remaining attributes (risk score <56) including those without a quantitative readout were assessed by Tier 3 methods. Tier 1 statistical evaluation of assay results consists of equivalence testing. For Tier 2 assessments, results were evaluated by using quality ranges; analytical similarity for the attribute would meet Tier 2 criteria if 90% or greater of test values fall within the statistical quality range (3 standard deviations of estimated mean of the comparator product). QAs evaluated in Tier 3 are assessed using a descriptive evaluation of the raw data, and a simple dot plot is used for quantitative QAs.

A total of 36 drug product (DP) batches of US-Licensed Humira (expiry 08/2009 to 07/2018) and 44 DP batches of EU-approved Humira (expiry 10/2008 to 07/2018) were purchased and included as licensed adalimumab in the similarity assessment. A total of 22 DP batches (from 11 DS batches) and 6 additional DS batches of GP2017 were included in the similarity assessment. The GP2017 DS and DP batches were all produced at the commercial scale and commercial manufacturing sites (Table 3.2.R.1-1).

Table 3.2.R.1-1: GP2017 DP and DS batches used for similarity assessment

DP Batch #	DS Batch #	DS Production Site	DS/DP Production Date	Purpose of material
7005939	B074918	BPS (b) (4)	April 2012	Stability
7006285			August 2012	Clinical, stability
7006286			August 2012	Pre-clinical, stability
7006715	B079500	BPS	February 2013	Clinical, stability
7006716				Stability
7007138	B083248	BPS	August 2013	Stability
7007139				
7007386	B153820	BPS	February 2014	Stability
7007387				
7007389				Clinical, stability

² As defined in the 2017 Draft FDA Guidance *Statistical Approaches to Evaluate Analytical Similarity Guidance for Industry*

7007388	B170052	BPS, (b) (4)	February 2014	Stability
7007466			May 2014	
7007606			October 2014	
7007468	B232323	(b) (4)	May 2014	Clinical, stability
7007469				Stability
7007467	B170053	BPS, (b) (4)	May 2014	Clinical, stability
7007966			October 2015	Clinical
7007741	B247197	BPS, (b) (4)	January 2015	PV, stability
7007742				
7007743	B247198	BPS, (b) (4)	January 2015	PV, stability
7007981	B291058	(b) (4)	November 2015	Stability
7007982	B305991	(b) (4)	November 2015	Stability
Not tested	B247199	BPS, (b) (4)	June 2014	PV, stability
Not tested	B247204	BPS, (b) (4)	July 2014	PV, stability
Not tested	B247205	BPS, (b) (4)	July 2014	PV, stability
Not tested	B247206	BPS, (b) (4)	August 2014	PV, stability
Not tested	B291059	(b) (4)	July 2014	PV, stability
Not tested	B315432	BPS, (b) (4)	July 2015	GMP

Reviewer comments:

1. The 22 batches of GP2017 DP used in the analytical similarity assessment are from 11 GP2017 DS batches. We consider an “independent” lot to be a single DP lot produced from a single DS lot, or a single DS lot where no subsequent DP lot is included in the analysis. For attributes that depend primarily on the sequence, 3-dimensional structure, and glycosylation of the product, which is determined primarily by the DS manufacturing process, such as binding affinity to TNF α and Fc-mediated functions, we assess the similarity based on independent DP lots from single DS lot and independent DS lots. In this way, the “total number” of tested GP2017 DP batches may decrease in case there are multiple DP batches from a single DS lot. For attributes, such as aggregates or deamidated species that may be impacted by DP manufacture or long term storage, it is acceptable to use all DP lots regardless of the DS lot they were derived from.

On April 18, 2018, CMC Statistics reviewers sent an IR requesting the re-evaluation of both Tier 1 attributes using independent DP batches. In the response on May 09, 2018 (amendment #0028), the sponsor excluded all dependent GP2017 DP data and included additional data from independent DS batches and performed the equivalence testing for both Tier 1 assays. These independent DS batches are included in Table 3.2.R.1-1, the DP batches manufactured from these DS batches were not tested in the similarity assessment and the manufacturing dates of these DS batches are provided in the table. The detailed review of Tier 1 attributes is in 3.2.R.2.1 of this memo.

2. *On Jan 31, 2018, the sponsor submitted a CMC information amendment to report and correct inconsistencies identified in the initial CMC documents, including similarity assessment (Module 3.2.R Biosimilarity with Reference Product) and DS characterization data (Module 3.2.S.3.2 Impurities). The data inconsistencies were identified due to installation of an electronic data management system- electronic Target Specification Database (eTSD)- at Sandoz Biopharmaceuticals. The eTSD enables tracking of the analytical data and directly links them to the corresponding raw data. The GP2017 characterization data were transferred to eTSD and subjected to an additional data integrity check. During the transfer, inconsistencies between the raw data and the similarity report were identified in the datasets of CEX, Pepmap MS, extractable volume, AUC, extinction coefficient, TNF- α RGA, ADCC, CDC, and apoptosis inhibition assay. The related sections in this review are updated with the correct values and the corrections have no impact on the conclusions of the similarity assessment.*
3. *On November 21, 2017, an IR was sent to sponsor requesting the specific analytical similarity tests performed at each site listed in Table 9-2 Testing sites only used during development of section 3.2.S.2.6 Manufacturing process development. On November 29, 2017, the sponsor responded (amendment eCTD 0007) that Sandoz Oberhaching conducted the majority of the physicochemical and biophysical tests including the Tier 1 TNF α target binding SPR assay; Novartis performed the bioassays included in all three tiers. The analytical similarity testing performed at these two sites comprises most of the Tier 1 and Tier 2 data included in the submission. The OBP team participated in a pre-approval inspection at these two analytical similarity testing sites: Sandoz Biopharmaceuticals c/o Hexal AG located at Oberhaching, Germany and Novartis Pharma AG at Basel, Switzerland from April 16-20, 2018. No observation was made for either site.*

A summary of the analytical similarity results prepared by the reviewer are presented in the following Table 3.2.R.1-2.

1. *The sponsor analyzed assay results from independent DS and DP batches in the two Tier 1 statistical assessments. Tier 2 statistical assessment was performed on independent batch results for some assays but not for others. The “Number of batches” column on the table below shows the total number of batches the sponsor tested, including independent and dependent DP batches. Our conclusions on similarity for these Tier 2 assessments are based on independent DP batches.*
2. *The sponsor ranked the quality attributes (QAs) in the similarity assessment study. The two quantitative assays selected for evaluation by Tier 1 statistical method (equivalence test) reflect the known clinical mechanism of action (MoA), which is TNF- α binding and blocking of its activity. The bioassays evaluated by Tier 2 method include assays that reflect the plausible MoA of Fc domain effector function and mTNF binding and reverse signal activities. The other QAs evaluated by the Tier 2 approach are relevant to drug quality and safety and are quantitative. Assays evaluated by Tier 3 either reflect same bioactivities as the bioassays evaluated by Tier 1 and Tier 2, or are relevant to the protein primary and higher order structure. Assays evaluated by Tier 3 are either qualitative or otherwise not amenable to statistical analysis or reflect less critical attributes. The assessment by Tier of statistical methods is consistent with our expectations and precedent for previous Humira biosimilars, and we agree with the sponsor’s evaluation.*
3. *On March 6, 2018, an IR was sent to the sponsor for clarification of the reference standard batches used in each analytical similarity test which reports a result relative to a reference standard. Sponsor responded on March 30, 2018 (amendment #0021) with the request data set. The reference standard usage in the analytical similarity assessment is reviewed below in each method section.*
4. *A pairwise comparison was performed between GP2017, US-licensed Humira and EU-approved Humira. Initially, the sponsor conducted comparisons between GP2017 and US-licensed Humira in the file called “Biosimilarity with Reference Product” and between US-licensed Humira and EU-Humira in the file called “Bridging Humira US-EU”. On Feb 18, 2018, we sent an information request to the sponsor for statistical analysis results from the comparison between GP2017 and EU-approved Humira. The sponsor responded on Mar 05, 2018 with the requested data set (amendment eCTD 0018). The Table 3.2.R.1-2 and corresponding review sections are updated accordingly.*
5. *Regarding Tier 2 statistical assessments, Sandoz established quality ranges using the mean of the US-licensed Humira ± 3 standard deviations (SD) for comparisons to US-Humira and mean of the EU-approved Humira ± 3 SD for comparisons to EU-Humira. We evaluated the Sandoz established quality ranges for each assay. We concur with this range in all cases, and our conclusions of similar or not are based on these quality ranges we determined as suitable. The ranges for GP2017 in the table represent the range of minimum and maximum results.*

6. *“Similar/comparable” means that the comparison met criteria of statistical equivalence test for quality attributes evaluated by Tier 1 statistics, statistical quality range test for attributes evaluated by Tier 2 statistics and visual comparison for attributes evaluated by the Tier 3 approach. “Comparable” refers only to the comparison between US-licensed Humira and EU-approved Humira. “Not similar” means the comparison didn’t meet the statistical or visual comparison criteria. The “not similar” results are discussed in detail in the following sections of the review. A “not similar” designation does not necessarily mean the product failed the overall assessment of similarity; similarity is determined by scientific evaluation of all the available evidence.*

Table 3.2.R.1-2. GP2017 Analytical Similarity Assessment Results

Parameter	Quality Attribute	Test Method	Analysis Tier	Number of Batches (GP: US-licensed Humira: EU-approved Humira)	US-licensed Humira Range or Quality Range ^a	GP min – max Range	EU-approved Humira Range or Quality Range	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
Primary Structure and variants thereof	Amino Acid Sequence	RP-HPLC-UV reducing peptide mapping	3	4:2:2	Peak pattern of UV chromatograms is visually superimposable	Peak pattern of UV chromatograms is visually superimposable	Peak pattern of UV chromatograms is visually superimposable for US-licensed	similar/similar/comparable
		LC-MS/MS (orthogonal peptide maps)	3	1:1:1	Identical amino acid sequence for the heavy chain and light chain.	Identical amino acid sequence for the heavy chain and light chain for US-licensed Humira	Identical amino acid sequence for the heavy chain and light chain for US-licensed Humira	similar/similar/comparable
	Disulfide bonds	LC/MS Non-Reduced Peptide Mapping	3	6:3:3	Similar relative percentage of correctly linked disulfide bonds	Similar relative percentage of correctly linked disulfide bonds to US-licensed	Similar relative percentage of correctly linked disulfide bonds to US-licensed	similar/similar/comparable
	Free thiols	Ellman's assay	3	9 (7 independent):9:10	Low amount of free thiols (≤ 0.4 mol/mol)	Similar amount of free thiols to US-licensed Humira (≤ 0.4 mol/mol)	Similar amount of free thiols to US-licensed Humira (≤ 0.4 mol/mol)	similar/similar/comparable
	Thioether bonds	Reduced CE-SDS	3	4:2:2	Low amount of thioether bonds from heavy-light chain peak.	Similar amount of thioether bonds to US-licensed Humira	Similar amount of thioether bonds to US-licensed Humira	similar/similar/comparable

Parameter	Quality Attribute	Test Method	Analysis Tier	Number of Batches (GP: US-licensed Humira: EU-approved Humira)	US-licensed Humira Range or Quality Range ^a	GP min – max Range	EU-approved Humira Range or Quality Range	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
	Molecular Mass	ESI-qTOF MS of intact protein	3	6:3:3	Similar molecular mass and size	Similar molecular mass and size to US-licensed Humira	Similar molecular mass and size to US-licensed Humira	similar/similar/comparable
		LC/MS-reduced mAb, F(ab') ₂ and Fc'	3	6:3:3	Identical primary structure and similar PTM at the subunit/domain level.	Identical primary structure and similar PTM at the subunit/domain level to US-licensed Humira	Identical primary structure and similar PTM at the subunit/domain level to US-licensed Humira	similar/similar/comparable
		SEC-MALL	3	4:2:2	Similar molecular mass and size	Similar molecular mass and size to US-licensed Humira	Similar molecular mass and size to US-licensed Humira	similar/similar/comparable
Purity	Monomer	SEC	2	21 (11 independent): 28:32	99.5-99.9%	99.4-99.8%	99.4-99.9%	similar/similar/comparable
	HMW variants	SEC	2	21 (11 independent): 28:32	0.1-0.4%	0.2-0.5%	0-0.5%	Not similar /similar/comparable
		AUC	2	18:13:13	0-2.2%	0.3-1.6%	0-2.2%	similar/similar/comparable
	Dimers	AUC	3	18:13:13	0.5-2.3%	0.4-2.6%	0.2-2.7%	similar/similar/comparable
	Antibody fragments	SEC	2	21 (11 independent): 28:32	0-0.2%	0-0.1%	0-0.2%	similar/similar/comparable
		nrCE-SDS	2	22 (11 independent): 29:31	LC: 0.1-0.9% HHL: 1.4-3.1%	LC: 0.4-0.6% HHL: 2.1-3.1%	LC: 0-1.0% HHL: 1.4-3.4%	similar/similar/comparable
	Intact IgG	nrCE-SDS	2	22 (11 independent): 29:31	95.6-97.9%	95.7-97.1%	94.9-98.0%	similar/similar/comparable
Glycosylation	Site occupancy Fc N-glycan	rCE-SDS	3	22:27:27	97.7-98.6%	99.3-99.6%	97.8-98.7%	similar/similar/comparable

Parameter	Quality Attribute	Test Method	Analysis Tier	Number of Batches (GP: US-licensed Humira: EU-approved Humira)	US-licensed Humira Range or Quality Range ^a	GP min – max Range	EU-approved Humira Range or Quality Range	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
	N-glycan galactosylated	HILIC	2	17 (10 independent): 34:41	14.7-23.1%	23.7-37.4%	13.5-25%	Not similar/not similar/comparable
	N-glycan non-fucosylated	HILIC	2	17 (10 independent): 34:41	0.5-0.9%	2.4-3.2%	0.4-1.0%	Not similar/not similar/comparable
	N-glycan high mannose	HILIC	2	17 (10 independent): 34:41	3.9-6.6%	0.9-1.3%	3.5-7.0%	Not similar/not similar/comparable
	Glycation	Boronate affinity chromatography	3	17:32:35	0.1-0.6%	0.3-0.5%	0.1-0.5%	Similar/similar/co mparable
Charge	Acidic variants	CEX	2	15 (9 independent): 31:41	8.2-12.6%	6.8-10.7%	8.1-13.6%	Not similar/not similar/comparable
	Basic variants	CEX	2	15 (9 independent): 31:41	20.6-31.5%	12.9-17.7%	18.5-32.8%	Not similar/not similar/comparable
	pI variants	iCE	3	6:3:3	Similar charge pattern and pI variants	Similar charge pattern and pI variants to US-licensed Humira	Similar charge pattern and pI variants to US-licensed Humira	Similar/similar/co mparable
		2D-DIGE	3	1:1:1	Similar image	Similar image to US-licensed Humira	Similar image to US-licensed Humira	Similar/similar/co mparable
Hydrophobicity		Hydrophobic interaction chromatograp	3	17:27:29	Similar profile	Similar profile to US-licensed Humira	Similar profile to US-licensed Humira	Similar/similar/co mparable
Amino acid modifications/sequence variants	Met256 oxidation	RP-HPLC-UV reducing peptide	2	18:30:31	0.9-2.9%	0.4-1.1%	0.9-2.6%	Not similar/not similar/comparable
	Deamidation on peptides LH27 and LH30	Peptide mapping LC-MS	3	18:34:41	1.3-4.4%	1.6-2.4%	1.7-4.2%	Similar/similar/co mparable

Parameter	Quality Attribute	Test Method	Analysis Tier	Number of Batches (GP: US-licensed Humira: EU-approved Humira)	US-licensed Humira Range or Quality Range ^a	GP min – max Range	EU-approved Humira Range or Quality Range	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
	Isomerization of Asp	ISOQUANT	3	15:34:37	0.8-2.7%	0.7-2.3%	0.9-2.9%	Similar/similar/comparable
		RP-HPLC-UV reducing peptide	3	18:34:41	0.5-2.8%	0.3-0.7%	0.6-2.3%	Similar/similar/comparable
	N-terminal extension	Peptide mapping LC-MS	3	6:3:3	No incomplete cleavage of signal peptide detected	Low amount ($\leq 0.5\%$) of incomplete cleavage of signal peptide detected	No incomplete cleavage of signal peptide detected	Not similar/not similar/comparable
	N-terminal (pyro glutamate)	Peptide mapping LC-MS	3	18:34:41	1.2-2.3%	1.1-2.1%	1.2-2.7%	Similar/similar/comparable
	C-terminal lysine	RP-HPLC-UV reducing peptide mapping	3	17:35:40	13.3-18.7%	3.1-6.0%	12.2-18.1%	Not similar/not similar/comparable
	C-terminal proline amide	RP-HPLC-UV reducing peptide mapping	3	17:35:40	0.1-1.4%	0.7-1.9%	0.1-1.2%	Similar/similar/comparable
Higher Order Structure	Secondary Structure	Far-UV CD	3	6:3:3	Similar secondary structure	Similar secondary structure to US-licensed Humira	Similar secondary structure to US-licensed Humira	Similar/similar/comparable
		FTIR		6:3:3				
	Tertiary Structure	Near-UV CD	3	6:3:3	Similar tertiary structure	Similar tertiary structure to US-licensed Humira	Similar tertiary structure to US-licensed Humira	Similar/similar/comparable
		X-ray crystallography	3	1:1:1	Similar crystal structure	Similar crystal structure to US-licensed Humira	Similar crystal structure to US-licensed Humira	Similar/similar/comparable

Parameter	Quality Attribute	Test Method	Analysis Tier	Number of Batches (GP: US-licensed Humira: EU-approved Humira)	US-licensed Humira Range or Quality Range ^a	GP min – max Range	EU-approved Humira Range or Quality Range	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
		H/D-exchange	3	1:1:1	3D structure	Similar 3D structure to US-licensed Humira	Similar 3D structure to US-licensed Humira	Similar/similar/comparable
	Melting temperature	DSC	3	6:3:3	Tm1: 71.06 Tm2: 81.56	Tm1: 71.05 Tm2: 81.57	Tm1: 71.09 Tm2: 81.63	Similar/similar/comparable
	3D structure	1D ¹ H NMR 2D ¹ H- ¹ H NOESY NMR	3	3:2:2	NMR 1D and 2D spectra	Similar NMR 1D and 2D spectra to US-licensed Humira	Similar NMR 1D and 2D spectra to US-licensed Humira	Similar/similar/comparable
Drug product related attributes	Extractable volume	Weighing	2	19:31:35	771-831 µL	804-840 µL	782-828 µL	Similar/similar/comparable
	Particulate contamination	Vision inspection	3	6:3:3	Free from extraneous particles	Free from extraneous particles	Free from extraneous particles	Similar/similar/comparable
		Micro-flow imaging (Particles/mL)	3	3:3:3	≥10 µm: 104-208 ≥25 µm: 1-2	≥ 10µm: 42-199 ≥ 25µm: 0-1	≥ 10µm: 42-241 ≥ 25µm: 3-11	Similar/similar/comparable
		Resonant mass measurement (1000 particles/mL)	3	5:3:3	Neg. buoyant > 0.3µm: 5000-9000 Pos. buoyant > 0.5µm: 2000-	Neg. buoyant > 0.3µm: 500-7000 Pos. buoyant > 0.5µm: 500-3000	Neg. buoyant > 0.3µm: 7000-12000 Pos. buoyant > 0.5µm: 4000	Similar/similar/comparable
	Concentration of active ingredient (mg/mL)	UV absorbance	2	22:35:42	44.9-52.4	47.2-51.3	45.1-52.5	Similar/similar/comparable

Parameter	Quality Attribute	Test Method	Analysis Tier	Number of Batches (GP: US-licensed Humira: EU-approved Humira)	US-licensed Humira Range or Quality Range ^a	GP min – max Range	EU-approved Humira Range or Quality Range	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
Biological Activity— Proven MoA: TNF α Binding to Fab Domain	Binding TNF	Inhibition of sTNF- α induced cell apoptosis	1	15:16:21	84-118%	75-122%	80-120%	Equivalent/equivalent/ comparable
		Binding to TNF α Target Antigen by Surface Plasmon Resonance (SPR)	1	14:18:18	80-120%	92-124%	78-114%	Equivalent/equivalent/ comparable
		TNF- α neutralization reporter gene assay	2	22 (11 independent): 32:40	78-115%	89-107%	80-116%	Similar/similar/co mparable
		Binding to Cell Surface TNF Antigen by flow	2	15 (9 independent): 10:15	80-113%	84-120%	79-115%	Similar/similar/co mparable
		Reverse Signaling by flow	2	10:10:10	72-115%	73-112%	66-135%	Similar/similar/co mparable
		Off-target binding to cytokines:TGF- β 1, IL-1 β , IFN- γ , APRIL, IL-6, IL-8, IL-10, TNF-beta, sCD40L,	3	1:1:1	No	No	No	Similar/similar/co mparable
Biological Activity—Functional	ADCC Activity	NK Cell ADCC Assay	2	11 (8 independent): 26:28	54-182%	75-114%	67-174%	Similar/similar/co mparable



Parameter	Quality Attribute	Test Method	Analysis Tier	Number of Batches (GP: US-licensed Humira: EU-approved Humira)	US-licensed Humira Range or Quality Range ^a	GP min – max Range	EU-approved Humira Range or Quality Range	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
Characterization of Fc Domain		Mixed Lymphocyte Reaction (MLR) Assay	3	4:3:3	Inhibit proliferation of T-cells in a dose-dependent manner	Similar dose-dependent response curve to US-licensed Humira	Similar dose-dependent response curve to US-licensed Humira	Similar/similar/comparable
		Binding to FcγRIIIa V158 by SPR	2	10 (7 independent): 10:10	69-115%	93-105%	78-105%	Similar/similar/comparable
		Binding to FcγRIIIa F158 by SPR	2	10 (7 independent): 10:10	79-99%	92-106%	81-106%	Similar/similar/comparable
	CDC Effector Function	CDC Assay	2	11 (8 independent): 32:36	65-119%	97-109%	51-135%	Similar/similar/comparable
		CIq Binding ELISA	2	7 (6 independent): 6:6	70-111%	93-103%	85-105%	Similar/similar/comparable
	Additional Fcγ Receptor Binding SPR Assay	Binding to FcγRI M^*10^{-9}	3	4:2:2	20.3-24.5	19.0-23.1	20.7	Similar/similar/comparable
		Binding to FcγRIIa μ M	3	4:2:2	2.27-2.34	1.94-2.08	2.18-2.36	Similar/similar/comparable
		Binding to FcγRIIb/c μ M	3	4:2:2	9.48-10.0	7.82-8.51	9.09-9.12	Similar/similar/comparable
		Binding to FcγRIIIb	3	4:2:2	9.67-11.8	8.73-10.3	9.89-11.7	Similar/similar/comparable
	Biological Activity—half-life	Neonatal Fc receptor binding	Binding to FcRn by SPR assay	2	10 (7 independent): 10:10	67-150%	87-142%	61-164%

3.2.R.2 Analytical Similarity Assessment Results

3.2.R.2.1 Comparative Assessment for Assays evaluated by Tier 1 (Equivalence Test)

The blockade of TNF functionality by the binding of the Fab domain represents the primary MOA for GP2017.

3.2.R.2.1.1 Apoptosis Inhibition

TNF- α can induce target cells to undergo receptor-mediated apoptosis by interacting with its cell surface receptors. The activity of adalimumab to neutralize soluble TNF- α is assessed by inhibition of TNF- α induced cell apoptosis. In the apoptosis inhibition assay, U937 cells are treated with TNF- α and with graded amounts of adalimumab. The apoptosis indicators caspase-3 and caspase-7 are quantified using a luminometric assay. The degree of apoptosis inhibition is determined against the activity of a reference standard tested at the same time. Figure 3.2.R.2-1 shows the equivalence test for apoptosis inhibition activity for GP2017 DP and US-licensed Humira.

The similarity assessment included the comparison of 15 independent batches of GP2017 DS/DP to 16 US-licensed Humira and 21 EU-approved Humira drug product batches. A Tier 1 equivalence test was performed for these assay results and summarized in Table 3.2.R.2-1. Because the 90% confidence intervals fall within the corresponding equivalence acceptance limits, the sponsor concluded that GP2017 is like US-licensed Humira and EU-approved Humira in the inhibition of TNF- α induced apoptosis assay. The results also demonstrate that EU-approved Humira is similar to US-licensed Humira with respect to apoptosis inhibition activity.

Reference standards GP2017.01REF, GP2017.02REF and GP2017.01WST were used in the assay. The relative potency of GP2017.02REF was calculated as the geometric mean value of 7 measurements against GP2017.01REF. The relative potency of GP2017.02REF is 95% with a confidence interval of 90-112%. The relative potency of GP2017.01WST was not determined because it was derived from the same DS batch (B153820) as GP2017.02REF.

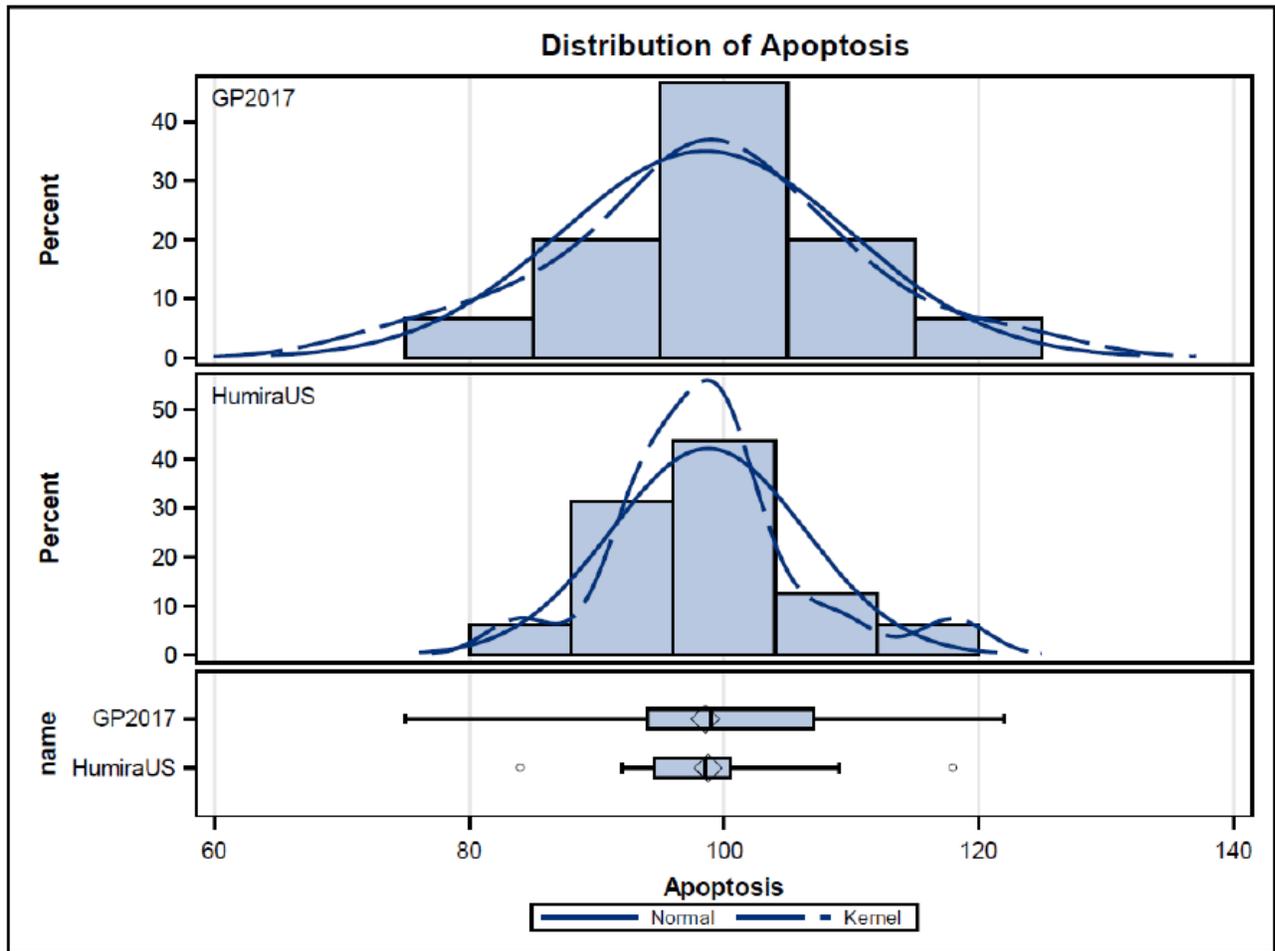


Figure 3.2.R.2-1 Equivalence test for apoptosis inhibition bioactivity for GP2017 DP/DS and US-licensed Humira.

Table 3.2.R.2-1 Equivalence Testing Results for TNF- α induced apoptosis inhibition assay (% Relative Potency)

Mean difference	-EAC	Lower bound CI	Upper bound CI	+EAC	assessment
GP2017 vs. US-licensed Humira	-11.3644	-6.1969	5.7636	11.3644	equivalent
GP2017 vs. EU-approved Humira	-16.4698	-8.4763	4.4001	16.4698	equivalent
US vs. EU Humira	-11.3644	-3.3400	6.9829	11.3644	equivalent

Assay Qualification: The apoptosis inhibition assay was qualified, and its linear range is 50-200% relative potency (RP). The assay has an accuracy of 92-104% at target and a precision of 2-16% geometric relative standard deviation (RSD).

Reviewer comment: *On March 06, 2018, an IR was sent to request the sponsor to evaluate the apoptosis inhibition assay results using Tier 1 equivalence testing. On March 19, 2018, the sponsor responded (amendment eCTD 0020) with apoptosis inhibition assay data from 10 independent GP2017 DS/DP batches, 16 batches of US-licensed Humira and 21 batches of EU-approved Humira.*

On April 18, 2018, the CMC statistics reviewer sent an IR regarding the batches selection for GP2017, US-licensed Humira, and EU-approved Humira for the equivalence test. On May 09, 2018, the sponsor responded (amendment eCTD 0028) with equivalence testing results of apoptosis inhibition assay data from 15 independent GP2017 DS&DP batches and the rationale of reference product batch selection. The data in Figure 3.2.R.2-1 and Table 3.2.R.2-1 reflect the most recently updated equivalence testing results.

Results from 10 GP2017 DP batches were initially analyzed with a Tier 2 quality range method. Results from batches 7007966 and 7007742 were excluded due to not meeting the independent batch requirement. Results from seven GP2017 DS batches (the corresponding DP batches that were not tested with the apoptosis inhibition assay) were added to the statistical evaluation. The use of DS batches is acceptable because the TNF α neutralization activity depends on the molecular properties and is not affected by the DP manufacturing process. The relative potency (RP) results from the initial ten DP batches ranged from 85% to 110%. The RP from 15 independent DS/DP batches ranged from 75% to 122%. The RP from 16 US-licensed Humira batches is 84-118%, and the RP from 21 EU-approved Humira is 80-120%. The equivalence test results show that DP2017, US-licensed Humira and EU-approved Humira are similar in the three-way pairwise comparison.

The sponsor initially analyzed the results from the apoptosis inhibition assay with a Tier 2 quality range method. It is more appropriate to use Tier 1 equivalence test for this attribute because this assay reflects the mechanism of action of adalimumab and captures a whole-cell functional outcome following TNF α inhibition.

The sponsor developed a TNF α neutralization reporter gene assay (RGA) as the primary method to measure adalimumab activity of TNF α binding and inhibition. The apoptosis inhibition assay was developed later as an orthogonal method to measure the same mechanism of action activity. Not all Humira product batches were tested with this method due to their expiration dates. The Humira batches were sampled randomly and the distribution of the RP did not show any trends. During the inspection at Hexal AG on April 16-17, 2018, the sponsor confirmed the reference product batch selection strategy. I agree that the Humira batches used in the analysis are representative. Three reference standards were used during the similarity assessment with the apoptosis inhibition assay. The relative potency of GP2017.02REF was determined against GP2017.01REF (first reference used in this assay) and showed

no significant difference in potency. GP2017.01WST was derived from the same DS batch as GP2017.02REF. It is acceptable to conclude that all three reference standards have equivalent potency for the apoptosis inhibition assay.

3.2.R.2.1.2 TNF- α Target Binding by SPR

The binding affinities of GP2017, US-licensed Humira, and EU-approved Humira to the TNF target antigen were evaluated using surface plasmon resonance (SPR) technology. The similarity assessment included the comparison of 14 independent GP2017 DS/DP batches, to 18 US-licensed Humira and 18 EU-approved Humira drug product batches. A Tier 1 equivalence test was performed on the data. The results are presented in Figure 3.2.R.2-2 and summarized in Table 3.2.R.2-2. Because the 90% confidence intervals fall within the corresponding equivalence acceptance limits, the sponsor concluded that GP2017 is similar to US-licensed Humira and EU-approved Humira for TNF- α binding.

The five reference standards GP2017.01WSTD, GP2017.02WSTD, GP2017.01REF, GP2017.02REF, and GP2017.01WST were used for generating TNF- α target binding SPR data. TNF- α neutralization RGA was used to establish the analytical bridge between the reference standards and all reference standards are equivalent in potency of TNF- α neutralization RGA. Because TNF- α neutralization RGA measures the binding as well as neutralization activity of adalimumab to TNF- α , Sandoz omitted the bridging measurement between standards using TNF- α binding SPR. In addition, no shift was observed in the relative potency of TNF- α binding SPR from all the product batches tested against difference reference standards.

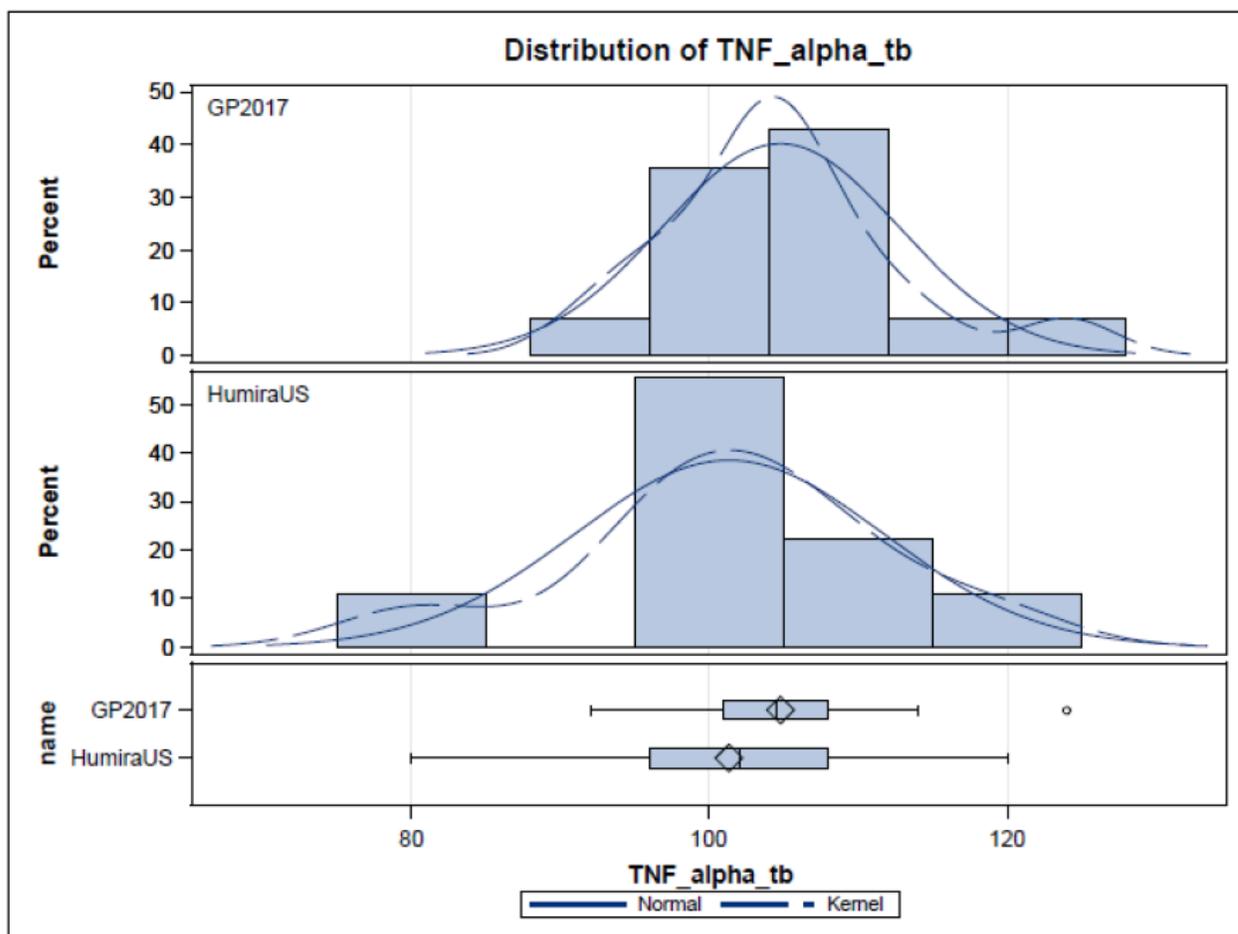


Figure 3.2.R.2-2 Equivalence test for TNF- α target binding by SPR for GP2017 and US-licensed Humira.

Table 3.2.R.2-2 Equivalence Testing Results for TNF- α Binding by SPR (% Relative Potency)

Mean difference	-EAC	Lower bound CI	Upper bound CI	+EAC	assessment
GP2017 vs. US-licensed Humira	-15.5374	-2.039	8.944	15.5374	equivalent
GP2017 vs. EU-approved Humira	-12.1113	-0.6738	9.0230	12.111	equivalent
US vs. EU Humira	-15.5374	-5.9654	4.5209	15.5374	equivalent

Assay qualification: The affinity of adalimumab binding to TNF- α was determined by surface plasmon resonance (SPR)-based measurements. The binding of a concentration range of TNF α (0.5 - 10 nM) to

GP2017 and the Humira products was analyzed for each data point. The equilibrium dissociation constant (K_D) for the reaction between TNF α and adalimumab was calculated from the on (k_a) and off (k_d) rate constants measured at these concentrations. Adalimumab reference material was included in each run. Relative binding affinity (K_A) was calculated by dividing mean K_D value of the reference material by K_D value of a test sample. The intra- and inter-assay precision (CV) were demonstrated to be 4.0% and 7.5% respectively. And the method can differentiate two anti-TNF α antibodies (adalimumab and infliximab) based on their binding affinity.

Reviewer comment: *On March 06, 2018, an IR was sent to request the method qualification report for the TNF α binding SPR assay. On March 20, 2018, sponsor responded (amendment eCTD 0020) with the method qualification report. I reviewed the SPR assay protocol and method qualification report during the April 16-17, 2018 Inspection at Hexal AG. The assay was evaluated and is suitable for the intended purpose.*

On April 18, 2018, the CMC statistics reviewer sent an IR regarding the batches selection for GP2017, US-licensed Humira and EU-approved Humira for the equivalence test. On May 09, 2018, the sponsor responded (amendment eCTD 0028) with TNF- α target binding SPR assay data from 14 independent GP2017 DS&DP batches and the rationale for the reference product batch selection. The data in Figure 3.2.R.2-2 and Table 3.2.R.2-2 reflect the most recent updated equivalence testing results.

Results from 15 GP2017 DP batches were initially analyzed with Tier 1 equivalence testing. Results from batches 7006286, 7007389, 7007606, 7007966, 7007469 and 7007742 were excluded due to not meeting the independent batch requirement. Results from five GP2017 DS batches (the corresponding DP batches were not tested by TNF- α target binding SPR) were added to the statistical evaluation. Because the TNF- α binding activity depends on the molecular properties and is not affected by DP manufacturing process, it is acceptable to include independent DS results in the similarity assessment. The relative potency (RP) results from the initial 15 DP batches ranged from 92% to 124%. The RP from 14 independent DS/DP batches remain at the same range. The RP from 18 US-licensed Humira batches is 80-120%, and the RP from 18 EU-approved Humira is 78-114%. The equivalence test results show that DP2017, US-licensed Humira and EU-approved Humira are similar in the three-way pairwise comparison.

The TNF- α target binding SPR assay was developed as an orthogonal method of TNF- α neutralization RGA for measuring TNF- α binding activity of adalimumab. Not all reference product batches were tested with this method. But the selection of reference product batches was random over the development period. From a product quality perspective, it is acceptable to use a subset batches of adalimumab products in the similarity assessment. The batches selected are representative and do not appear to have been chosen in a manner that would bias the results.

All the reference standards were equivalent in potency measured by TNF- α neutralization RGA and the TNF- α binding SPR data did not show significant shift. It is acceptable to conclude that all reference standards were equivalent in potency in TNF- α target binding SPR.

3.2.R.2.2 Similarity Assessment for Tier 2 (Quality Range Approach)

Quality attributes evaluated by Tier 2 are those of moderate to high risk for impact on quality for which quantitative data can be obtained. A quality range approach is used for the Tier 2 statistical analysis. Sandoz calculated the quality range as the estimated mean (of US-licensed Humira) ± 3 standard deviations (SD). Analytical similarity would be established for the quality attribute if at least 90% of the batches of GP2017 or EU-approved Humira are within the quality range of US-licensed Humira.

3.2.R.2.2.1 TNF- α Neutralization Reporter Gene Assay

Biological activity of GP2017, US-licensed Humira, and EU-approved Humira was assessed by a TNF- α neutralization reporter gene assay. This assay is the current lot release potency assay for GP2017. The assay measures the *in vitro* neutralization of soluble TNF- α by GP2017. A HEK293 cell line transfected with a firefly luciferase is used in the assay. The cells express luciferase while responding to the TNF- α and endogenous TNF receptors interactions. The luciferase assists oxidation of luciferin which then emits light. The luminescence is measured and it is inversely proportional to TNF- α neutralization. The activity of test samples is determined against a reference standard tested at the same time.

The similarity assessment included the comparison of 11 independent batches of GP2017 DP to 32 US-licensed Humira and 40 EU-approved Humira drug product batches. Graphical presentation of the relative potency results is shown in Figure 3.2.R.2-3. Sandoz derived the statistical quality range of 78-115% relative EC50 for TNF- α neutralization RGA from the 32 US-licensed Humira batches. 100% of GP2017 and EU-approved Humira lots were within quality range for TNF- α neutralization. The quality range derived from 40 EU-approved Humira is 80-116%, and 100% GP2017 DP lots fall in the range. GP2017 is similar to US-licensed Humira and EU-approved Humira.

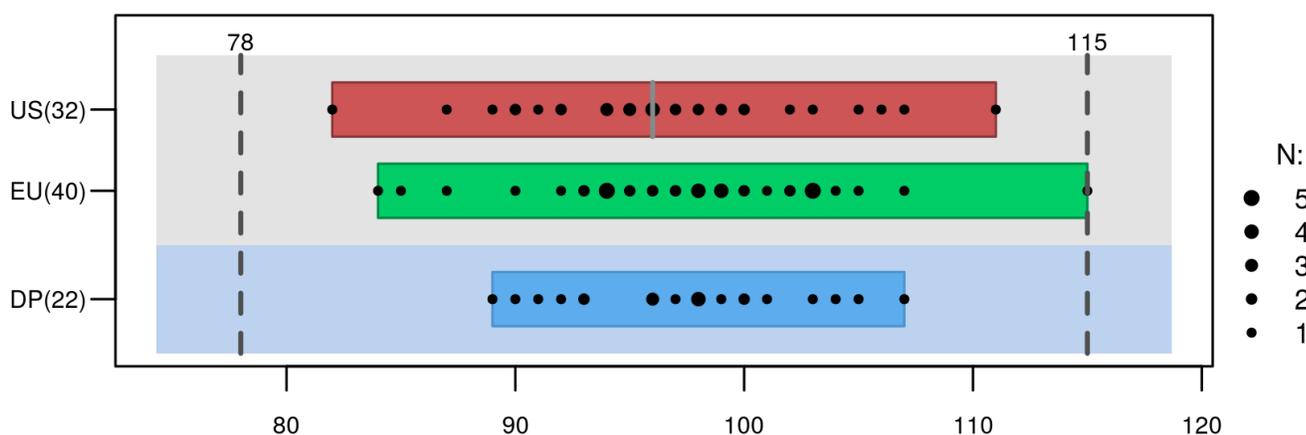


Figure 3.2.R.2-3 Comparison of TNF- α neutralization RGA for GP2017 DP and Humira. The min-max range of US-licensed (red box), EU-approved Humira[®] (green box) and GP2017 DP (blue box) is shown. The total number of batches contributing to the respective min-max range is shown in parentheses; the data

range is shown in brackets. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right).

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

This assay is a release test and the method validation is reviewed by Chih-Jung Hsu.

Reviewer comment: *The validated assay is adequate to support the testing results. The SD of US-licensed Humira TNF- α neutralization results was 7.6%, reflecting method and lot to lot variability. Five reference standard batches were used in this similarity assessment. All reference standards were equivalent in potency measured with the TNF- α neutralization RGA.*

On March 06, 2018, an IR was sent requesting sponsor to evaluate the RGA results as a Tier 2 attribute instead of a Tier 1. Sandoz responded on March 20, 2018 (amendment eCTD 0020) with the re-calculated results. Relative potency results from all GP2017 DP batches were within the quality ranges of US-licensed Humira and EU-approved Humira. The adalimumab neutralization of TNF- α related to NF- κ B gene expression is similar for all pairwise comparisons between GP2017, US-licensed Humira, and EU-approved Humira.

3.2.R.2.2.2 Binding to Membrane-associated TNF- α (mTNF- α)

A competitive binding assay was employed to assess the binding of GP2017, US-licensed Humira, and EU-approved Humira to mTNF expressed on HEK293T cells. The tested adalimumab is used to displace a fluorescently labeled adalimumab which is associated to mTNF on the cell surface. Cell-associated fluorescence is quantified by flow cytometry and the relative potency of each sample is calculated against the reference standard. Figure 3.2.R.2-4 shows a graphical presentation for relative potency values for all batches tested. Sandoz derived the statistical quality range of 80-113% relative potency for mTNF binding from the 10 US-licensed Humira batches. 100% EU-approved Humira batches were within quality range for mTNF binding. Two GP2017 DP batches (120% for batch 7006285, 115 for batch 7007389) were outside the quality range. The quality range from EU-approved Humira is 79-115% and one GP2017 DP batch was outside the quality range. Sandoz used 15 GP2017 DP batches from 9 independent DS batches in this test. DP batch 7006286 was from the same DS batch as batch 7006285 and its relative potency is 104%. Batches 7007386 and 7007387 were from the same DS batch as batch 7007389 and their relative potency were 107% and 96%, respectively. Sandoz considered the two higher results reflecting the assay variability and concluded that GP2017 is similar to US-licensed Humira and EU-approved Humira in terms of mTNF α binding activity.

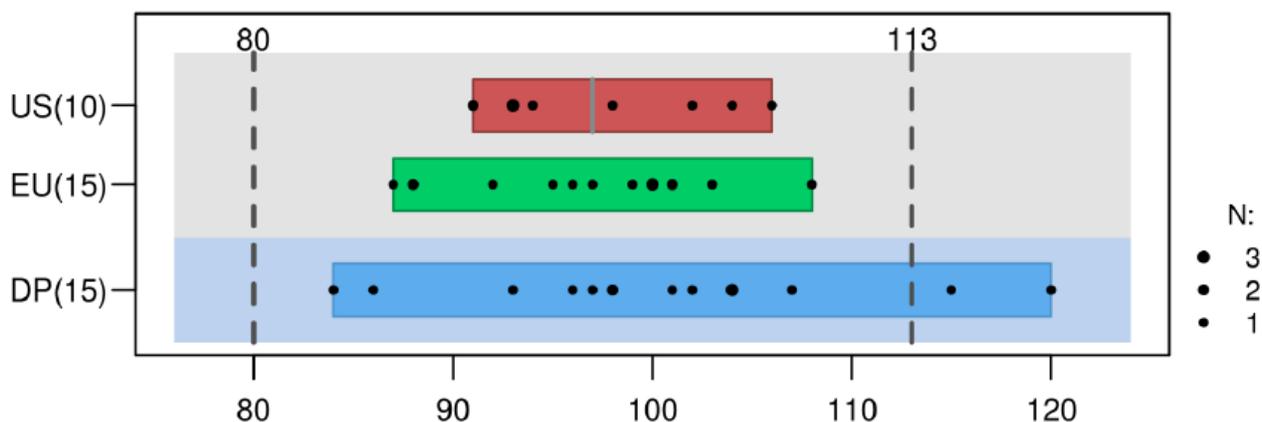


Figure 3.2.R.2.-4 Comparison of mTNF- α binding for GP2017 DP and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira[®] US are shown in a red box, values of Humira[®] EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

Assay Qualification: The mTNF binding assay was qualified, and its linear range is 50-200% relative potency (RP). The assay has an accuracy of 95-107% at target and a precision of 4-7% geometric relative standard deviation (RSD).

Two reference standard batches GP2017.02REF and GP2017.01WST were used in this assay. The relative potency of GP2017.01WST is considered equivalent to GP2017.02REF because they were derived from the same DS batch.

Reviewer comment: *In amendment eCTD 0018 section 2.1.16, Sandoz indicated that additional data for mTNF α binding were generated after BLA submission. On March 19, 2018, an IR was sent requesting those additional data and re-calculation of the three-way comparison. On March 30, 2018, sponsor responded (amendment eCTD 0021) with the results and re-calculation. Sandoz tested 5 additional GP2017 DP, 2 additional US-licensed Humira and 7 additional EU-approved Humira batches. The resulting range of GP2017 DP and US-licensed Humira did not change with the additional data. Results from EU-approved Humira ranged wider but are within the quality range of US-licensed Humira.*

The qualified assay is adequate to support the testing results. The SD of US-licensed Humira mTNF binding results was 5.6%, reflecting method and lot to lot variability. The quality range is reasonable for similarity assessment.

Batch 7006285 with the highest potency of 120% is from the same DS batch as batch 7006286 which has potency of 104% (within the quality range). Batch 7007389 with the second highest potency of 115% is from the same DS batch as batches 7007386 and 7007387 which have potency of 107% and

96%, respectively. The mTNF α binding activity depends on the molecule structure and is not affected by the DP manufacturing process. In this assay, each sample was tested twice on two plates. Sandoz also examined the individual potency for batches 7006285 and 7007389. The result of each batch on the first plate is about 110%; the results on the second plate were significant higher (131% and 118.8%). Therefore, the final mean potency for each batch is higher and outside of the quality range. Given the potency of other DP batches from the same DS batches and the individual assay results, the observed higher potency for batch 7006285 and 7007389 reflects the method variability. In addition, GP2017 is similar to Humira in the reverse signaling event, which is directly linked to mTNF α binding activity. The adalimumab binding to mTNF expressed on cell surface is similar for all pairwise comparisons between GP2017, US-licensed Humira, and EU-approved Humira.

3.2.R.2.2.3 Apoptosis Induction (Reverse Signaling)

Reverse signaling is a likely mechanism of action for adalimumab involving the binding of the Fab domain to mTNF- α on certain cell types. The adalimumab/mTNF complex can initiate reverse signaling or outside-to-inside signaling in the TNF-bearing cell and lead to cell apoptosis or suppression of cytokine expression in the cell. In the apoptosis induction assay, adalimumab binds to mTNF expressed on the Jurkat cell surface, resulting in signal transduction which initiates dose dependent apoptotic events. Phosphatidylserine, presenting on the apoptotic cells, are labeled with Annexin V coupled with fluorescein (FITC) and are quantified by flow cytometry.

Reverse signaling activity was assessed for 10 independent GP2017 DS/DP batches, 10 US-licensed Humira and 10 EU-approved Humira batches. Reference standard GP2017.01WST is used in the assay. Figure 3.2.R.2-5 shows a graphical presentation for relative potency values for all batches tested. Sandoz derived the quality range of 72-115% relative EC50 using the mean \pm 3 SD from the 10 US-licensed Humira batches, and the quality range of EU-approved Humira is 68-135%. The relative potency of GP2017 ranged from 73-112% and all the batches of GP2017 were within the quality ranges of US-licensed Humira and EU-approved Humira. Two EU-approved Humira batches were out of US quality range by 1 and 3% (11242XH09 and 14270XD17). Sandoz considered that this difference is due to method variability, and EU-approved Humira is comparable to US-licensed Humira in the mTNF α binding activity. So EU-approved is comparable to US-licensed Humira..

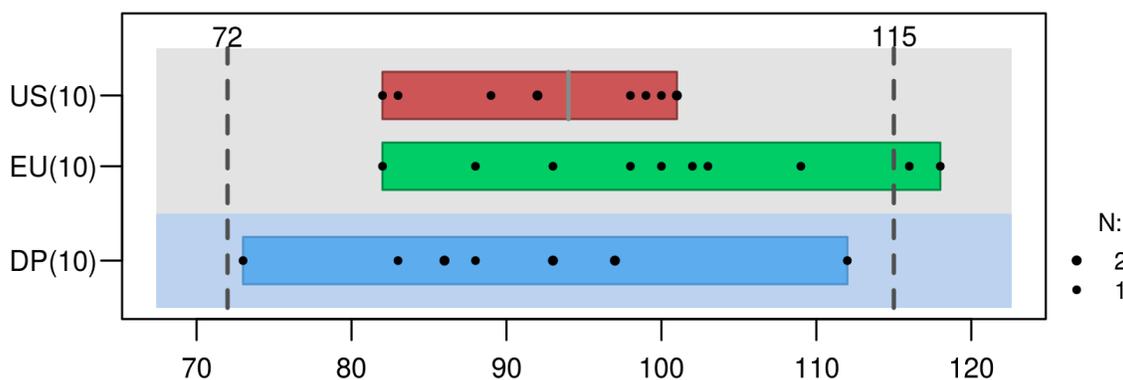


Figure 3.2.R.2-5 Comparison of apoptosis induction activity of GP2017 and Humira. The solid grey line in the red box indicates the mean value of all US-Humira batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US-Humira batch values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of US-Humira are shown in a red box, values of EU-Humira are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

Assay qualification: The assay was qualified with a linear range of 67-150% relative potency (RP). The assay has an accuracy of 84-114% at target and a precision of 11-22% geometric relative standard deviation (RSD).

Reviewer comment: *On March 06, 2018, an IR was sent to request additional data for this apoptosis induction assay. On April 28, 2018, the Sponsor responded with the requested data (amendment eCTD 0027). In the initial submission, 4 batches of GP2017 DP were tested in the assessment. The Sponsor excluded two GP2017 DP batches 7007742 and 7008198 because they were not independent batches and added 8 independent DS/DP batches. The US-licensed Humira and EU-approved Humira batches were extended from 3 to 10 of each and the quality range was re-calculated.*

The qualified assay is adequate to support the testing results. The quality range of \pm 3 standard deviations is reasonable. Adalimumab reverse signaling mediated by mTNF- α expressed on cell surface is similar for all pairwise comparisons between GP2017, US-licensed Humira, and EU-approved Humira.

Fc-mediated effector functions

Humira has moderate Fc domain effector function, antibody-dependent cell mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC). Sandoz used a group of in vitro bioassays for ADCC and CDC quantitation and the results were evaluated by Tier 2 statistical assessment. The Fc glycosylation pattern can influence effector functions. Increase of terminal galactosylation can promote CDC activity by increasing C1q binding in vitro and has modest effects on ADCC. Decreases in core-fucose levels lead to an increase in ADCC via increased affinity of IgG1 for Fc γ RIIIa on immune cells.

3.2.R.2.2.4 ADCC Assay

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

The ADCC assay uses two cell lines: the immortalized natural killer cell line NK3.3 as the effector cells and an HEK293 expressing mTNF- α as the target cell line. In this assay, the target cells are labeled with an intracellular fluorescent dye; then the target cells are combined with NK3.3 cells and graded amounts

of adalimumab. The death of target cells is quantified by measuring the fluorescence released from dying cells. The ADCC assay quantifies this antibody-dependent target cell death.

26 batches of US-licensed Humira, 28 batches of EU-approved Humira and 8 independent batches of GP2017 DP were tested with the ADCC assay. Figure 3.2.R.2-6 shows a graphical presentation of the relative potency of ADCC for all batches tested as originally reported in the BLA.

Reference standards GP2017.01REF, GP2017.02REF and GP2017.01WST were used in this assay. GP2017.02REF has a relative potency of 105% against GP2017.01REF and GP2017.01WST was not tested because it is from the same DS batch as GP2017.02REF.

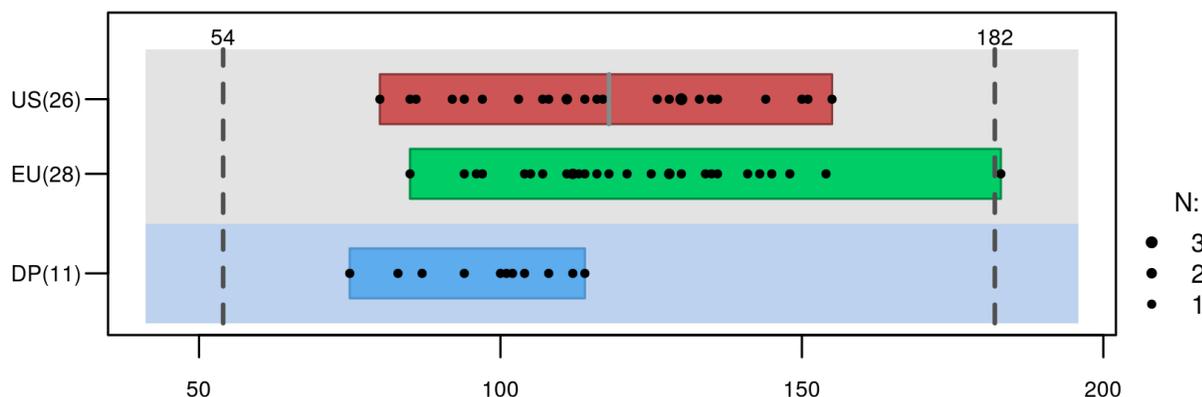


Figure 3.2.R.2-6 Comparison of ADCC for GP2017 DP and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira[®] US are shown in a red box, values of Humira[®] EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

Assay qualification: The ADCC assay was qualified with a linear range of 50-200% relative potency (RP). The assay performed with an accuracy of 92-110% at target and an intermediate precision of 8% RSD at 100% RP, 8-24% geometric RSD.

Reviewer comment: On January 31, 2018, Sandoz submitted a CMC amendment (eCTD 0016) to correct data errors in the similarity assessment. The ADCC results were updated. During the inspection on April 19-20, 2018 at Novartis, I reviewed the ADCC assay and results and no observation was made. 11 GP2017 DP batches, 8 of which are independent batches, were tested and the relative potency range was 75-114%. The ADCC relative potency range of 26 US-licensed Humira batches is 80-155% and that of the 28 EU-approved Humira is 85-183%. The relative potency of EU-approved Humira batch 23342XH04 was initially reported at 110% and later corrected to 183%. This sample was tested twice and 183% and 110% were the first and second test result, respectively. Sandoz’s protocol is to report the first result when a sample is tested twice. Due to the high variability between these two values, the sponsor investigated and reported the outcome in CMC amendment II (eCTD 0022). No laboratory error was identified for either data set. The sponsor re-measured the sample with 8 single

determinations by two analysts on 8 separate plates. A control sample derived from reference standard at 80% or 150% relative potency was measured parallelly on each plate. The result of a single plate is valid if the control sample has a potency within 80-125% of nominal potency value. All plates were valid and the mean potency of batch 23342XH04 is 133% with 8% SD. So, 133% was declared as the reportable result for batch 23342XH04 and 183% and 110% were invalid. Based on the new value, the range of EU-approved Humira is 85- 154% and the quality range is 67-174%.

The ADCC potency of Humira varied and resulted in a wide quality range especially towards the upper end. The mean potency of US-licensed Humira is 118% with 21% SD and EU-approved Humira is 121% with 18% SD. The mean potency of GP2017 is 98% with 12% SD. The results from GP2017 are tighter than Humira, which may indicate a better product control. All results are within method capability. All pairwise comparisons passed the sponsor-established quality range analysis. The assay qualification data support that this method is suitable for its intended use. The data for the ADCC assay support similarity with respect to this ADCC activity.

3.2.R.2.2.5 Binding to FcγRIIIa 158V and 158F by SPR

Binding of the antibody Fc domain to FcγRIIIa on effector cells is the first step in the ADCC mechanism. FcγRIIIa 158V and 158F are two genetic variants of FcγRIIIa. SPR binding assays were employed to assess the binding affinity and kinetics of GP2017, US-licensed Humira, and EU-approved Humira to FcγRIIIa 158V and 158F. The Fc receptors were immobilized on a sensor chip and the adalimumab samples were injected at different concentrations. The apparent binding constant K_D is calculated from single-cycle kinetic analysis. In the SPR assays, 10 (7 independent) batches of GP2017, 10 batches of US-licensed Humira, and 10 batches of EU-approved Humira were tested. All samples were tested against reference standard GP2017.01WST.

A Tier 2 statistical analysis was performed on the results. Figure 3.2.R.2-7 shows the quality range of 69-115% relative K_A for the FcγRIIIa 158V binding, which Sandoz derived from the 10 US-licensed Humira batches. The range of GP2017 DP batches is 93-105%. The results indicate that 100% of GP2017 and EU-approved Humira batches were within the quality range meeting the Tier 2 acceptance criterion. The quality range of EU-approved Humira is 78-105% and all GP2017 DP batches are within the range.

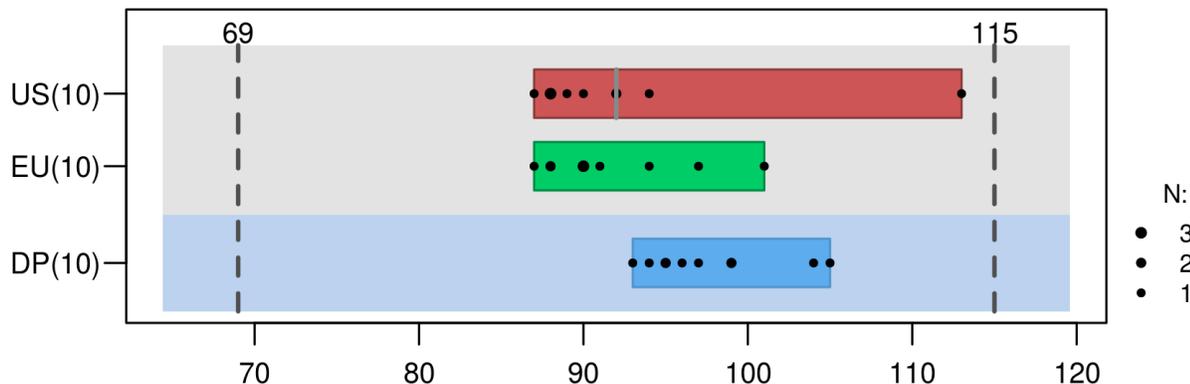


Figure 3.2.R.2-7 Comparison of FcγRIIIa(V) results for GP2017 DP and Humira. The solid grey line in the red box indicates the mean value of all US-Humira batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US-Humira batch values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of US-Humira are shown in a red box, values of EU-Humira are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

Figure 3.2.R.2-8 shows the quality range of 79-99% relative K_A for the FcγRIIIa 158F binding, which Sandoz derived using the mean \pm 3SD from the 10 US-licensed Humira batches. 90% of EU-approved Humira batches were within the quality range meeting the Tier 2 acceptance criterion. The range of GP2017 DP batches is 92-106%. Two out of 10 GP2017 DP batches fell outside the US quality range. The quality range of EU-approved Humira is 81-106% and all GP2017 DP batches are within the range.

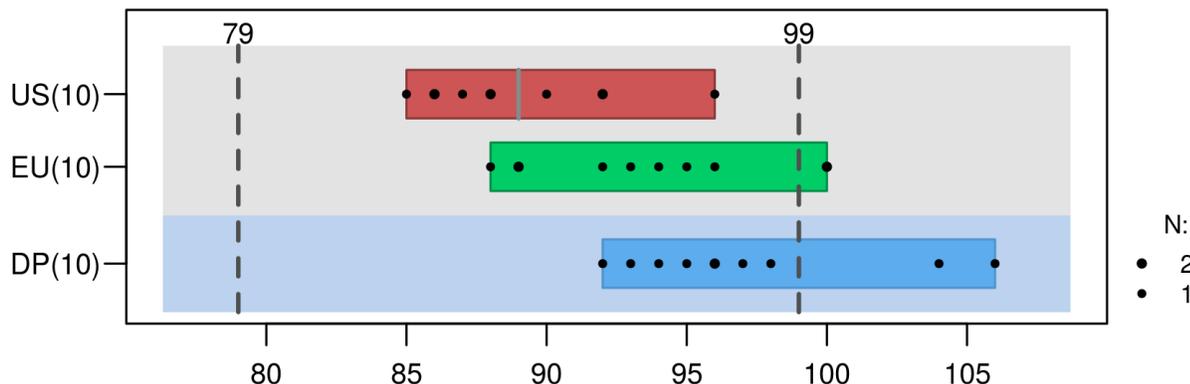


Figure 3.2.R.2-8 Comparison of FcγRIII(F) results for GP2017 DP and Humira. The solid grey line in the red box indicates the mean value of all US-Humira batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US-Humira batch values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of US-Humira are shown in a red box, values of EU-Humira are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

Assay qualification: The SPR Binding Assays for Fc γ RIIIa (158V and 158F) were qualified for working range (0.5-100 μ M), method precision of K_A is 1.9% and intermediate precision is 2.3%.

Reviewer comment: *On February 16, 2018, an IR was sent to request additional data for the SPR binding assays for Fc γ RIIIa and FcRn. Sandoz responded on March 05, 2018 with additional data and a re-calculation of the similarity assessment (amendment eCTD 0018). After reviewing the amendment, an IR was sent on March 19, 2018, requesting numerical results and the EU-approved Humira quality range calculation for the SPR assays. The sponsor responded on March 30 with the requested data (amendment eCTD 0021).*

On March 06, 2018, an IR was sent to request the method qualification reports for the SPR binding assays. Sandoz responded on March 30, 2018 (amendment eCTD 0021) with summary qualification report of the SPR assays measuring the adalimumab binding to FcRn, Fc γ RIIIa F158/V158. During the inspection at Hexal AG, on April 16-17, 2018, I reviewed the detailed reports. Method qualification data for the assay are adequate to support the suitability of the assay.

The quality ranges are appropriate. The SPR Fc γ RIIIa(V) binding analysis of GP2017 was within the US quality ranges. For SPR Fc γ RIIIa(V) binding, all pairwise comparisons between GP2017, US-licensed Humira, and EU-approved Humira passed the Tier 2 statistical criteria for similarity. This established similarity on Fc γ RIIIa binding is indicative of similar ADCC activity between the products. The SPR Fc γ RIIIa(F) binding activity of GP2017 DP batches 7007468 (106%) and 7007966 (104%) are slightly outside of the US-licensed Humira quality range. Batch 7007966 is not an independent batch and should not be included in the calculations. In addition, batch 7007467 from the same DS batch as 7007966 was tested and its relative K_A is 97% within the quality range. When only independent batches are considered in the evaluation, 89% of GP2017 batches, are within the US-licensed Humira and EU-approved Humira. In addition, the ADCC activity of batch 7007468 is 114%, which is well within the quality ranges calculated for ADCC. Considering the totality of evidence, the Fc γ receptor SPR binding activity of GP2017 DP is similar to US-licensed Humira and EU-approved Humira.

3.2.R.2.2.6 Neonatal Fc receptor (FcRn) Binding SPR Assay

FcRn binding was measured to complete the assessment of functional similarity between GP2017, US-licensed Humira, and EU-approved Humira because FcRn mediates an endocytic salvage pathway that prevents degradation of an antibody and impacts the half-life of IgG. FcRn binding was measured by SPR. Results for FcRn binding activity in 10 (7 independent) GP2017 DP batches ranged from 87% to 142%, which was within the quality range of 10 US-licensed Humira batches (67-150%). All the results for 10 EU-approved Humira batches (91%-145%) also fell within the US-licensed Humira quality range (Figure 3.2.R.2-9). The quality range of EU-approved Humira is 61-164% and all GP2017 DP batches fell into the range. All the samples were tested against DS batch B153820, from which reference standard GP2017.02REF was derived.

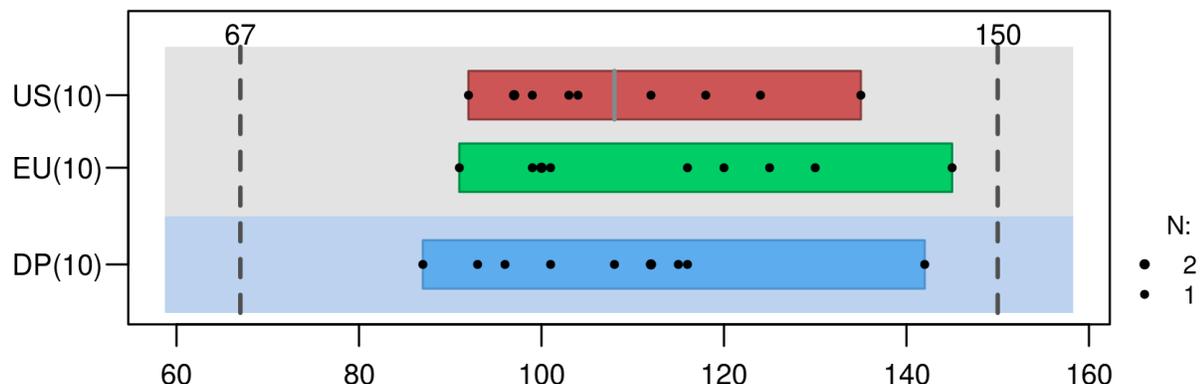


Figure 3.2.R.2-9 Comparison of FcRn binding results of GP2017 DP and Humira. The solid grey line in the red box indicates the mean value of all US-Humira batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US-Humira batch values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of US-Humira are shown in a red box, values of EU-Humira are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

Assay Qualification: The binding activity of the sample is compared to the binding activity of the reference standard and the result is reported as percent relative binding activity K_A . The SPR Binding Assays for FcRn were qualified for working range (2.4-5000 nM), method precision of 14.6% CV and an intermediate precision of 2.9% CV, and specificity.

Reviewer comment: *FcRn is thought to be involved in the salvage pathway of IgG antibodies, and the most likely impact of FcRn differences between products would be the clearance of serum adalimumab. The FcRn binding activities for all GP2017 DP batches and EU-approved Humira batches were within the quality range of the US-licensed Humira. The results support the conclusion that adalimumab FcRn binding activity is similar for all pairwise comparisons between GP2017, US-licensed Humira, and EU-approved Humira.*

3.2.R.2.2.7 Complement-dependent Cytotoxicity (CDC) Assay

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

The CDC assay uses Jurkat T cells expressing mTNF- α as the target cells. The target cells are combined with graded amounts of adalimumab, and incubated with human complement. Viable cells are quantified with a luciferase-based reagent for determination of ATP concentrations. 11 (8 independent) batches of GP2017, 32 batches of US-licensed Humira and 36 batches of EU-approved Humira were evaluated in the CDC assay. Figure 3.2.R.2-9 shows the statistical quality range of 65-119% relative potency for the CDC assay derived from 32 US-licensed Humira batches. The relative CDC activity of GP2017 ranges

from 97 to 109% and 100% of GP2017 and 94% of EU-approved Humira batches fall within the quality range meeting the Tier 2 acceptance criterion. The quality range of EU-approved Humira is 51-135% and all GP2017 batches are within the range.

The CDC activity was measured against the reference standard GP2017.02WSTD, GP2017.01REF, GP2017.02REF and GP2017.01WST. The relative potency of GP2017.01REF (103%) and GP2017.02REF (94%) were calculated as the geometric mean value of multiple single potency measurement against the previously used reference. GP2017.01WST was not tested for CDC activity because it was derived from the same DS batch as GP2017.02REF.

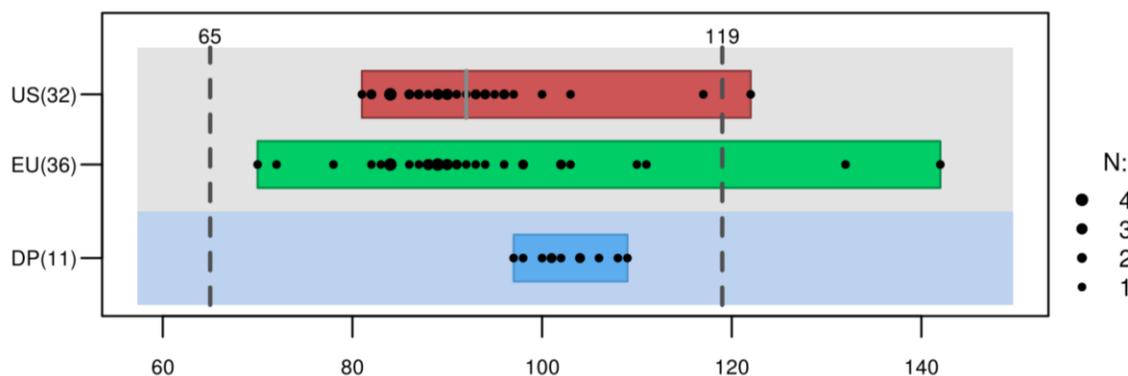


Figure 3.2.R.2-10 Comparison of CDC for GP2017 DP and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira[®] US are shown in a red box, values of Humira[®] EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

Assay Qualification: CDC activities were evaluated in the *in vitro* test in which the death of Jurkat T cells, transfected to express mTNF, is measured after incubation with adalimumab dilutions and human complement. This CDC assay was assessed for linearity (50-200%), accuracy of 94-106% at target RP and a precision of 5% relative standard deviation (CV) at 100% RP.

Reviewer comment: Assay qualification data adequately demonstrated that the analytical procedure is suitable for measurement of relative CDC activity of GP2017. Two EU-approved Humira batches 26370XD15 and 28387XD04 had out of range CDC potency of 132% and 142%, respectively. Batch 28387XD04 was also tested for C1q binding which is directly related to CDC activity and the binding activity is 91% within the quality range. The high values of these two batches may reflect the assay variability. The quality range is appropriate. Results for CDC activity for all GP2017 and >90% of EU-approved Humira are within the quality ranges of US-licensed Humira. The data support similarity with respect to this biological activity.

3.2.R.2.2.8 C1q Binding ELISA

The binding of complement protein C1q to the Fc region of antibody:antigen complexes on target cell surface is the prerequisite first step in the complement cascade leading to CDC. Binding of human C1q to GP2017 was assessed by an ELISA binding assay. Figure 3.2.R.2-11 shows the statistical quality range of 70-111% RP for the C1q binding assay, and are derived from the 6 US-licensed Humira batches. The range of 7 (6 independent) GP2017 DP batches is from 93-103% and 100% GP2017 DP batches and 100% EU-approved Humira batches (91-100%) fall within quality range meeting the Tier 2 acceptance criterion. The quality range of 6 EU-approved Humira is 85-105% and all GP2017 DP batches are within the range. Reference standard GP2017.02REF and GP2017.01WST were used in this assay.

Assay qualification: The objective of the qualification was to qualify the ELISA-based binding assay to measure the binding of Adalimumab to C1q. The results showed that linearity (50-200% RP), precision (intermediate precision: 1-5%CV at target), accuracy (99-110% at Target).

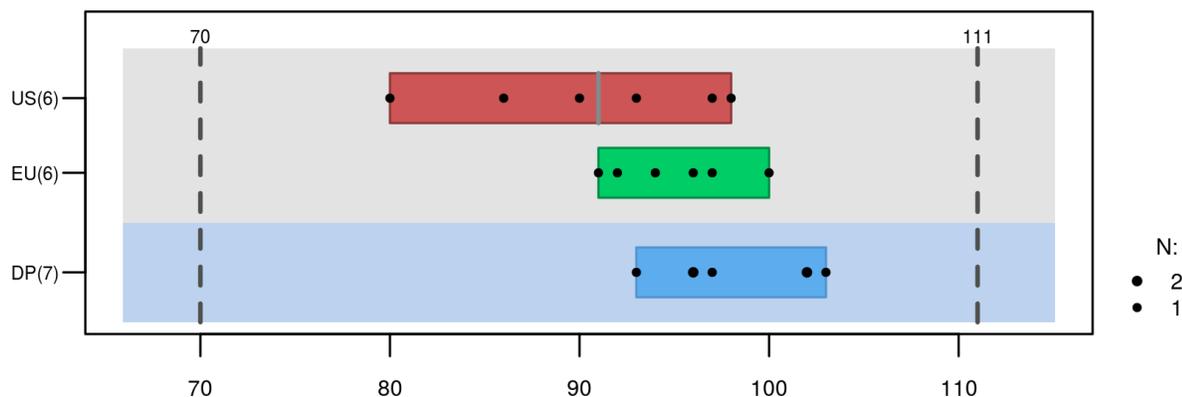


Figure 3.2.R.2-11 Comparison of relative C1q binding for GP2017 DP and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values $\pm 3SD$. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira[®] US are shown in a red box, values of Humira[®] EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

Reviewer comment: The assay is adequately qualified demonstrating that the ELISA procedure is suitable for measurement of C1q binding activity of GP2017. The quality range of $\pm 3SD$ is appropriate. Results for C1q binding for all GP2017 and EU-approved Humira are within the quality ranges of US-licensed Humira. The data support pairwise similarity with respect to this biological activity.

3.2.R.2.2.9 Heterogeneity due to glycosylation

The N-linked glycan assessment is important because of the possible impact on effector function activity. The level of total non-fucosylation has been linked to ADCC and the level of terminal galactosylation has been linked to CDC. It is known that high-mannose glycan can have an impact on

PK. The N-glycans are released by PNGase F, labeled with 2-aminobenzamide (2-AB), separated by normal phase hydrophilic interaction chromatography and identified via mass spectrometry or quantified via fluorescence spectroscopy. The galactosylated, afucosylated and high mannose N-glycans of 17 (10 independent) batches of GP2017 and 41 batches of EU-approved Humira were compared to the quality ranges of 34 US-licensed Humira batches (Figure 3.2.R.2-12, 3.2.R.2-13 and 3.2.R.2-14). All EU-approved Humira batches fall within the US-licensed Humira quality range for terminal galactosylation, afucosylation, and high mannose, meeting the acceptance criteria for comparability between US- and EU-Humira.

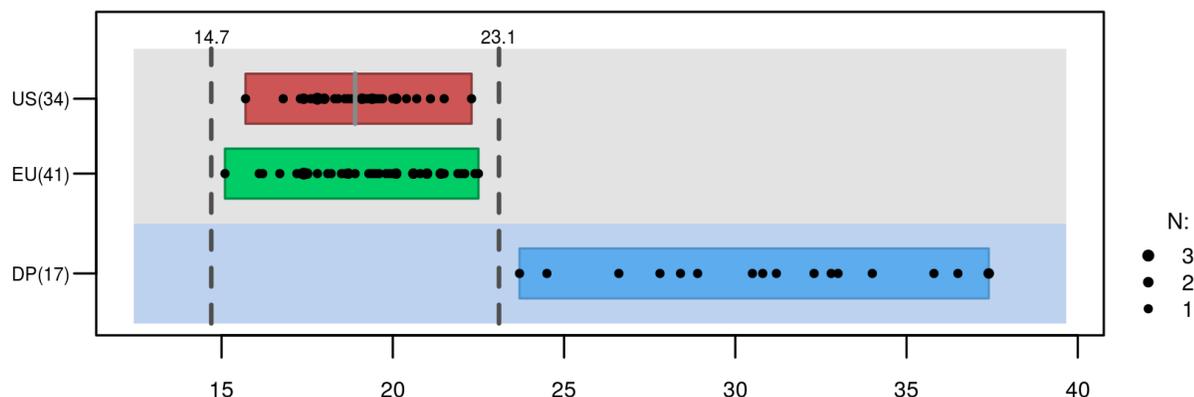


Figure 3.2.R.2-12 Comparison of galactosylation for GP2017 and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira® US are shown in a red box, values of Humira® EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

The amount of galactosylated N-glycan ($bG1(1,6) + bG1(1,3) + 2 \times bG2$) of all GP2017 batches (23.7-37.4%) exceeded the quality range of US-licensed Humira (14.7-23.1%). Two GP2017 batches 7007741 and 7007742 (count as one independent batch) are within the quality range of EU-approved Humira (13.5-25%).

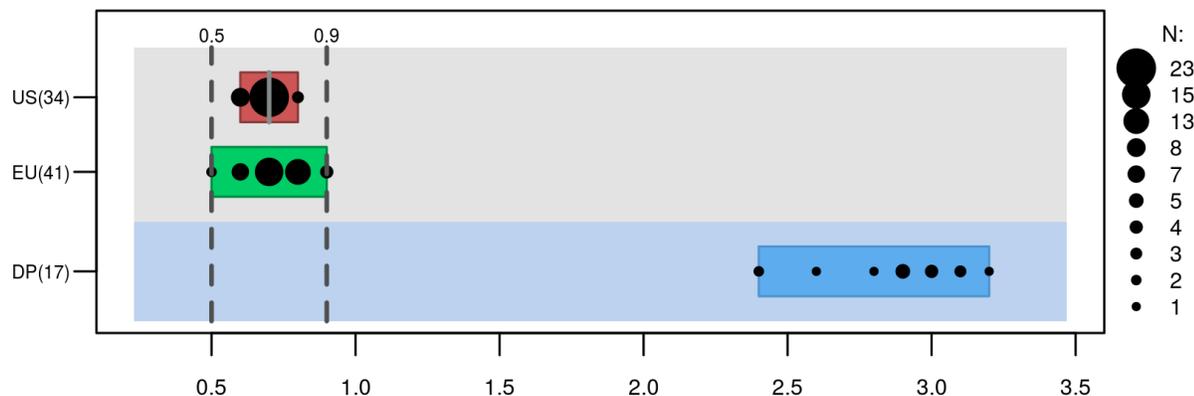


Figure 3.2.R.2-13 Comparison of afucosylated N-glycan for GP2017 DP and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira[®] US are shown in a red box, values of Humira[®] EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

The amount of afucosylated N-glycan of all GP2017 batches (2.4-3.2%) exceeded the quality range of US-licensed Humira (0.5-0.9%) and EU-approved Humira (0.4-1%).

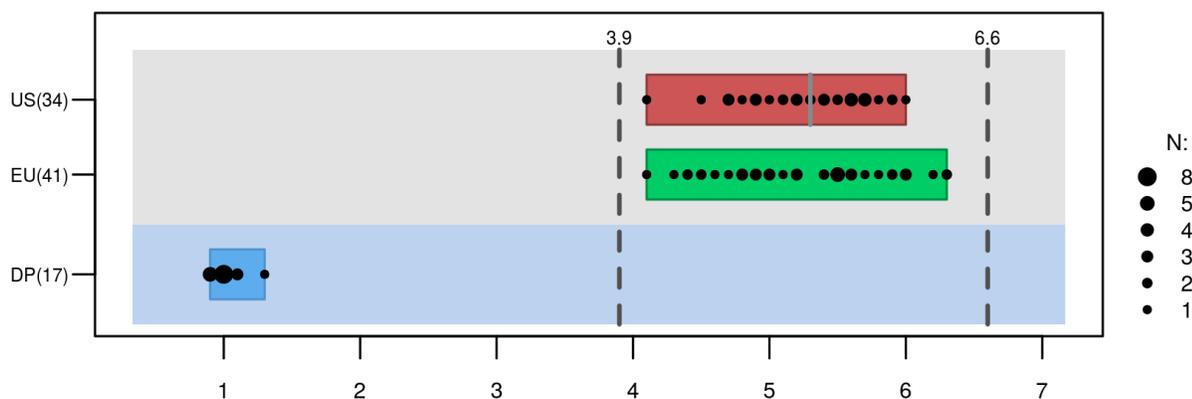


Figure 3.2.R.2-14 Comparison of high mannose for GP2017 DP and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira[®] US are shown in a red box, values of Humira[®] EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

The amount of high mannose glycans of GP2017 batches (0.9-1.3%) was below the quality range of US-licensed Humira (3.9-6.6%) and EU-approved Humira (3.5-7%).

Assay Qualification: Hydrophilic interaction liquid chromatography (HILIC) was validated for the content determination of each of the main N-linked glycan species in GP2017. The method is used as DS release assay to verify that the N-linked glycan content of the sample is comparable to that of the reference material.

Reviewer comment: *The HILIC assay is suitable for content determination of N-glycan species. The HILIC assay validation was reviewed in section 3.2.S.4.3 Validation of Analytical Procedures. The quality ranges are appropriate. The GP2017 level of terminal galactosylation and afucosylation exceeded the quality ranges of US-licensed Humira; the high mannose content of GP2017 is below the quality range of US-licensed Humira.*

The level of terminal galactosylation may impact CDC activity. GP2017 DP shows similarity to US-licensed Humira in both CDC assay and C1q binding assay. The higher level of terminal galactosylation in GP2017 does not appear to impact its CDC activity. An evaluation of the data provided by Sandoz, indicates that there is a direct correlation between galactosylation and CDC activity at low galactosylation levels; however, at levels around 20% or higher, the level of galactosylation does not impact CDC activity.

It is known that higher levels of afucosylated glycans and high mannose glycans increase ADCC activity by increasing the binding affinity of adalimumab to FcγRIIIa. In the case of GP2017, the level of afucosylated glycans is higher than for US-licensed and EU-approved Humira (2.4-3.2% vs. ≤1%) and the level of high mannose is lower than for US-licensed and EU-approved Humira (~1% vs. 3.9-6.6%). The higher afucosylation would be expected to increase ADCC activity and the lower high mannose content would be expected to lower ADCC activity. The ADCC assay and FcγRIIIa binding SPR assay results both show similarity between GP2017 and Humira.

In addition, high mannose content could affect PK; moieties with higher mannose content would be expected to be cleared faster. However, the FcRn binding results and the PK study GP17-104 results meet their respective similarity acceptance criteria.

Considering the totality of the data and keeping into consideration that effector function is not the main mechanism of action of GP2017, failure to show similarity on the glycan HILIC assay results does not preclude the conclusion of similarity between GP2017 and US-licensed Humira. (b) (4)

[REDACTED] for commercial GP2017 batches. In addition, the sponsor will be asked to implement release testing for effector function properties, as a PMC. This will minimize the risk that attributes related to CDC and ADCC will drift from the levels established to be similar to US-licensed Humira.

Reviewer notes: *The N-linked glycosylation characterization, including glycosylation site occupancy, glycan distribution profile, and glycation were assessed as Tier 3 attributes, and review details refer to section 3.2.R.2.2.3.2 N-linked Glycan Structure.*

3.2.R.2.2.10 Charge Variants by CEX

Product charge heterogeneity is important because of the possible impact on efficacy, safety, and immunogenicity. Sandoz developed a cation exchange chromatography (CEX) method to analyze charge variants of adalimumab. The relative peak area of charge variants is calculated to evaluate the overall charge heterogeneity. Tier 2 statistical analysis was performed on this data set for both acidic and basic species. Figure 3.2.R.2-15 shows the statistical quality range of 8.2-12.6% for acidic species Sandoz derived from the 31 US-licensed Humira batches. 98% of 41 EU-approval Humira batches were within the quality range, meeting the Tier 2 acceptance criterion. 15 (9 independent) GP2017 DP batches were tested and 6 batches have acidic variants below the lower limit of US-licensed Humira quality range or EU-approved Humira quality range (8.1-13.6%). The total acidic variants of GP2017 DP are not similar to US-licensed Humira or EU-approved Humira

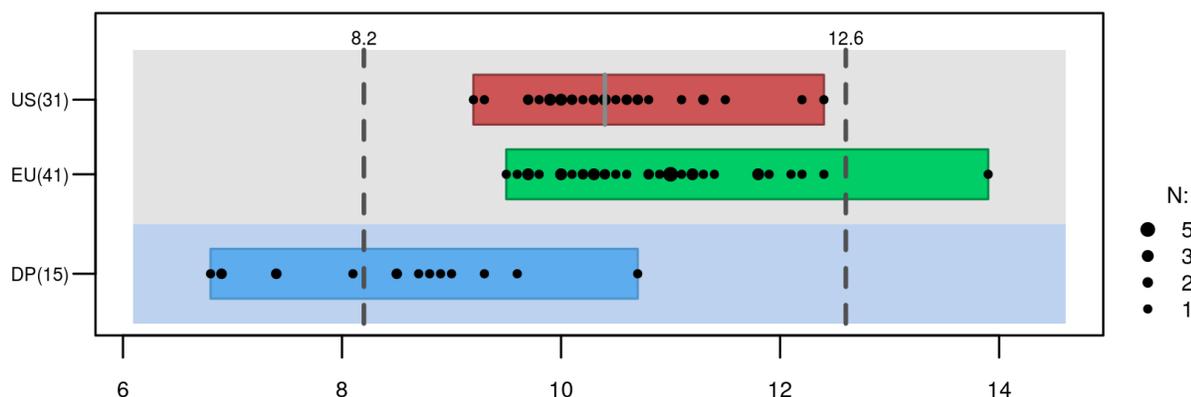


Figure 3.2.R.2-15 Comparison of the sum of acidic variants for GP2017 DP and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira® US are shown in a red box, values of Humira® EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

Figure 3.2.R.2-16 shows the statistical quality range for basic species Sandoz derived from the 31 US-licensed Humira batches (20.6-31.5%). The results indicate that 98% of 41 EU-approved Humira batches fall within the established range, meeting the acceptance criterion for similarity; however, all the GP2017 batches (12.9-17.7%) fall below the lower limit of the quality range of US-licensed Humira or EU-approved Humira (18.5-32.8%).

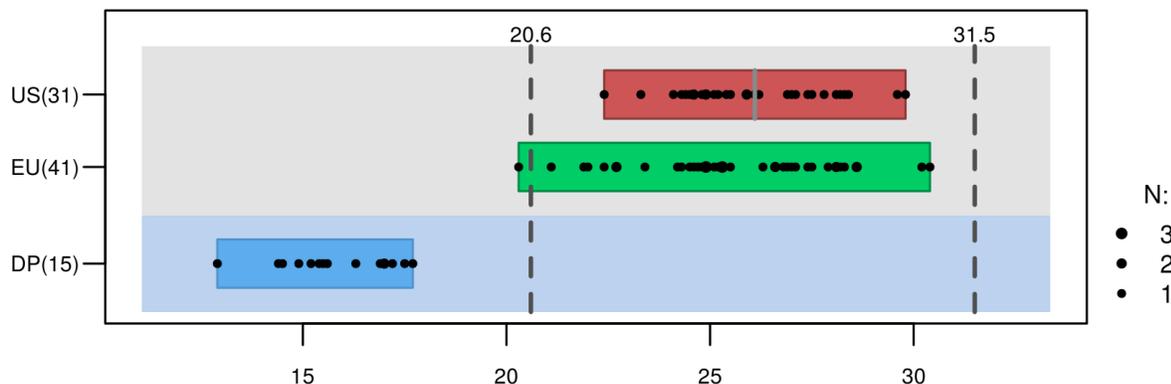


Figure 3.2.R.2-16 Comparison of the sum of basic variants for GP2017 DP and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira[®] US are shown in a red box, values of Humira[®] EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

US-licensed Humira and EU-approved Humira contain higher levels of acidic and basic species with a corresponding decrease in the main peak, when compared to GP2017 DP. The acidic variants mainly consist of deamidated, fragmented, and sialylated species. The major component of the basic species was one or both heavy chains terminated with lysine. The GP2017 samples were treated with carboxypeptidase B, and the CEX basic peaks shift towards the main peak, thereby verifying the presence of C-terminal lysine variants. The basic variants in the GP2017 also contain C-terminal proline amidation caused by enzyme activity in the production cell line. The basic species are commonly observed structural features in mAbs, and do not impact safety or immunogenicity^{3,4}. The C-terminal region of a mAb is not involved in target antigen binding and Fc-functions.

Sandoz performed extended characterization of the charge variants using one lot from each product (US #1024661, EU #34434XD11 and GP2017 #7007389). CEX fractions were collected from each sample and their bioactivity was tested using TNF- α binding SPR and TNF- α neutralization RGA. Each charge variant fraction has comparable potency to its main peak fraction, and its counterpart of the other two products.

Assay Qualification: The CEX analytical procedure was validated as a quantitative method for determining the charge heterogeneity (percent acidic, main, and basic species) of GP2017 drug substance and drug product.

³ Cai B, Pan H, et al (2011) C-terminal lysine processing of human immunoglobulin G2 heavy chain in vivo. *Biotechnol Bioeng*; 108(2): 404-12.

⁴ Johnson KA, Paisley-Flango K, et al (2007) Cation exchange-HPLC and mass spectrometry reveal C-terminal amidation of an IgG1 heavy chain. *Analytical biochemistry*; 360(1): 75-83.

Reviewer comment: The CEX method is validated for use and the quality range is appropriate. The amounts of acidic and basic variants of GP2017 are lower than those in US-licensed Humira and EU-approved Humira. C-terminal Lysine is enzymatically cleaved in serum, and consequently the presence or absence of this lysine does not affect in vivo performance. Scientific literature supports that proline amidation of the C-terminus of monoclonal antibody does not exert effect on the Fc region mediated effector function. The bioassay results from each CEX fraction indicated that the difference in charge variants does not affect biological activity of the molecule.

Reviewer notes: The charge variants characterization, including charge identity and distribution were assessed as Tier 3 attributes, and review details refer to section 3.2.R.2.3.3 charge variants.

3.2.R.2.2.11 Product Purity-- Size-exclusion chromatography

Product purity is important because of the impact it may have on efficacy, safety, immunogenicity or PK. This SEC procedure is validated for the quantitative determination of the monomer, high molecular weight variants (HMW), and P50 fragment of GP2017. Tier 2 statistical analysis was performed on these data. Figure 3.2.R.2-17, 3.2.R.2-18 and 3.2.R.2-19 show the statistical quality ranges Sandoz derived from the 28 US-licensed Humira batches for monomer (99.5-99.9%), HMW (0.1-0.4%) and p50 fragment (0-0.2%), respectively. All 32 EU-approved Humira batches were within the US quality range, meeting the acceptance criteria for similarity. 21 (11 independent) GP2017 DP batches were tested and the ranges for monomer, HMW and p50 are 99.4-99.8%, 0.2-0.5% and 0-0.1%, respectively. One GP2017 DP batch (7007466) is out of quality range for monomer and all GP2017 DP batches were within the quality range for p50 fragment, meeting the Tier 2 acceptance criteria. The HMW of 5 (from 3 independent) GP2017 batches fell out of quality range, not meeting the Tier 2 acceptance criterion. The quality ranges derived from 32 EU-approved Humira batches from monomer, HMW and p50 fragment were 99.4-99.9%, 0-0.5% and 0-0.2%, respectively and all GP2017 DP batches were within the quality range for the size variants.

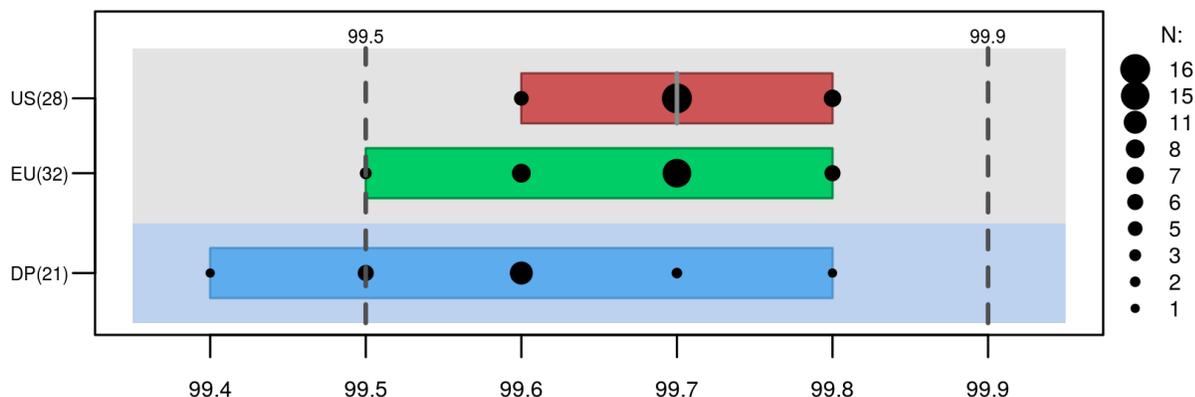


Figure 3.2.R.2-17 Comparison of purity monomer by SEC for GP2017 and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated.

Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira[®] US are shown in a red box, values of Humira[®] EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

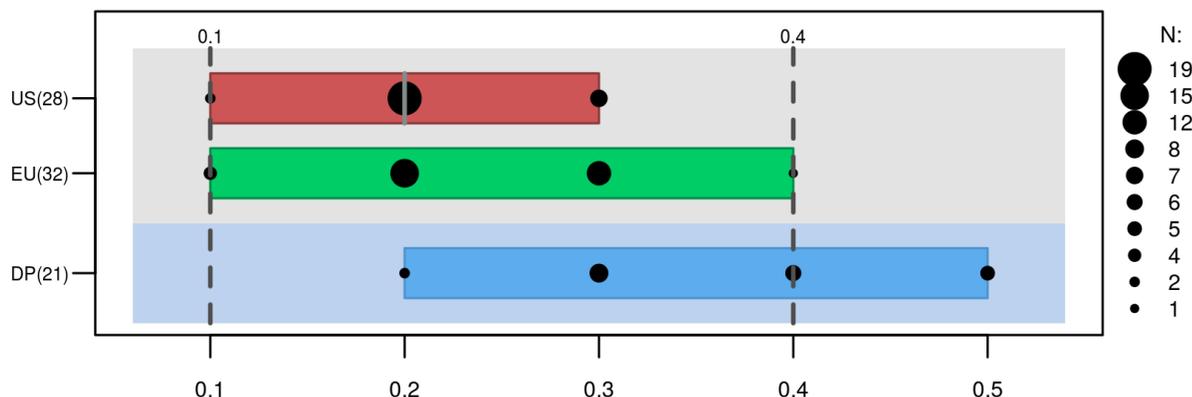


Figure 3.2.R.2-18 Comparison of HMW variants of GP2017 and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira[®] US are shown in a red box, values of Humira[®] EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

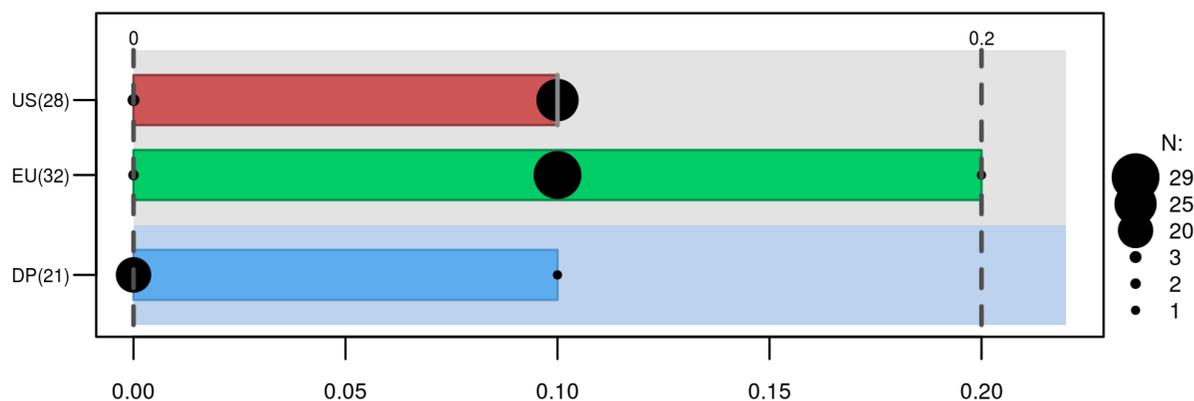


Figure 3.2.R.2-19 Comparison of p50 fragment of GP2017 and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira[®] US are shown in a red box, values of Humira[®] EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

Assay Qualification: The SEC method was validated for quantifying monomer HMW and p50 fragment and is used as release method for DS and DP.

Reviewer comment: *The assay is adequate to support the testing results. The SEC assay validation was reviewed by Chih-Jung Hsu. The quality ranges are appropriate. All the batches of GP2017 were within the statistical quality range of the US-licensed Humira for monomer and p50 fragment, except for batch 7007466 (99.4% for monomer). GP2017 DP batches 7007388 and 7007606 are from the same DS batch (B170052) as 7007466 and their monomer results are both 99.5%. Five GP2017 DP batches have 0.5% HMW, exceeding the quality range. Among these 5 GP2017 DP batches, 7007138 and 7007139 are from the same DS batch B083248; 7007466 and 7007606 are from the same DS batch B170052, a third DP batch (7007388) from the same DS batch has 0.4% HMW; 7007966 is from DS batch B170053 and another DP batch (7007467) from the same DS batch has 0.4% HMW. All three DS batches have 0.4% HMW at release. In addition, the stability study in section 3.2.S.7 indicated that HMW increase slightly under DS long-term storage conditions. The DP batches with higher HMW were all manufactured months later than the DP batches with lower HMW from the same DS batches. The HMW content of 0.5% is very low and the difference between GP2017 and US-Humira is too small to be significant. Sandoz also did analytical ultracentrifugation (AUC) to compare the multimer levels of GP2017 and Humira (reviewed in section 3.2.R.2.2.13). The totality of data support that the difference in HMW does not preclude the conclusion of analytical similarity with respect to monomeric forms, high molecular weight species and p50 fragment.*

Sandoz used SEC coupled with multi-angle laser light scattering (SEC-MALLS) to compare the molecular size of GP2017 and Humira. Light scattering measures the amount of scattered light of a protein solution and determines the absolute molar mass, molecular root mean square (rms) radius size and aggregation state. Four GP2017 batches and two batches of each Humira were analyzed by SEC-MALLS. The molar mass of the adalimumab monomer determined by SEC-MALLS is similar between GP2017 DP, US-licensed Humira and EU-approved Humira.

3.2.R.2.2.12 Product purity- Capillary Gel Electrophoresis with sodium dodecyl sulfate (CE-SDS)

The level of intact IgG and product-related fragment species present in GP2017, US-licensed Humira, and EU-approved Humira was analyzed by CE-SDS performed under non-reducing condition. The non-reducing CE-SDS electropherograms of adalimumab consist of one predominant peak, which is the intact IgG. The products all have some trace level peaks as fragments. Sandoz performed Tier 2 statistical analysis on the data of purity (% intact IgG) and % fragments. Figure 3.2.R.2-20, 3.2.R.2-21 and 3.2.R.2-22 show the statistical quality ranges Sandoz derived from the 28 US-licensed Humira batches for intact IgG (95.6-97.9%), HHL fragment (1.4-3.1%) and LC fragment (0.1-0.9%), respectively. 22 (11 independent) GP2017 DP batches were tested and all were within the quality range for intact IgG (95.7-97.1%), HHL fragment (2.1-3.1%) and LC fragment (0.4-0.6%), meeting the Tier 2 acceptance criteria for similarity. In addition, more than 96% of EU-approved Humira batches were within the established ranges from US-licensed Humira. The quality ranges of intact IgG, HHL fragment

and LC fragment derived from 31 EU-approved Humira were 94.9-98.0%, 1.4-3.4% and 0-1.0%, respectively and all GP2017 DP batches were within the ranges.

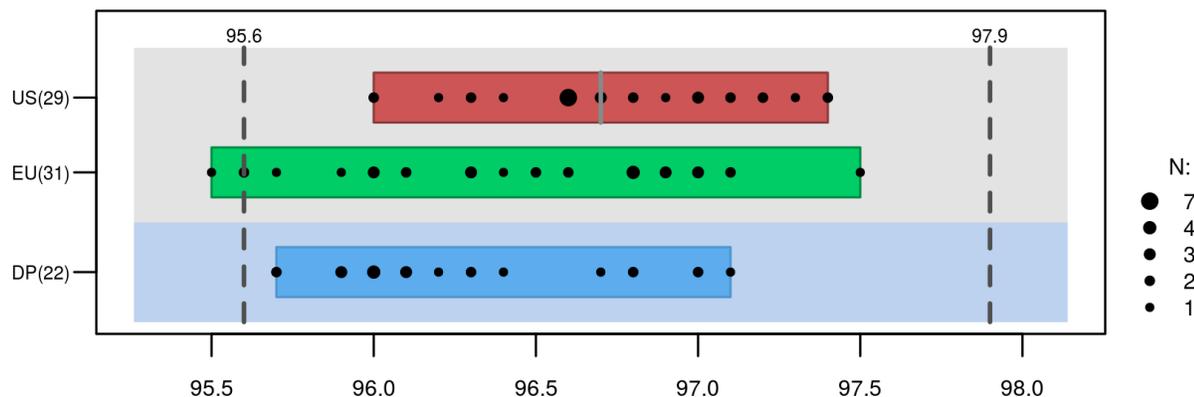


Figure 3.2.R.2-20 Comparison of purity by non-reducing CE-SDS for GP2017 DP and Humira.

The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira® US are shown in a red box, values of Humira® EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

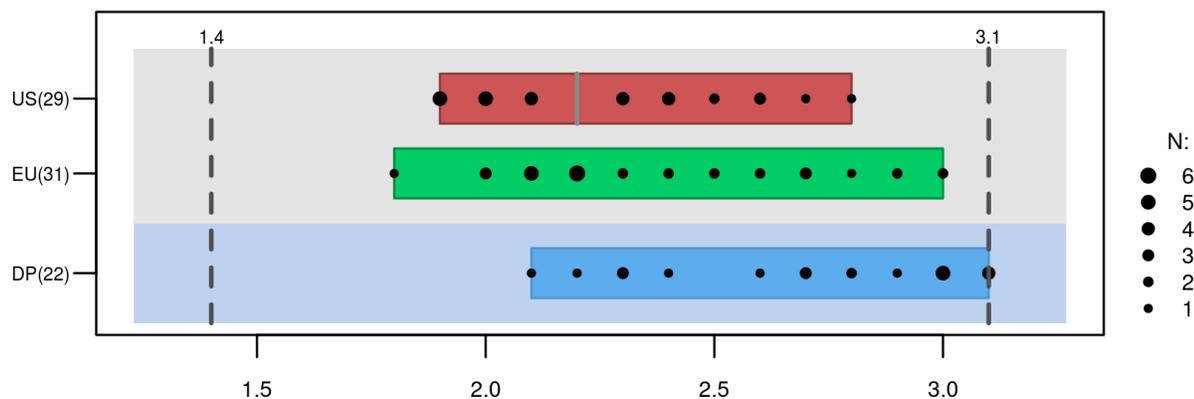


Figure 3.2.R.2-21 Comparison of the HHL fragment abundance for GP2017 DP and Humira.

The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira® US are shown in a red box, values of Humira® EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

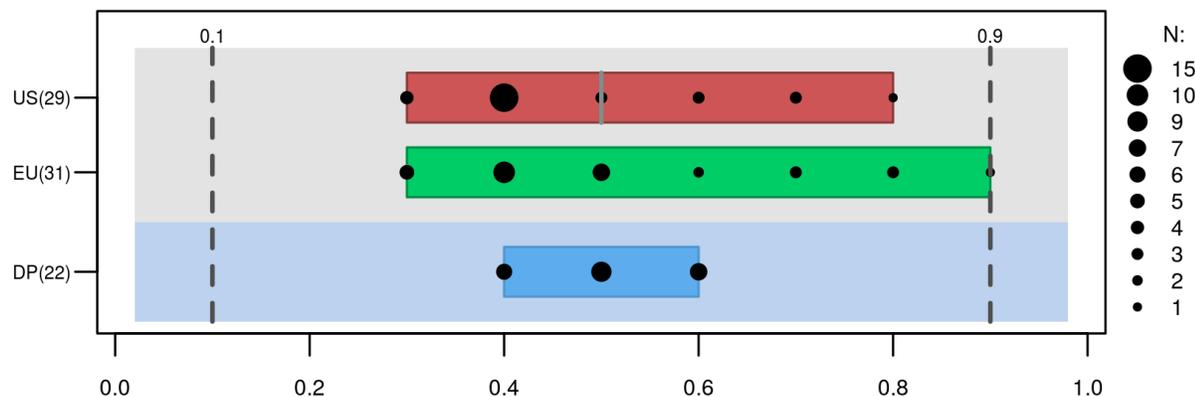


Figure 3.2.R.2-22 Comparison of the LC fragment abundance for GP2017 DP and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira® US are shown in a red box, values of Humira® EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

Assay Qualification: The CE-SDS (non-reduced) method was validated for quantifying intact IgG, and is used as release method for DS and DP.

Reviewer comment: *The CE-SDS (non-reduced) method was validated for DS and DP release testing. The % intact IgG is controlled in the release test for purity of the product. The purity of GP2017 DP meets the Tier 2 similarity assessment criterion. Increased levels of fragments may pose a risk to impact potency. Sandoz measured the relative quantities of fragments HHL, HH, HL, HC and LC, and selected the two most abundant fragments HHL and LC for Tier 2 analysis. The other fragments were below 0.5%. We calculated the total fragment from the data Sandoz provided, the quality range derived from US-licensed Humira is 2.1-4.5%. GP2017 DP batches range from 2.9 to 4.3%. All pairwise comparisons between GP2017 DP, US-licensed Humira and EU-approved Humira meet Tier 2 similarity criterion for total fragment.*

3.2.R.2.2.13 High molecular weight variants by AUC

Analytical ultracentrifugation (AUC) separates macromolecules by sedimentation velocity difference, which is determined by molecular weight, density and shape. The time-dependent protein gradients are detected by UV absorption and the molar mass of each sedimenting species is calculated from the UV trace. AUC is used to assess aggregates, as a complementary technique to SEC. Sandoz compared multimer levels of GP2017 DP and Humira using AUC and the pairwise comparison results meet Tier 2 similarity assessment criterion (Figure 3.2.R.2-23).

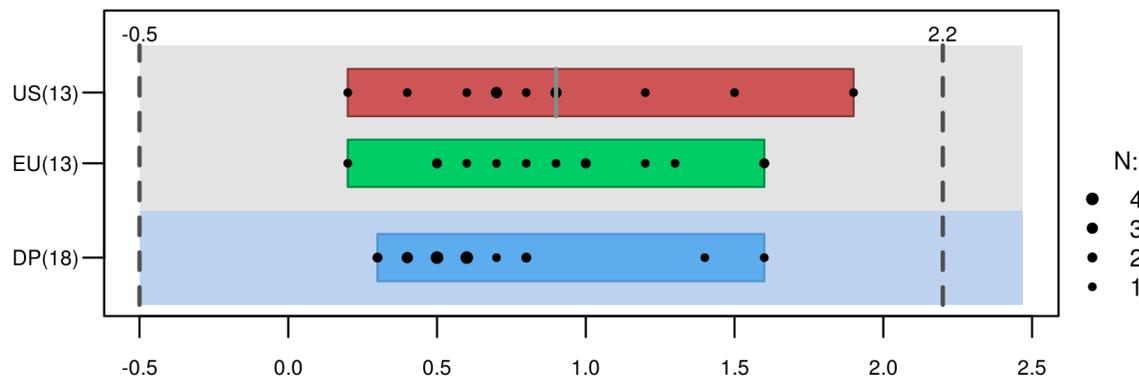


Figure 3.2.R.2-23 Comparison of multimers for GP2017 DP and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values $\pm 3SD$. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira[®] US are shown in a red box, values of Humira[®] EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

Sandoz performed a Tier 3 descriptive evaluation for the AUC results of dimers because literature^{5,6} indicate that small HMW variants are not immunogenic. The dimer level of GP2017 DP is similar to US-licensed Humira and EU-approved Humira.

Assay qualification: AUC is suitable for monitoring aggregates. For adalimumab experiments, Beckman XL-I was operated at 50000 rpm and species from 20 kDa up to 2 MDa can be separated. The largest adalimumab oligomer found is a hexamer. The LOQ is 0.5-1%.

Reviewer comments: *The AUC method is suitable for monitoring the aggregate levels in the products. We calculated the dimer AUC results provided by Sandoz using the Tier 2 quality range assessment. All pairwise comparisons meet the acceptance criterion. GP2017 DP is similar to Humira in the level of high molecular weight species.*

3.2.R.2.2.14 Concentration of active ingredient

Protein concentration is a critical quality attribute which is directly linked to dosing and strength. The protein concentration of GP2017 DP batches and Humira was determined by ultraviolet spectroscopy (UV) at 280 nm. Protein concentration is assessed using the Tier 2 statistical analysis. Figure 3.2.R.2-24 shows a statistical quality range of 44.9-52.4 mg/mL derived from the 35 US-licensed Humira batches. The results indicate that all 22 GP2017 DP batches (47.2-51.3 mg/mL) and 42 EU-approved Humira

⁵ Eon-Duval A, Broly H, et al (2012) Quality attributes of recombinant therapeutic proteins: an assessment of impact on safety and efficacy as part of a quality by design development approach. *Biotechnol Prog*; 28(3): 608-22.

⁶ Rosenberg AS (2006) Effects of protein aggregates: an immunologic perspective. *AAPS J*; 8(3): E501-7.

batches are within the quality range meeting the Tier 2 acceptance criterion for similarity. The quality range derived from 42 EU-approved Humira is 45.1-52.5 mg/mL and all GP2017 DP batches were within the range.

Assay qualification: The ultraviolet (UV) spectroscopy procedure is validated as a quantitative method for the determination of the protein concentration of GP2017 drug substance and drug product.

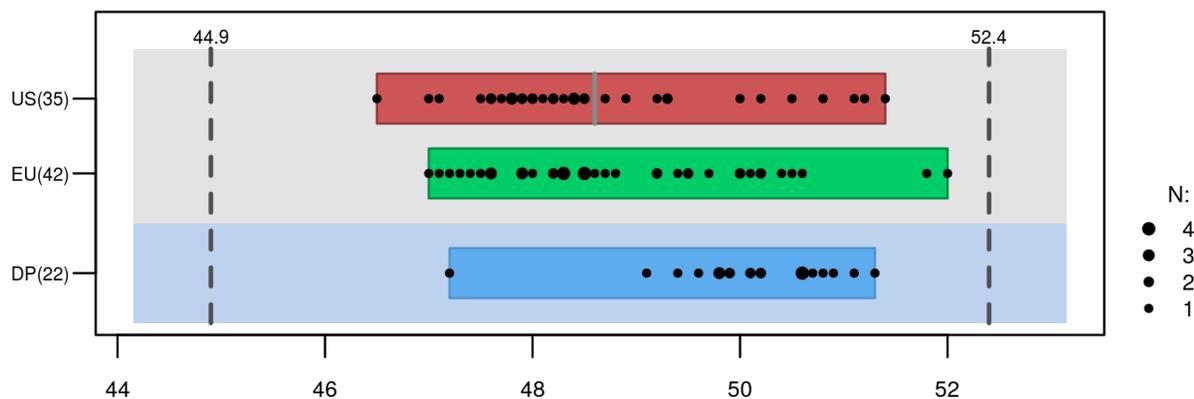


Figure 3.2.R.2-24 Comparison of GP2017 DP and Humira concentrations. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira[®] US are shown in a red box, values of Humira[®] EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

Reviewer comments: *The UV spectroscopy procedure is validated for measuring the protein concentration for GP2017 DS and DP release. The protein concentration for all GP2017 DP batches and EU-approved Humira batches were within the quality range of the US-licensed Humira. The results support the conclusion that DP protein concentration is similar for all pairwise comparisons between GP2017, US-licensed Humira, and EU-approved Humira.*

Sandoz determined the concentration for GP2017, US-licensed Humira, and EU-approved Humira by UV absorbance at 280 nm using an extinction coefficient of $210686 \text{ mol}^{-1}\text{cm}^{-1} \pm 7165$. The sponsor determined this value by two strategies:

- Measuring the absorbance of 10 batches of US-licensed Humira and 14 batches of EU-approved Humira and calculating the extinction coefficient from the labeled content of the originator product.
- Combining amino acid analysis (AAA) and UV absorbance for one lot each of GP2017 and Humira. The protein is hydrolyzed into free amino acids followed by derivatization and

separation. The amount of protein is correlated to the UV absorbance. The protein concentration is calculated from the sum of all stable amino acid concentrations.

The extinction coefficient was calculated from 24 Humira batches randomly sampled, and confirmed by amino acid analysis (relative difference < 6%). The AAA determined extinction coefficient of GP2017 (214346 M⁻¹cm⁻¹) is similar to US-licensed Humira (218046 M⁻¹cm⁻¹). The extinction coefficient determined from 24 batches of Humira is applied for UV measurement.

Reviewer comments: Sandoz used the same extinction coefficient of 210686 M⁻¹cm⁻¹ for all calculations of protein concentration throughout the similarity assessment. Thus, the calculation of concentration from raw 280 nm absorbance data is consistent throughout the analysis, allowing for meaningful comparison of concentration data between products as part of the analytical similarity assessment. The value of 210686 M⁻¹cm⁻¹ derived from a combination of the Humira labeled content and experimentally determined absorbance agrees with the extinction coefficient derived by the amino acid sequence. The sequences of GP2017 and US-licensed Humira are identical (see below). Sandoz’s extinction coefficient is reasonable for use in the analytical similarity assessment and for use in routine determination of protein concentration in commercial manufacture and release.

3.2.R.2.2.15 Extractable volume

Reviewer note: Extractable volume (mL) and fill weight data reviewed as part of manufacturing process controls. The sponsor also evaluated extractable volume as part of the analytical similarity assessment.

The extractable volumes of 19 GP2017 DP batches, 31 US-licensed Humira and 35 EU-approved Humira were compared and the results were analyzed using a Tier 2 quality range assessment. Figure 3.2.R.2-25 shows the results of the extractable volume tests. The quality range derived from US-licensed Humira is 771-831 µL and the quality range from EU-approved Humira is 782-828 µL. The range of GP2017 DP batches is 804-840 µL. GP2017 DP batch 7006716 (840 µL) is out of quality ranges of both Humira products and 7007966 (830 µL) is out of EU-approved Humira range.

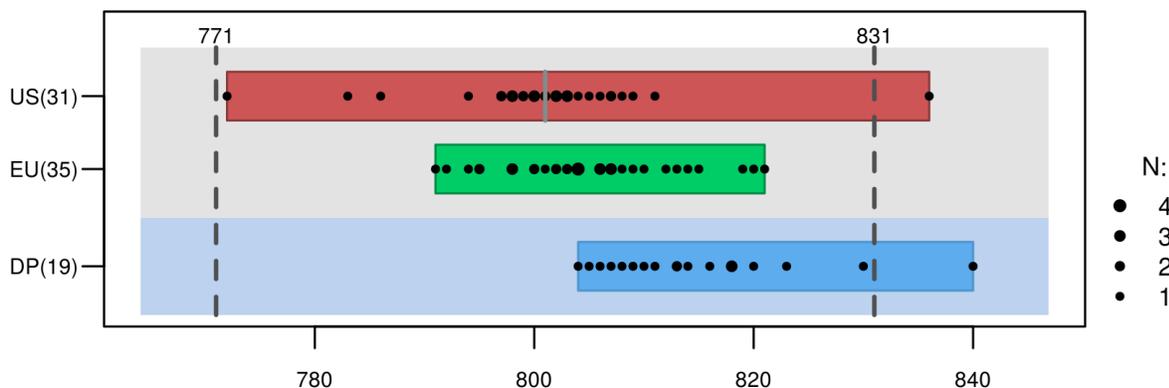


Figure 3.2.R.2-25 Comparison of extractable volume for GP2017 DP and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values ± 3SD. Black dots indicate the distribution of data points, and the

size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira® US are shown in a red box, values of Humira® EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

Assay qualification: The extractable volume was determined by weighing the liquid extracted from the syringe and calculating with the density of the solution. The procedure is described in Ph.Eur.2.9.17.

Reviewer comments: *US-licensed Humira batch 130482E (836µL) was out of the upper limit of mean + 3SD. 95% of GP2017 DP batches and 100% EU-approved Humira batches are within the quality range derived from 31 batches of US-licensed Humira, meeting the Tier 2 assessment criterion. 90% of GP2017 DP batches were within the EU-approved Humira quality range.*

3.2.R.2.2.16 Oxidation of methionine

Oxidation is a common degradation pathway in proteins and methionine is the most susceptible residue for oxidation. For adalimumab, Met256 in the Fc region is the main site of oxidation. Sandoz used reduced peptide mapping with HPLC-UV to monitor the oxidation level of Met256. The peptide containing oxidized Met256 is separated from non-oxidized peptide in HPLC and the relative quantity of the oxidized peptide was calculated by comparing the areas under the chromatogram peaks. Figure 3.2.R.2-26 shows the comparison of the Met256 oxidation level between 18 (9 independent) GP2017 batches, 30 US-licensed Humira batches and 31 EU-approved Humira batches and GP2017 has lower Met256 oxidation level than Humira.

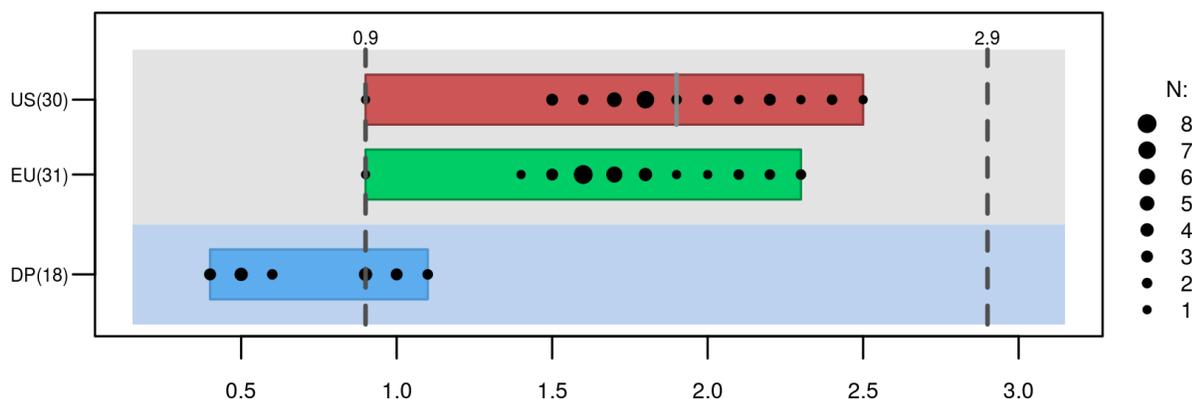


Figure 3.2.R.2-26 Comparison of MetOx256 for GP2017 DP and Humira. The solid grey line in the red box indicates the mean value of all US batches from which the standard deviation is calculated. Dashed grey lines represent the mean of US values \pm 3SD. Black dots indicate the distribution of data points, and the size of the dots is proportional to the number of data points at a certain value (see legend on the right). The values of Humira® US are shown in a red box, values of Humira® EU are shown in a green box, and GP2017 DP results are shown in a blue box. The total number of batches contributing to the respective range is given in parentheses.

Reviewer comments: *The quality range of Met256 oxidation is 0.9-2.9% derived for 30 batches of US-licensed Humira. The quality range of EU-approved Humira is 0.9-2.6%. EU-approved Humira has a comparable range to US-licensed Humira. The range of GP2017 DP batches (0.4-1.1%) is lower than the quality ranges of both Humira products. Lower level of Met256 oxidation in GP2017 is advantageous because methionine oxidation occurs upon aging and stress. Literature reported that Met256 oxidation might reduce thermal stability and decrease Protein A and FcRn binding as well as in vivo serum half-life. Even if the Tier 2 quality ranges criteria are not met, this does not constitute a concern and the differences do not impact the mechanism of action.*

3.2.R.2.3 Similarity Assessment for Tier 3 Attributes (Raw Data/Graphical Comparison)

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

3.2.R.2.3.1 Primary Structure and sequence variants

The characterization tests for the primary structure analyses of GP2017, US-licensed Humira and EU-approved Humira included:

- Amino acid sequencing using LC/UV and LC/MS/MS peptide mapping with bioinformatics
- Molecular weight determination by mass spectrometry (ESI-qTOF-MS) for intact IgG
- Primary structure and post-translation modification by MS subunit analysis
- Identification of disulfide bonds using LC/MS and quantification of free thiol groups by Ellman's assay
- Evaluation of thioether bonds, non-reducible linkage between two cysteines, by reduced CE-SDS.
- Analysis and quantification of amino acid modifications included methionine oxidation (Met oxidation), asparagine deamidation/isomerization, N-terminal extension and N-terminal pyroglutamate

Study results show that the GP2017 primary structure and amino acid sequence for the variable and constant regions is identical to those of US-licensed Humira and EU-approved Humira. The identity and locations of post-translational modifications of GP2017 and Humira were similar.

The experimental results indicate that the disulfide bond connectivity are at the expected cysteines and are the same in GP2017, US-licensed Humira, and EU-approved Humira. The free sulfhydryl and thioether levels are very low and similar in all three products.

Peptide mapping with HPLC-UV/MS was used to identify and quantify amino acid modifications and sequence variants. The chromatograms of GP2017 and Humira samples overlap and the relative quantification of each modification and variant is calculated using the area under the corresponding peak. Table 3.2.R.2-3 lists the relative quantification ranges of amino acid modifications in GP2017 and Humira.

Table 3.2.R.2-3 Relative quantification of amino acid modifications and sequence variants

AA modification/ sequence variants	US-licensed Humira	GP2017	EU-approved Humira
LH27 deamidation	1.2-3.5%	0.9-1.9%	1.3-3.4%
LH30 deamidation	0.1-1.9%	0.3-0.7%	0.2-1.9%
Isoaspartate LH27	0.5-2.8%	0.3-0.7%	0.6-2.3%
Isoaspartate total	0.8-2.7%	0.7-2.3%	0.9-2.9%
N-terminal Pyro glutamate	1.2-2.3%	1.1-2.1%	1.2-2.7%
C-terminal lysine variants	13.3-18.7%	3.1-6%	12.2-18.1%
C-terminal proline amide variant	0.1-1.4%	0.7-1.9%	0.1-1.2%

Reviewer comment: *The assays evaluated in Tier 3 and used in the studies were qualified, and the mass accuracy, sensitivity and resolution of instruments were confirmed before data acquisition. All the methods were suitable for their intended use. The primary structure and post-translational modifications of GP2017 are similar to US-licensed Humira and EU-approved Humira. The amino acid modifications and sequence variants are similar between GP2017 and Humira and are all at low levels, except for C-terminal lysine variants. Sandoz analyzed the protein modifications and found that the modifications were located neither in the antigen binding region nor in the FcR binding region. Therefore, the modifications should have no impact on activity or PK. In addition, deamidation, pyro glutamate formation and C-terminal lysine removal occur in vivo⁷ and represent low risk for drug quality.*

3.2.R.2.3.2 N-linked Glycosylation

⁷ Liu YD, van Enk JZ, et al (2009) Human antibody Fc deamidation in vivo. *Biologicals*; 37(5): 313-22.

N-linked glycan mapping by HILIC/MS supports that GP2017, US-licensed Humira, and EU-approved Humira are similar with respect to the most abundant N-linked glycan bG0. Differences in low abundance glycan species are observed between GP2017 and US-licensed Humira and EU-approved Humira products. Figure 3.2.R.2-27 presents side-by-side comparison of the N-linked glycan profiles from GP2017, US-licensed Humira and EU-approved Humira.

The predominant N-linked glycan are complex biantennary with low levels of high mannose type of glycan. The most abundant glycan is bG0, which is 60.9-71.6% in GP2017 and 61.4-70.1% in US-licensed Humira. GP2017 contains a slightly higher level of sialylated glycan (0.3-0.5%) compared to the reference products (< LOQ).

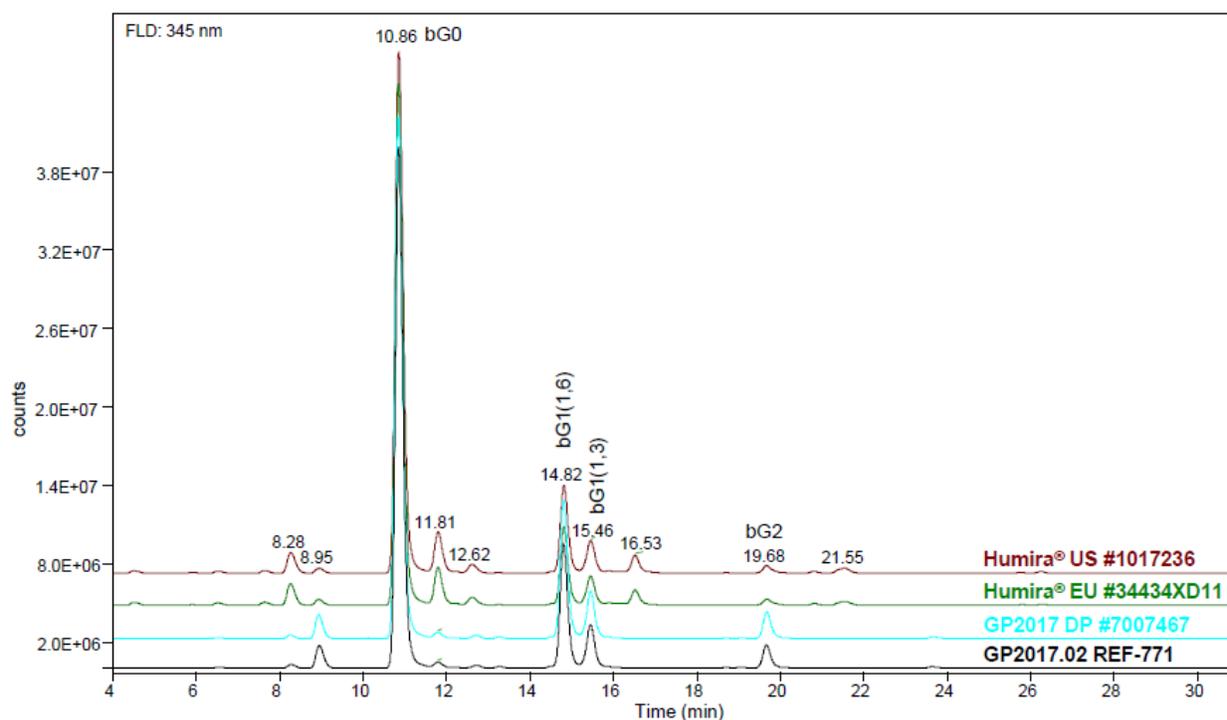


Figure 3.2.R.2-27 HILIC-MS 2-AB labeled N-Glycan Mapping

The degree of glycosylation and site occupancy of Asn301 was tested using reduced CE-SDS. The adalimumab sample was reduced with 2-mercaptoethanol and the light chain (LC) and heavy chain (HC) were separated in electrophoresis. The non-glycosylated HC (HC_{NG}) was separated from glycosylated HC in the electropherogram and the calculated as:

$$\text{Degree of glycosylation [\%]} = \frac{\text{Area HC}}{\text{Area HC} + \text{Area HC}_{\text{NG}}} \times 100\%$$

The glycosylation site occupancy of GP2017 is 99.3- 99.6%, for US-licensed Humira it is 97.7-98.6% and for EU-approved Humira it is 97.8-98.7%.

Glycation is a non-enzymatic process in which lysine residues are modified by reducing sugars and it may occur during fermentation. Boronate affinity chromatography (BAC) was used to detect and quantify glycation of adalimumab. Glycation of GP2017 DP is 0.3-0.5% and both US-licensed and EU-approved Humira are 0.2-0.4%. The glycation rate of GP2017 is similar or slightly higher than the reference product. But the levels of glycation for all three products are low and this attribute does not impact drug quality.

Reviewer comment: *The major glycan species are similar between GP2017 and Humira. The glycosylation site occupancy of GP2017 DP is slightly higher than US-licensed Humira, but all three products show high site occupancy in the same range (> 97%). The totality of the in vitro data, including Fc receptor binding affinities, C1q receptor affinity, and cell-based bioassays for ADCC, CDC, reverse signaling, and inhibition of regulatory macrophages, support that these minor differences in glycoforms and site occupancy do not significantly impact functions related to the mechanism of action of these products. Of note, the levels of sialylated glycan in GP2017 were shown to be at trace level (<1%) and do not affect product quality. No unusual or potentially immunogenic glycans were identified in GP2017 or Humira. The glycoforms in GP2017 are similar to US-licensed Humira and EU-approved Humira.*

3.2.R.2.3.3 Charge Variants

The difference in charge variants observed between GP2017 and the reference product was further characterized using imaged capillary isoelectric focusing (iCE) and two-dimensional difference gel electrophoresis (2D-DIGE).

Protein variants are separated according to their isoelectric points (pI) in iCE. Six batches of GP2017, 3 batches of US-licensed Humira, and 3 batches of EU-approved Humira were analyzed by iCE and the pI values of the charge variants were compared. Six pI variants of adalimumab were identified from the electropherograms. GP2017 DP showed similar iCE charge pattern and pI variants to Humira.

In 2D-DIGE, proteins are separated based on their pI and size, then detected by fluorescence. Two or more samples labeled with different fluorophores can be analyzed and compared on the same gel. One batch from GP2017 (7007467), US-licensed Humira (1017236) and EU-approved Humira (34434XD11) were compared and the 2D-DIGE image of GP2017 is similar to Humira.

Reviewer comment: *The iCE electropherograms of GP2017 and the pI values of each charge variant are similar to Humira. The 2D-DIGE image of GP2017 is similar to Humira.*

The basic species includes C-terminal lysine variants (1K or 2K) and proline amide variant (P-NH₂). Sandoz identified and quantified the C-terminal lysine and proline amide peptides using RPLC-UV peptide mapping. Figure 3.2.R.2-28 shows the peptide maps of C-terminal variants in GP2017 DP and Humira.

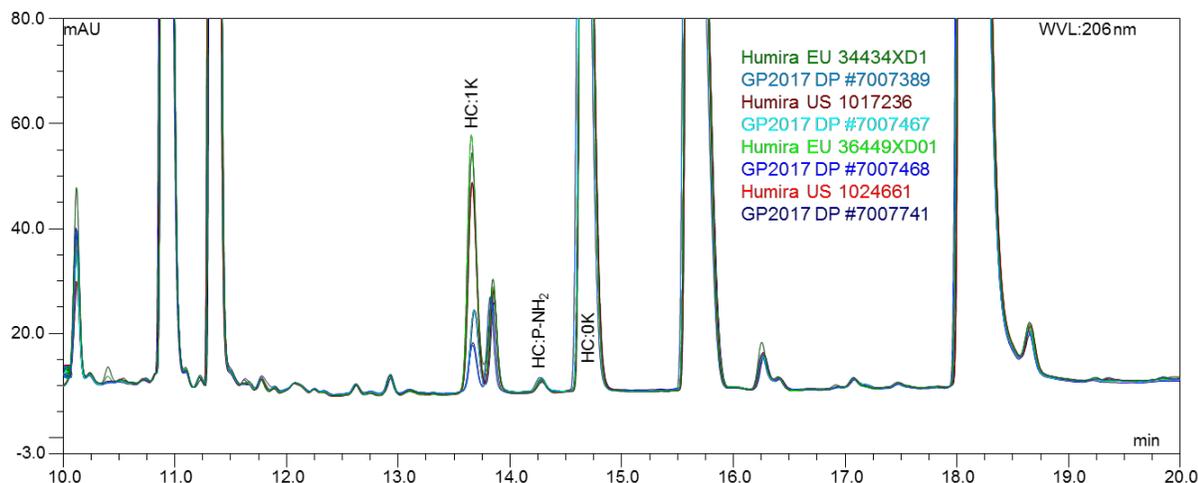


Figure 3.2.R.2-28 Overlay of peptide maps to visualize C-terminal variants in GP2017 DP and Humira. HC: 1K – with C-terminal lysine on heavy chain; HC: 0K – without C-terminal lysine on heavy chain; HC: P-NH₂ – C-terminal proline amide variant

GP2017 showed lower amount of lysine variants (3.1-6.0%) than US-licensed Humira (13.3-18.7%); GP2017 has slightly higher amidated proline (0.7-1.9%) compared to US-licensed Humira (0.1-1.4%). This difference is consistent with the CEX charge variants results (section 3.2.R.2.2.10).

Deamidation is the process that asparagine (Asn) converts to a mixture of aspartate (Asp) and isoaspartate (IsoAsp) during regular storage or in the bloodstream. Acidic variants consist of deamidated proteins. Sandoz used LC/MS peptide mapping to identify and quantify deamidated peptides. Two heavy chain LysC peptides of adalimumab, LH27 and LH30, were identified to be potentially deamidated peptides. GP2017 DP has lower deamidation level on LH27 (0.9-1.9%) than US-licensed Humira (1.2-3.5%); GP2017 has a similar level of deamidation on LH30 (0.3-0.7%) as US-licensed Humira (0.1-1.9%). Overall, a low amount of deamidation/isomerization (< 5%) of the peptides LH27 and LH30 was detected in GP2017 and Humira.

Reviewer comment: *The deamidation and C-terminal variants contribute to charge heterogeneity. The quantification results of amino acid modifications and sequence variants agree with the CEX comparison of GP2017 and Humira.*

3.2.R.2.3.4 Hydrophobicity by HIC

Sandoz used hydrophobic chromatography (HIC) to compare hydrophobicity between GP2017 DP and Humira. Figure 3.2.R.2-29 shows the head-to-head comparison of GP2017 and Humira in terms of hydrophobicity. GP2017 exhibits similar HIC pattern to US-licensed Humira. The amounts of hydrophobic variants of GP2017 are similar to US-licensed Humira; the GP2017 has less amount of hydrophilic variants than US-licensed Humira.

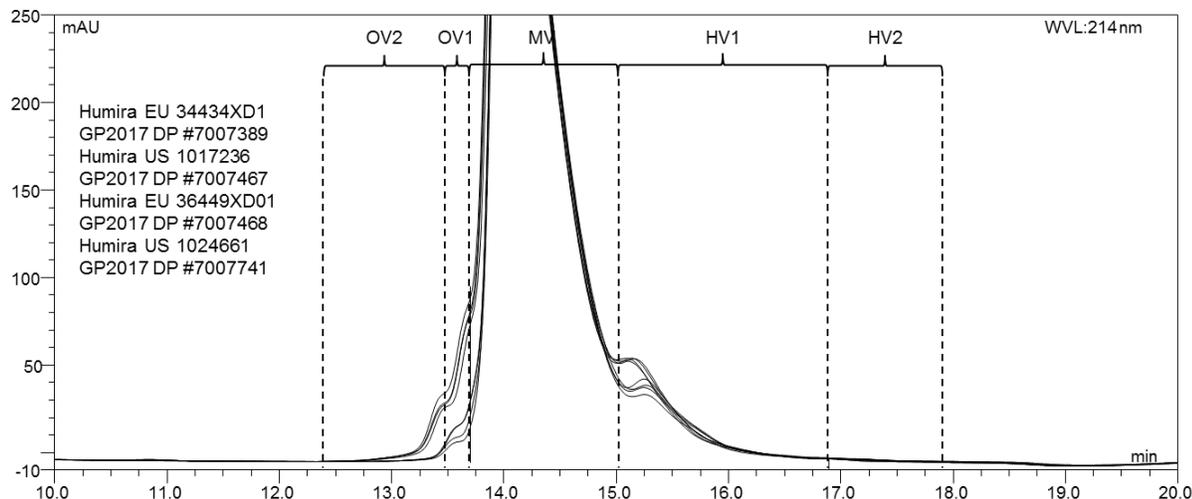


Figure 3.2.R.2-29 Overlay of HIC chromatogram of GP2017 DP and Humira. Legend: OV1 – Oxidized variant 1; OV2 – Oxidized variant 2; MV – Main variant; HV1: Hydrophobic variant 1; HV2: Hydrophobic variant 2

3.2.R.2.3.5 Higher Order Structure

The similarity of the higher order structure of GP2017, US-licensed Humira and EU-approved Humira was evaluated by orthogonal biophysical techniques. These techniques include far and near-UV circular dichroism (CD), Fourier transform infrared (FT-IR), differential scanning calorimetry (DSC), H/D exchange mass spectrometry, 1D and 2D NMR, and X-ray crystallography.

Reviewer comment: *The sponsor conducted higher order structure analyses to assess the similarity between GP2017 and reference products. 6 independent batches of GP2017, 3 batches for US-licensed Humira and 3 batches for EU-approved Humira were included for far- and Near-UV CD test, FT-IR and DSC. Three batches of GP2017, and 2 batches each for US-licensed Humira and EU-approved Humira were analyzed by 1D and 2D NMR analysis. One lot from each product was analyzed by X-ray crystallography and H/D exchange MS. The raw data for all these assays were provided in the submission but not reproduced in this review. Data from the biophysical techniques support the conclusion that GP2017 is structurally like US-licensed Humira and EU-approved Humira.*

3.2.R.2.3.6 Particulate contamination

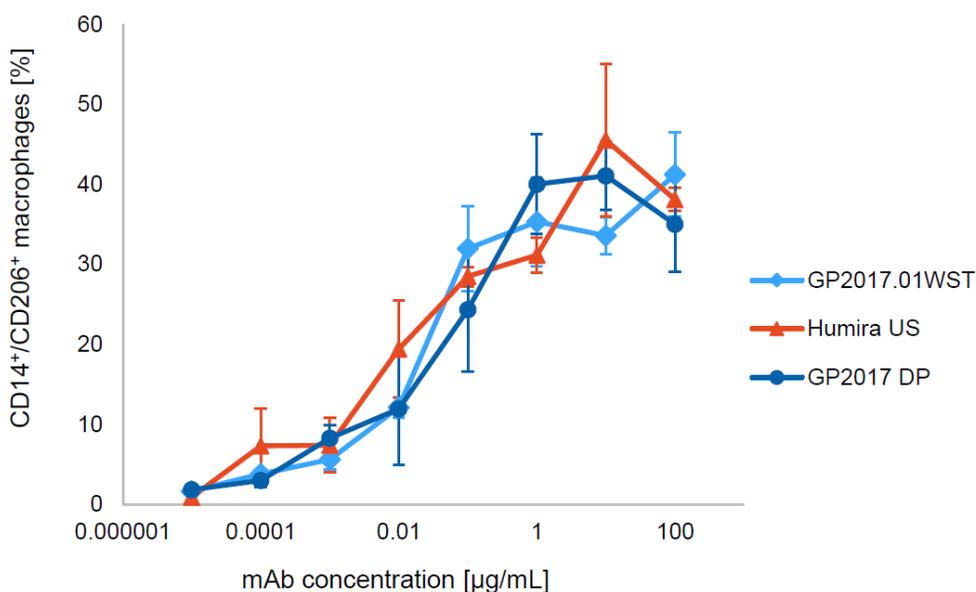
Foreign particles may cause serious immunogenic reactions and be a safety concern. Sandoz compared GP2017 with Humira for particles of difference size ranges. Sandoz conducted inspections on visible particles according to Ph.Eur.2.9.20 and USP<790>, and GP2017 and Humira are practically free from extraneous particles. Sandoz used micro-flow imaging (MFI) to detect transparent particles $\geq 2\mu\text{m}$, and GP2017 DP has similar sub-visible particle levels to US-licensed and EU-approved Humira. Sandoz used resonant mass measurement (RMM) to evaluate particles size over a range of approx. 300 nm to 5 μm , and the results indicated that GP2017 DP exhibited similar particle levels to Humira.

Reviewer comment: The sponsor measured the particulate levels (visible and sub-visible) to assess the similarity between GP2017 and the reference products. Visual inspection, MFI, and RMM were used for different particle size ranges, and the results from each analysis support that GP2017 is similar to US-licensed Humira and EU-approved Humira in terms of particulate contamination.

3.2.R.2.3.7 Induction of Regulatory Macrophages-Mixed Lymphocyte Reaction (MLR) Assay

Binding of adalimumab to mTNF- α on activated T cells induces regulatory macrophages with immunosuppressive capacities, which suppress pro-inflammatory cytokine secretion and inhibit T-cell proliferation. As in ADCC effector function, both binding to mTNF- α and to Fc receptor are required⁸. The mixed lymphocyte reaction (MLR) assay was used to compare the ability of Humira and GP2017 DP to induce regulatory macrophages. The MLR assay employed here used peripheral blood mononuclear cells (PBMCs) from two donors. In MLR assay, PBMC were treated with graded concentrations of adalimumab samples. The population of regulatory macrophages were identified by measuring by the two cell surface markers CD14 and CD206 via flow cytometry.

Four batches of GP2017 DP, and three batches each of US-licensed Humira, and EU-approved Humira product were evaluated over the dose-response range for increase of CD14+/CD206+ cells in MLR assays. All batches of EU-approved Humira, US-licensed Humira, and GP2017 yielded qualitatively similar CD14+/CD206+ cells in a dose-dependent manner in the MLR. Figure 3.2.R.3.2-21 shows the MLR assay dose-response curves of GP2017 (batch #7007742), US-licensed Humira (batch 1049950) and reference material (GP2017.01 WST).



⁸ Vos ACW (2011), Anti-Tumor Necrosis Factor- Antibodies Induce Regulatory; Macrophages in an Fc Region-Dependent Manner. Gastroenterology; 140: 221-30.

Figure 3.2.R.2-30 Representative MLR assay data of GP2017 DP and Humira

Reviewer comment: The CD14+/CD206+ cells increased with increased adalimumab concentration in the assay. The dose-response curves of GP2017 and US-licensed Humira show similar up trend and overlapped each other. The ranges of macrophage induction activity of each product are close and overlap. The graphic comparison of the data indicated that GP2017 has similar induction activity of regulatory macrophages to US-licensed Humira and EU-approved Humira.

3.2.R.2.3.8 Additional Fcγ Receptor Binding and Binding to Cytokines SPR Assays

Binding of GP2017, US-licensed Humira, and EU-approved Humira to Fcγ receptors, Fcγ RI, RIIa 131H, RIIa 131R and RIIb was assessed by SPR.

K_D values of GP2017, US-licensed Humira, and EU-approved Humira batches were calculated for FcγRI, FcγRIIa, FcγRIIb/c and FcγRIIIb (Table 3.2.R.3-6). K_D of GP2017, US-licensed Humira, and EU-approved Humira are overlapping within a very narrow range. The results indicate similar FcγR binding activity of GP2017, US-licensed Humira, and EU-approved Humira.

Table 3.2.R.2-4. Summary of FcγR SPR Binding Affinity K_D of GP2017 and Humira

Source	Batch	FcγRI [nM]	FcγRIIa [μM]	FcγRIIb/c [μM]	FcγRIIIb [μM]
EU	34434XD11	20.7±1.68	2.18	9.12	9.89
	36449XD01	20.7±2.00	2.36	9.09	11.7
GP2017	7007389	19.8±2.21	1.97	8.14	8.73
	7007467	19.0±1.77	1.94	8.09	10.3
	7007468	21.1±1.82	1.97	7.82	9.94
	7007741	23.1±1.74	2.08	8.51	9.42
US	1017236	20.3±2.04	2.34	10.0	11.8
	1024661	24.5±1.91	2.27	9.48	9.67

Off-target binding can affect the pharmacokinetics (PK), tissue distribution, efficacy and toxicity of a therapeutic antibody. The ability of adalimumab to bind to cytokines was assessed by SPR. One batch of each of GP2017 DP, US-licensed Humira and EU-approved Humira were used. None of the adalimumab products show specific binding activity to cytokines, including TGF-β1, IL-1β, IFN-γ, APRIL, IL-6, IL-8, IL-10, TNF-β, sCD40L, BAFF and RANKL.

Reviewer comment: The sensorgrams of GP2017 and Humira binding to each FcγR overlapped very well. The calculated K_D of FcγRI and FcγRIIIb of GP2017 and Humira are within similar range. The K_D of FcγRII binding of GP2017 are slightly lower than Humira. However, the different binding activity to

the low affinity receptors does not affect the ADCC activity. GP2017 and Humira do not have specific binding activity to cytokines that are related to TNF- α . GP2017 shows similar Fc γ receptor binding activity to US-licensed Humira and EU-approved Humira.

3.2.R.3 Comparative Forced Degradation Studies

Forced degradation studies were carried out to support similarity of GP2017, US-licensed Humira, and EU-approved Humira. The forced degradation studies included 14 different stress conditions, such as elevated temperature storage, light exposure, chemical and mechanical stress. Table 3.2.R.3-1 summarizes the stress conditions and analytical methods applied to the samples derived from the different stress conditions. Four batches of GP2017 DP (7007389, 7007467, 7007741 and 7007468), 1 batch of US-licensed Humira (1017236), and 1 batch of EU-approved Humira (34434XD11) were compared in these studies. Sandoz provided the analytical results from each stress condition, as well as the absolute differences between each pull point comparing to the non-stressed samples (T₀) or negative controls. The force degradation study results to compare the degradation trending between GP2017 and Humira are listed in the Appendix Table 1.

Table 3.2.R.3-1 Stress conditions and analytical methods applied for different stress conditions

Stress conditions		Content	pH	SEC	HIC	CEX	CE	MetOx	C-terminal variants	deamidation
Initial		X	X	X	X	X	X	X	X	X
Temperature for 1d, 1w, 2w and 1m	40 \pm 2°C	X	X	X	X	X	X	X	X	X
	50 \pm 3°C	X	X	X	X	X	X	X	X	X
Oxidation for 0.5, 1,3 and 6 hrs at 40 \pm 2°C	0.05% H ₂ O ₂	X	X	X	X	X	X	X		X
	0.5% H ₂ O ₂	X	X	X	X	X	X	X		X
pH for 1d, 2d, and 1w at 40 \pm 2°C	3.0	X	X	X	X	X			X	X
	7.5	X	X	X	X	X			X	X
	8.5	X	X	X	X	X			X	X
Light	7 hrs	X	X	X	X	X	X			
	14 hrs	X	X	X	X	X	X			
Freeze/thawing 5, 10 cycles		X		X			X			
Metal ion 1 μ M Cu (II) for 1d, 2d, and 1w at 40 \pm 2°C		X	X	X	X		X			
Vortex at full speed for 60 and 180 s at 23-25°C		X		X			X			
Horizontal shake at 180rpm for 6 and 16 hrs at 23-25°C		X		X			X			
Stir with 600rpm for 1, 6 and 16hrs at 23-25°C		X		X			X			

Reduce with 0.1mM DTT for 1,5 and 20 min at 40°C	X					X			
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Reviewer comment: *The stress conditions, including high temperatures, oxidation/reduction, extreme pH, light, freeze/thaw, metal and mechanical stress, are adequate to cover the potential protein degradation conditions and the test methods are suitable for detecting protein degradations.*

3.2.R.3.1 Forced Degradation Studies at Elevated Temperature

Two forced degradation studies at elevated temperature were performed using drug product batches of GP2017, US-licensed Humira, and EU-approved Humira: 1) drug product was held at 40 °C, samples were collected at 1 day, 1 week, 2 weeks and 1 month; 2) drug product was held at 50 °C, samples were collected at 1 day, 1 week and 2 weeks. From these studies, the following quality attributes were measured:

- Protein content (UV spectroscopy)
- pH
- HMW variants and fragments (SEC)
- Intact IgG (non- reduced CE-SDS)
- Oxidation and hydrophobic variants (HIC)
- Charge variants (CEX)
- Identity of modified peptides (peptide mapping)

Under high temperature, the purity of the three products decreased as shown by SEC, HIC, CEX and CE-SDS. The abundance of fragments, acidic species and hydrophobic variants increased in all three products. Basic variants in GP2017 slightly increased in GP2017, while decreased in Humira over the storage period (Figure 3.2.R.3-1). Peptide mapping showed a slight increase in deamidated LH27 and oxidized variants in all three products. C-terminal variants did not change for all three products. Protein content, pH and HMW variants did not change. Products degrade faster at 50°C than at 40°C.

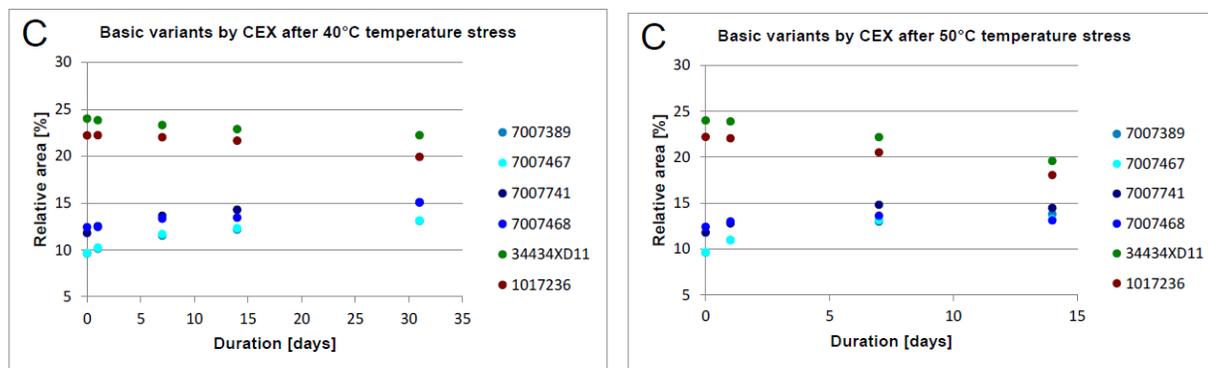


Figure 3.2.R.3-1 Basic variants result in CEX. Left: 40°C, right: 50°C.

Reviewer comments: The basic variants of GP2017 increased, while decreased in Humira under the degradation conditions. Peptide mapping showed no significant change for the C-terminal variants. The charge heterogeneity of GP2017 showed difference from Humira such as higher main peak, and smaller acidic and basic species. The different trends of basic species probably reflect the difference in charge variants, formulation or both. But the basic species change in GP2017 is small and agrees with the stability results. The basic species degradation difference under high temperatures is not significant. The testing results of the quality attributes are similar between GP2017 and US-licensed Humira and EU-approved Humira.

3.2.R.3.2 Forced Degradation Studies at Oxidation Stress

Sandoz conducted two forced degradation studies under oxidation stress using drug product batches of GP2017, US-licensed Humira, and EU-approved Humira: drug product was incubated with 0.05% or 0.5% H₂O₂ at 40°C, samples were collected at 0.5 hr, 1 hr, 3 hrs and 6 hrs.

Under oxidation stress, oxidized variants in HIC, basic variants and oxidized methionine 256 increased significantly, while the intact IgG decreased slightly. The protein content, pH, aggregates and fragments, acidic variants, and deamidation variants didn't change.

Reviewer comment: Degradation behavior under oxidation stress are similar between GP2017 and Humira.

3.2.R.3.3. Forced Degradation Study at pH Stress

Drug products were incubated in pH 3.0, pH 7.5 and pH 8.5 at 40°C, and samples were collected for test at 1 day, 2 days and 1 week. The drug products were characterized using the following analytical techniques, UV, pH, SEC, HIC, CEX, and peptide mapping.

The results suggest that the predominant routes of degradation include increase in acidic variants, oxidized and hydrophobic variants. Peptide mapping indicated that deamidation and isomerization

increased on the LH27 for all three products in similar abundances. All products have minor increases in fragments, and a small decrease in basic variants. Both Humira samples precipitated at pH 3.0 and were not analyzed in this study.

***Reviewer comment:** Similar degradation profiles and levels are observed in the GP2017 drug product when compared to US-licensed Humira and EU-approved Humira under pH stress.*

3.2.R.3.4. Forced Degradation Study by Light Exposure (Photodegradation)

All three products were placed in a light chamber and exposed for 7 and 14 hours, covering an overall illumination of ≥ 1.2 million lux hours and an integrated near UV energy of ≥ 400 watt hours/m². The drug product samples were characterized using the following analytical techniques: UV, pH, SEC, HIC, CEX, and CE (non-reduced).

The GP2017, US-licensed Humira and EU-approved Humira degraded in a similar manner when exposed to light. The results suggested that the predominant routes of degradation include increase in HMW and fragments, acidic and basic species and oxidized variants, and decrease in intact IgG and hydrophobic variants.

***Reviewer comment:** All drug product degraded in a similar manner while exposed to light.*

3.2.R.3.5. Force Degradation Study at Reduction Stress

The drug products were incubated with 0.1 mM DTT for 1 min, 5 min and 20 min at 40°C. The intact IgG decreased significantly under reduced condition and GP2017 degraded similarly to US-licensed Humira and EU-approved Humira.

***Reviewer comment:** All drug products degraded similarly under reduced conditions.*

3.2.R.3.6 Force Degradation Study under Other Conditions

The freeze/thawing, metal ion and mechanical stress (vortexing, horizontal shaking and stirring), do not impact the stability of all three drug products.

***Reviewer comment:** The sponsor provided forced degradation comparison study data with GP2017 and Humira DP batches under elevated temperature, oxidation, pH, light exposure, reduction and mechanical stress conditions. Forced degradation studies revealed all the drug products degrade in a similar manner. The results support the conclusion that GP2017 and US-licensed Humira and EU-approved Humira shared similar stability profiles and degradation pathway.*

3.2.R.4 Stability Assessment

Sandoz performed stability studies to compare the long-term stability behavior of GP2017, US-licensed Humira, and EU-approved Humira in the primary package. Nine batches of GP2017 DP, 3 batches of US-licensed Humira, and 4 batches of EU-approved Humira were tested in the study. Three conditions were investigated: 1) the intended storage condition of $5 \pm 3^{\circ}\text{C}$ for up to 30 months; 2) accelerated storage conditions of $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$ for up to 6 months; and 3) temperature stress conditions of $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}$ for up to 6 months. The analytical tests include appearance of container, UV spectroscopy (content), SEC (fragments and HMW), CEX (main, acidic and basic variants), non-reduced CE-SDS (intact IgG), reduced CE-SDS (aglycosylated HC), LC/UV peptide mapping (MetOx256), TNF- α neutralization RGA, and subvisible particles.

Fragment and HMW variants increased over time and the stability trends are similar for GP2017, US-licensed Humira, and EU-approved Humira. The acidic variants increased, the main CEX peak decreased and basic variants didn't show significant trend of change. Similar trends of charge variants were observed between GP2017 DP and Humira. The intact IgG decreased over time similarly for GP2017 DP, US-licensed Humira, and EU-approved Humira.

The protein content, aglycosylated HC, MetOx256, and bioactivity are constant over time, and the similar trends were observed for GP2017 DP and Humira.

Reviewer comment: *The sponsor compared the stability behavior of GP2017 DP, US-licensed Humira, and EU-approved Humira under the intended storage conditions, accelerated storage conditions and temperature stress conditions. All GP2017 DP and Humira drug products were tested with the same analytical methods as those in the GP2017 stability protocol. The analytical testing results indicated that the long term stability of GP2017 DP, US-licensed Humira, and EU-approved Humira are similar.*

Appendix Table 1 Force Degradation Study Results

Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
Drug product held at 40 ±2 °C (change from T=0)	1 day	UV spectroscopy (mg/mL)		0	-0.1-0	0	Similar /similar/comparable
	1 week			0	0	0	
	2 weeks			0	0	0	
	1 month			0	0	0	
	1 month		pH	0	0	0	Similar /similar/comparable
	1 day	SEC	Monomer	-0.1	-2.6- -2.2	-0.2	Similar /similar/comparable
			HMS	0	-0.4- 0	0	
			fragments	0.1	0.1-0.5	0.2	
	1 week		Monomer	-0.6	-0.9- -0.5	-0.7	
			HMS	0	-0.1-0	-0.1	
			fragments	0.6	0.6-1	0.7	
	2 weeks		Monomer	-1.2	-1.4- -1.0	-1.2	
			HMS	0	-0.1-0	-0.1	
			fragments	1.2	1.1-1.5	1.3	
	1 month	Monomer	-2.4	-2.6- -2.2	-2.3		
		HMS	0	-0.1-0	0		
		Fragments	2.3	2.2-2.6	2.3		
	1 day	HIC	Main	-0.6	0.3-2.9	0	Similar /similar/comparable
			Oxidized variants	0.4	-2.6- -1.1	-0.7	
			Hydrophobic variants	0.2	-0.4-0.8	0.7	
1 week	Main		-2.6	-3.9- 0	-2.3		
	Oxidized variants		0.8	-1.0-1.4	0		
	Hydrophobic variants		1.9	1.0-2.5	2.2		
2 weeks	Main		-5.0	-6.6- -2.6	-4.1		
	Oxidized variants		1.5	-0.4-2.4	0.6		
	Hydrophobic variants		3.6	3.0-4.2	3.5		
1 month	Main	-10.0	-11.0- -7.8	-9.8			
	Oxidized variants	3.2	1.5-3.4	2.6			

Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
			Hydrophobic variants	6.8	6.3-7.6	7.2	
	1 day	CEX	Main	-1.3	-0.8-0.8	-0.1	Similar /similar/comparable
			Acidic	1.2	-0.7- 0.5	-0.1	
			Basic	0.1	-0.1-0.5	0.2	
	1 week		Main	-4.1	-6.5- -5.2	-5.4	
			Acidic	4.2	4.2-4.7	5.8	
			Basic	-0.1	0.8-1.8	-0.3	
	2 weeks		Main	-7.3	-11.4- -9.5	-8.4	
			Acidic	7.8	8.6-9.2	9.2	
			Basic	-0.5	0.9-2.4	-0.8	
	1 month	Main	-15.6	-22.1- -20.6	-15.9		
		Acidic	17.8	18.1-18.9	17.3		
		Basic	-2.2	2.5-3.3	-1.4		
	1 day	nrCE-SDS	IgG	0	-0.1-0.2	-0.1	Similar /similar/comparable
	1 week		IgG	-0.9	-1.7- -0.9	-1.2	
	2 weeks		IgG	-1.6	-2.0- -1.4	-1.7	
	1 month		IgG	-3.6	-3.6- -3.1	-3.3	
	1 day	Peptide map	MetOx 256	0	-0.8-0	0	Similar /similar/comparable
			C-terminal 1K	0	-0.2-0.5	0.1	
			C-terminal LH31PA	-0.1	-0.1-0.1	-0.1	
			LH30 deamidation	0.2	0	0	
			LH27 isomerization/ deamidation	0	-0.1-0.2	0.1	
			LH27 deamidation	0.2	-0.3-0.1	0	
			1 week	MetOx 256	0.2	-0.5-0.2	
	C-terminal 1K	0		0-0.4	0		

Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
	2 weeks		C-terminal LH31PA	0	0-0.1	-0.1	
			LH30 deamidation	0.2	-0.1-0.1	0.1	
			LH27 isomerization/ deamidation	0.1	-0.2-0.2	0.2	
			LH27 deamidation	0.3	-0.4-0.6	0	
			MetOx256	0.5	-0.4-0.4	0.5	
			C-terminal 1K	0.1	-0.1-0.4	0	
			C-terminal LH31PA	-0.1	-0.1-0	-0.2	
			LH30 deamidation	0.1	-0.1-0	0	
			LH27 isomerization/ deamidation	0.2	0.1-0.4	0.3	
	LH27 deamidation		0.3	0-0.2	0		
	1 month		MetOx256	1.1	-0.8-0.9	1.0	
	C-terminal 1K		0.3	-0.1-0.4	0.3		
	C-terminal LH31PA		-0.1	0	-0.1		
	LH30 deamidation		0.2	0-0.1	0.1		
	LH27 isomerization/ deamidation		0.4	0.3-0.5	0.4		
LH27 deamidation	0.5	0.2-0.4	0.3				
Drug product held at 50 ± 3°C (Change from T=0)	1 day	UV spectroscopy (mg/mL)		0	-0.7-0	0	Similar /similar/comparable
	1 week			0.1	0-0.6	0	
	2 weeks			0.1	0-0.2	0.1	
	2 weeks	pH		0	0	0	Similar /similar/comparable
	1 day	SEC	Monomer	-0.3	-0.5 - -0.2	-0.3	Similar /similar/comparable
		HMS	0	-0.1-0	0		

Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira		
	1 week		Fragments	0.3	0.2-0.6	0.3			
			Monomer	-2.0	-2.1- -1.9	-2.2			
			HMS	0	-0.1-0	0			
	2 weeks		Fragments	2.0	1.9-2.2	2.2			
			Monomer	-3.8	-3.9- -3.6	-4.1			
			HMS	0.1	0-0.1	0.1			
	1 day		HIC	Main	-1.0	-0.7-2.0		-0.8	Similar /similar/comparable
				Oxidized variants	0.5	-2.5- -1.1		-0.8	
				Hydrophobic variants	0.5	0.5-1.8		1.6	
		1 week		Main	-8.6	-9.8- -7.0	-8.3		
				Oxidized variants	1.8	0.6-2.2	1.4		
				Hydrophobic variants	6.7	6.4-7.6	6.9		
		2 weeks		Main	-16.0	-16.8- -13.3	-15.9		
				Oxidized variants	4.7	1.9-4.5	4.3		
				Hydrophobic variants	11.3	11.3-12.3	11.7		
	1 day	CEX	Main	-0.6	-3.7- -2.7	-1.1	Similar /similar/comparable		
			Acidic	0.6	2.2-2.5	0.9			
			Basic	-0.1	0.5-1.2	0.3			
			1 week	Main	-12.9	-21.0- -18.0		-13.0	
				Acidic	14.5	16.9-17.8		14.4	
				Basic	-1.6	1.1-3.2		-1.5	
			2 weeks	Main	-23.7	-36.1- -30.5		-22.7	
				Acidic	27.7	30.0-32.1		26.7	
				Basic	-4.0	0.6-4.0		-4.1	
	1 day	nrCE-SDS	IgG	-0.4	-0.4-0	-0.3	Similar /similar/comparable		
			1 week	IgG	-2.6	-2.7- -2.3		-2.9	
				2 weeks	IgG	-5.1		-5.0- -4.6	-5.3

Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
	1 day	Peptide map	MetOx 256	0	-0.8-0	0	Similar /similar/comparable
			C-terminal variant 1K	-0.2	-0.1-0.3	-0.1	
			C-terminal variant LH31PA	-0.1	-0.1-0	-0.2	
			LH30 deamidation	-0.1	-0.3	-0.2	
			LH27 isomerization/ deamidation	-0.5	-0.4- -0.3	-0.5	
			LH27 deamidation	-0.1	-0.5- -0.2	-0.1	
	1 week		MetOx 256	0.7	-0.3-0.6	0.7	
			C-terminal variant 1K	0	-0.1-0.6	-9.2	
			C-terminal variant LH31PA	-0.1	-0.1-0	-0.1	
			LH30 deamidation	-0.1	-0.3	-0.2	
			LH27 isomerization/	-0.1	-0.3-0	0	
			LH27 deamidation	0.1	-0.2-0.5	-0.1	
	2 weeks		MetOx 256	1.6	0.3-1.2	1.5	
			C-terminal variant 1K	0	-0.1-0.5	0.1	
			C-terminal variant LH31PA	-0.1	-0.1-0.1	-0.1	
			LH30 deamidation	-0.1	-0.3- -0.2	-0.3	
			LH27 isomerization/	0.2	0.2-0.3	0.2	
LH27 deamidation	0.4	0.2-0.4	0.2				
Drug Product oxidized in 0.05% H ₂ O ₂ at 40 ±2 °C (Change from T=0)	6 hours	pH		0.1	0.1	0.1	Similar /similar/comparable
	0.5 hour	UV spectroscopy (mg/mL)		0.2	0.1-0.2	0.2	Similar /similar/comparable
	1 hour			0.2	0.2	0.2	
	3 hours			0.3	0.1-0.2	0.2	
	6 hours			0	-0.1-0	0	

Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
	0.5 hour	SEC	Monomer	0	0-0.1	0.1	Similar /similar/comparable
			HMS	0	-0.1-0	0	
			Fragments	0	0	0	
	1 hour		Monomer	0	0	0.1	
			HMS	0	0	0	
			Fragments	0	0	0	
	3 hours		Monomer	0.1	0-0.1	0.1	
			HMS	-0.1	-0.1-0	-0.1	
			Fragments	0	0	0	
	6 hours		Monomer	0.1	-0.1-0	0	
			HMS	-0.1	-0.1-0	-0.1	
			Fragments	0	0-0.1	0.1	
	0.5 hour	HIC	Main	-56.5	-57.5- -45.0	-45.3	Similar /similar/comparable
			Oxidized variants	61.9	48.2-61.0	49.3	
			Hydrophobic variants	-5.5	-3.8- -3.1	-4.0	
	1 hour		main	-66.2	-84.5- -60.9	-58.5	
			Oxidized variants	72.1	65.2-91.0	64.0	
			Hydrophobic variants	-5.8	-6.5- -4.1	-5.5	
	3 hours		Main	-81.8	-87.8- -84.6	-79.7	
			Oxidized variants	89.1	91.3-93.1	87.3	
			Hydrophobic variants	-7.0	-6.7- -3.7	-7.0	
	6 hours		Main	-78.2	-83.8- -82.9	-76.3	
			Oxidized variants	85.2	87.0-90.2	83.6	
			Hydrophobic variants	-7.0	-6.7- -3.7	-7.4	
	0.5 hour	CEX	Main	1.1	-0.2-1.9	1.4	
			Acidic variants	-0.5	-1.3- -0.1	-0.5	

Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira		
	1 hour		Basic variants	-0.6	-0.5-0.3	-0.9	Similar /similar/comparable		
			Main	1.1	-0.1-2.0	1.4			
			Acidic variants	-0.9	-1.5- -0.1	-0.1			
	3 hours		Basic variants	-0.5	-0.6-0.2	-0.8			
			Main	-29.8	-33.5- -27.9	-28.3			
			Acidic variants	-1.9	-2.4- -0.4	-0.9			
	6 hours		Basic variants	31.8	30.3-34.6	29.2			
			Main	-47.1	-58.2- -56.3	-45.0			
			Acidic variants	-3.7	-3.5- -1.6	-3.9			
	0.5 hour		nrCE-SDS		Basic variants	50.9		59.7-61.1	48.9
					IgG	-2.7		-2.4- -2.1	-2.4
					IgG	-2.8		-2.8- -2.2	-2.6
IgG		-2.7			-2.7- -2.9	-2.5			
1 hour			IgG	-3.8	-3.4- -2.9	-3.3			
			IgG	-3.8	-3.4- -2.9	-3.3			
0.5 hour	Peptide map		MetOx 256	31.5	21.8-28.8	24.9	Similar /similar/comparable		
			LH30 deamidation	0	-0.3-0	-0.3			
			LH27 isomerization/ deamidation	-0.4	-0.3-0.4	-1.0			
			LH27 deamidation	-0.4	-1.0-0.6	-1.1			
			1 hour	MetOx 256	40.6	32.4-37.0		36.0	
				LH30 deamidation	0	-0.3- -0.1		-0.3	
				LH27 isomerization/ deamidation	-0.3	-0.2-0.2		-1.0	
				LH27 deamidation	-0.4	-1.0-0.6		-1.2	
			3 hours	MetOx 256	68.5	64.5-67.2		65.9	
				LH30 deamidation	0	-0.2-0		-0.2	
LH27 isomerization/ deamidation	-0.3	-0.3-0.3		-0.9					

Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
	6 hours		LH27 deamidation	-0.2	-1.0-0.7	-1.1	
			MetOx 256	84.7	83.5-84.8	84.3	
			LH30 deamidation	0	-0.2-0	-0.3	
			LH27 isomerization/ deamidation	-0.3	-0.2-0.2	-0.8	
			LH27 deamidation	-0.4	-0.9-0.6	-1.2	
Drug Product oxidized in 0.5% H ₂ O ₂ at 40 ±2 °C (Change from T=0)	6 hours	pH		0.1	0-0.1	0.1	Similar /similar/comparable
	0.5 hour	UV spectroscopy (mg/mL)		0.2	0-0.2	0.2	Similar /similar/comparable
	1 hour			0.2	0-0.2	0.2	
	3 hours			0.2	0-0.2	0.2	
	6 hours			0.2	0.1-0.2	0.3	
	0.5 hour	SEC	Monomer	0.1	0-0.2	0.1	Similar /similar/comparable
			HMS	-0.1	-0.2- -0.1	-0.1	
			Fragments	0	0-0.1	0	
		1 hour	Monomer	0.1	0.1	0.1	
			HMS	-0.1	-0.1	-0.1	
			Fragments	0.1	0	0.1	
		3 hours	Monomer	-0.1	-0.4-0	-0.5	
			HMS	-0.1	-0.1	-0.1	
			Fragments	0.3	0.2-0.5	0.6	
	6 hours	Monomer	-0.2	-0.1	-0.1		
HMS		-0.2	-0.1	-0.1			
Fragments		0.9	0.6-0.8	1.5			
0.5 hour	HIC	Main	-82.2	-88.6- -85.5	-80.7	Similar /similar/comparable	
		HMS	89.5	92.4-94.6	88.2		
		Fragments	-7.2	-6.9- -5.2	-7.4		



Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira		
	1 hour		Main	-82.9	-90.4- -88.2	-82.2			
			HMS	89.7	94.1-95.7	89.4			
			Fragments	-6.9	-7.0- -5.3	-7.2			
	3 hours		Main	-84.2	-89.2- -87.0	-83.2			
			HMS	89.6	91.9-93.8	89.0			
			Fragments	-5.5	-5.2- -3.7	-5.8			
	6 hours		Main	-81.5	-88.4- -86.2	-82.2			
			HMS	83.8	89.2-89.6	81.1			
			Fragments	-2.2	-3.2- -1.3	1.2			
	0.5 hour		CEX	Main	-49.6	-57.8- -55.5		-45.5	Similar /similar/comparable
				Acidic variants	-2.5	-3.2 - -1.8		-2.0	
				Basic variants	52.1	58.4-60.9		47.6	
	1 hour			Main	-47.2	-65.4- -62.4		-53.0	
				Acidic variants	-14.3	-11.7- -9.8		-5.5	
				Basic variants	61.5	73.5-75.2		58.4	
3 hours	Main	-51.4		-69.4- -66.4	-47.9				
	Acidic variants	-9.8		-8.5- -6.9	-10.2				
	Basic variants	61.1		75.0-76.2	58.0				
6 hours	Main	-50.0		-68.6- -65.0	-46.8				
	Acidic variants	-6.2		-4.9- -3.5	-1.5				
	Basic variants	56.3		69.1-72.0	48.4				
0.5 hour	nrCE-SDS	IgG		-3.7	-3.6- -2.7	-3.8	Similar /similar/comparable		
		IgG		-4.9	-4.4- -4.1	-4.6			
		IgG		-8.8	-8.2- -7.5	-9.2			
		IgG	-15.5	-13.3- -12.7	-16.7				
0.5 hour	Peptide map	MetOx 256	91.2	87.6-91.0	89.5				

Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
	1 hour		LH30 deamidation	0.2	-0.1-0.2	0	Similar /similar/comparable
			LH27 isomerization/ deamidation	0	0-0.2	-0.1	
			LH27 deamidation	0	-0.7- -0.1	0	
	MetOx 256		96.1	95.5-96.6	95.4		
	LH30 deamidation		0.1	0-0.3	0.3		
	LH27 isomerization/ deamidation		0	0-0.2	0		
	LH27 deamidation		-0.2	-0.7-0.1	0.1		
	3 hours		MetOx 256	98.3	98.7-99.2	98.0	
	LH30 deamidation		n.a.	n.a.	n.a.		
	LH27 isomerization/ deamidation		0	0-0.2	-0.2		
	LH27 deamidation		0	-0.7-0	-0.2		
	6 hours		MetOx 256	98.2	98.8-99.3	98.1	
	LH30 deamidation		n.a	n.a.	n.a.		
	LH27 isomerization/ deamidation		-0.1	-0.1-0.2	-0.1		
LH27 deamidation	0	-0.7-0	0				
Drug product held at pH 3.0, 40 ±2 °C	1 week	pH		-0.1	0.1	0	Similar /similar/comparable
	1day	UV spectroscopy (mg/mL)		-0.7	-0.8	-0.3	Similar /similar/comparable
	2 days			-0.7	-0.8- -0.7	-0.4	
	1 week			-0.5	-0.8	-0.6	
	1 day	Peptide map	LH30 deamidation	1.7	0.1-0.4	2.4	Similar /similar/comparable
LH27 isomerization/ deamidation			47.9	-0.1-0.1	44.3		
LH27 deamidation			11.6	-0.2-0.7	13.1		



Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira			
	2 days		LH30 deamidation	2.3	0.2-0.6	2.0				
			LH27 isomerization/deamidation	50.4	-0.2-0.1	45.7				
			LH27 deamidation	11.6	-0.1-0.7	11.7				
	1 week		LH30 deamidation	3.2	1.5-1.8	3.3				
			LH27 isomerization/deamidation	59.1	0-0.3	56.6				
			LH27 deamidation	11.8	0.6-1.5	11.8				
Drug product held at pH 7.5, 40 ±2 °C	1 day	SEC	Monomer	-0.3	-0.6- -0.3	-0.3	Similar /similar/comparable			
			HMS	-0.1	-0.1-0	-0.1				
			Fragments	0.4	0.3-0.6	0.4				
	2 days		Monomer	-0.4	-0.7 - -0.4	-0.5				
			HMS	-0.1	0-0.1	-0.1				
			Fragments	0.5	0.4-0.7	0.6				
	1 week		Monomer	-1.0	-1.8- -1.5	-1.2				
			HMS	0	0.5-0.6	0.1				
			Fragments	0.9	1.0-1.3	1.1				
	1 day		HIC	Main	-3.1	-4.2- -2.7		-3.2	Similar /similar/comparable	
				Oxidized variants	1.2	1.2-1.3		1.4		
				Hydrophobic variants	1.9	1.4-3.1		1.8		
				2 days	Main	-5.1		-7.5- -5.5		-5.4
					Oxidized variants	2.9		2.7-4.7		2.7
					Hydrophobic variants	2.2		2.7-3.0		2.7
1 week	Main	-15.6		-16.8- -16.3	-16.6					
	Oxidized variants	9.3		9.0-9.2	10.4					
	Hydrophobic variants	6.3		7.2-7.7	6.2					
1 day	CEX	Main	-1.8	-5.2- -3.3	-2.5	Similar/similar/comparable				
		Acidic variants	3.5	3.4-4.5	4.2					

Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira	
	2 days		Basic variants	-1.7	-1.2-1.8	-1.8	Similar/similar/comparable	
			Main	-4.7	-7.6- -7.1	-4.9		
			Acidic variants	7.2	8.4-9.0	7.6		
			Basic variants	-2.5	-1.7- -1.2	-2.7		
			Main	-24.9	-24.9- -24.4	-24.8		
			Acidic variants	22.2	27.5-28.4	22.2		
	1 week			Basic variants	2.7	-3.9- -2.7		2.7
				C-terminal variant 1K	0.2	-0.2-0.3		6.0
				C-terminal variant LH31PA	0	0-0.2		1.7
				LH30 deamidation	0.1	-0.1-0.1		-0.1
				LH27 isomerization/ deamidation	0.6	0.4-0.9		0.6
				LH27 deamidation	1.3	0.3-2.5		0.5
	1 day	Peptide map		C-terminal variant 1K	0.2	-0.4-0		0.4
				C-terminal variant LH31PA	-0.1	0-0.1		-0.1
				LH30 deamidation	0.1	-0.1-0.1		-0.1
				LH27 isomerization/ deamidation	1.2	0.8-1.5		0.6
				LH27 deamidation	2.5	2.1-3.5		1.8
2 days			C-terminal variant 1K	0.5	-0.2-0.3	0.4		
			C-terminal variant LH31PA	0	-0.1-0.1	0		
			LH30 deamidation	0.1	-0.1-0.1	-0.1		
			LH27 isomerization/ deamidation	4.2	4.1-5.2	3.9		
			LH27 deamidation	8.1	7.2-8.9	7.6		
1 week			C-terminal variant 1K	0.5	-0.2-0.3	0.4		
			C-terminal variant LH31PA	0	-0.1-0.1	0		
			LH30 deamidation	0.1	-0.1-0.1	-0.1		
			LH27 isomerization/ deamidation	4.2	4.1-5.2	3.9		
			LH27 deamidation	8.1	7.2-8.9	7.6		



Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
Drug product held at pH 8.5, 40 ± 2°C	1 week	pH		-0.3	-0.3- -0.2	-0.3	Similar/similar/comparable
	1 day	UV spectrometry (mg/mL)		0	0-0.1	0.1	Similar/similar/comparable
	2 days			0	-0.1-0.1	0.1	
	1 week			0.1	0-0.1	0.1	
	1 day	SEC	Monomer	-0.4	-0.4-0	-0.6	Similar/similar/comparable
			HMS	-0.1	-0.1	-0.1	
			Fragments	0.5	0.1-0.4	0.7	
		2 days	Monomer	-0.5	-0.6-0	-0.9	
			HMS	-0.2	-0.1-0	-0.1	
			Fragments	0.7	0.1-0.6	1.0	
		1 week	Monomer	-1.4	-1.6- -1.3	-2.7	
			HMS	-0.1	-0.1-0	0.2	
			Fragments	1.5	1.3-1.6	2.5	
	1 day	HIC	Main	-3.9	-3.5- -3.1	-3.8	Similar/similar/comparable
			Oxidized variants	2.9	2.5-2.6	2.7	
			Hydrophobic variants	1.0	0.6-1.1	1.1	
		2 days	Main	-8.0	-6.9- -6.8	-8.2	
			Oxidized variants	5.8	4.5-5.4	5.9	
			Hydrophobic variants	2.1	1.4-2.4	2.2	
	1 week	Main	-17.8	-21.5- -20.8	-17.5		
Oxidized variants		12.6	15.1-16.3	11.9			
Hydrophobic variants		5.2	4.7-5.8	5.6			
1 day	CEX	Main	-4.2	-6.2- -5.5	-4.2	Similar/similar/comparable	
		Acidic variants	6.8	7.1-7.8	7.0		
		Basic variants	-2.6	-2.0- -1.4	-2.8		
	2 days	Main	-8.9	-12.7- -11.4	-8.7		
		Acidic variants	12.9	14.1-14.8	12.9		
		Basic variants	-4.0	-2.7- -2.1	-4.3		



Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
	1 week		Main	-36.3	-36.7- -34.6	-35.2	Similar/similar/comparable
			Acidic variants	36.1	40.2-41.1	35.7	
			Basic variants	0.2	-5.6- -4.3	-0.5	
	1 day	Peptide map	C-terminal variant 1K	0.2	-0.3-0.3	0.5	
			C-terminal variant LH31PA	-0.1	0.1	-0.1	
			LH30 deamidation	0	-0.2-0	-0.2	
			LH27 isomerization/ deamidation	0.9	0.1-0.4	0.3	
			LH27 deamidation	3.2	2.4-3.2	3.5	
			2 days	C-terminal variant 1K	0.2	-0.2-0.4	
	C-terminal variant LH31PA	-0.1		0-0.1	-0.1		
	LH30 deamidation	0		-0.2-0	-0.3		
	LH27 isomerization/ deamidation	1.7		1.2-2.2	1.6		
	LH27 deamidation	6.1		5.3-6.0	6.1		
	1 week	C-terminal variant 1K	0.4	-0.1-0.5	0.5		
		C-terminal variant LH31PA	-0.1	0-0.1	-0.1		
LH30 deamidation		0	-0.2-0	-0.2			
LH27 isomerization/ deamidation		6.5	6.7-7.4	6.9			
LH27 deamidation		17.1	15.9-16.7	16.9			
Light	14 hours	pH		0	0-0.1	0	Similar/similar/comparable
	7 hours	UV spectrometry (mg/mL)		-0.2	-0.9-0.1	-0.2	Similar/similar/comparable
	14 hours			-0.1	-0.1-0.7	0	
	7 hours	SEC	Monomer	-0.9	-1.8- -1.0	n.a.	Similar/similar/comparable
HMS			0.6	0.9-1.3	9.3		
Fragments			0.2	0.1-0.5	7.2		



Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira	
	14 hours		Monomer	-2.8	-4.0- -2.9	-2.5		
			HMS	2.2	2.4-3.3	1.8		
			Fragments	0.6	0.5-0.8	0.7		
	7 hours	HIC	Main	-24.9	-17.0- -15.2	n.a.	Similar/similar/comparable	
			Oxidized variants	27.7	15.1-17.1	n.a.		
			Hydrophobic variants	-2.8	-0.9-0	n.a.		
			14 hours	Main	-45.2	-46.6- -28.8		-41.5
				Oxidized variants	48.9	29.2-47.4		44.2
				Hydrophobic variants	-3.7	-0.9- -0.1		-2.7
	7 hours	CEX	Main	-18.9	-14.0- -6.1	n.a.	Similar/similar/comparable	
			Acidic variants	3.1	3.9-5.4	72.9		
			Basic variants	15.8	1.5-10.0	-23.2		
			14 hours	Main	-32.0	-25.6- -18.3		-29.0
				Acidic variants	9.3	8.5-22.7		4.4
				Basic variants	22.7	2.4-16.8		24.6
7 hours	nrCE-SDS	IgG	-3.4	-4.1- -3.8	n.a.	Similar/similar/comparable		
14 hours		IgG	-7.8	-9.3- -7.7	-7.2			
Drug product Freeze/thawing	5 times	UV spectrometry (mg/mL)		0.1	0.1	0.1	Similar/similar/comparable	
	10 times			0.1	0-0.1	0.2		
	5 times	SEC	Main	-0.1	-0.1-0	0	Similar/similar/comparable	
			HMS	0	0-0.1	0		
			Fragments	0	0	-0.1		
	10 times		Main	0	-0.1-0	0.1		
			HMS	0	0-0.1	0		
			Fragments	0	0	0		
	5 times	nrCE-SDS	IgG	-0.3	-0.1-0.2	0.1	Similar/similar/comparable	
	10 times		IgG	0	-0.3-0.2	0.2		
	1 week	pH		-0.1	-0.1	0	Similar/similar/comparable	
	1 day	UV spectrometry (mg/mL)		0	-0.1-0	0		

Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
Drug product in metal ion of 1 µM Cu(II) at 40 ± 2°C	2 days			0	0	0	
	1 week			0	0	0	
	1 day	SEC	Monomer	0.5	0.5-0.8	0.6	Similar/similar/comparable
			HMS	0	-0.1-0	0	
			Fragments	-0.5	-0.8- -0.4	-0.6	
	2 days		Monomer	0.4	0.3-0.5	0.4	
			HMS	0	0	0	
			Fragments	-0.4	-0.4- -0.3	-0.4	
	1 week		Monomer	-0.1	-0.2-0	-0.1	
			HMS	0	0	0	
			Fragments	0.1	0-0.1	0.1	
	1 day	HIC	Main	1.7	1.8-2.9	2.8	Similar/similar/comparable
			Oxidized variants	-0.9	-1.4 - -0.3	-1.0	
			Hydrophobic variants	-0.8	-1.6- -1.2	-1.8	
	2 days		Main	1.9	1.3-2.1	2.2	
Oxidized variants			-0.9	-0.9 - -0.1	-0.6		
Hydrophobic variants			-1.0	-1.6- -1.1	-1.6		
1 week	Main		0.4	-0.4-0.2	0.6		
	Oxidized variants		-0.7	0-0.3	-0.3		
	Hydrophobic variants		0.2	-0.2-0.2	-0.3		
	1 week	nrCE-SDS	IgG	0.1	-0.2-0	-0.1	Similar/similar/comparable
Drug product was vortex at full speed at 23-25 °C	60 seconds	UV spectrometry (mg/mL)		0.2	0.2-0.3	0.2	Similar/similar/comparable
	180 seconds			0.2	0.2-0.3	0.2	
	60 seconds	SEC	Monomer	0	-0.1-0	0.1	Similar/similar/comparable
			HMS	0	0-0.1	0	
			Fragments	0	0	-0.1	
	180 seconds		Monomer	0	-0.1-0	0.1	
HMS			0	0-0.1	0		
Fragments			0	0	-0.1		



Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
	60 seconds	nrCE-SDS	IgG	0	0.1-0.2	0.2	Similar/similar/comparable
	180 seconds		IgG	-0.5	-0.1-0.1	-0.2	
Drug product was shake horizontally at 180 rpm at 23-25°C	6 hours	UV spectrometry (mg/mL)		0.3	0.3	0.2	Similar/similar/comparable
	16 hours			0.2	0.2-0.3	0.2	
	6 hours	SEC	Monomer	0.1	-0.1-0	0.1	Similar/similar/comparable
			HMS	0	0-0.1	0	
			Fragments	-0.1	-0.1-0	-0.1	
	16 hours		Monomer	0.1	-0.1-0.1	0.1	
			HMS	0	0-0.1	0	
			Fragments	-0.1	-0.1-0	-0.1	
	6 hours	nrCE-SDS	IgG	-0.3	0-0.1	0.1	Similar/similar/comparable
			16 hours	IgG	-0.7	-0.6-0.4	
Drug product was stirred with 600 rpm at 23-25°C	1 hour	UV spectrometry (mg/mL)		0.1	0	0	Similar/similar/comparable
	6 hours			0	-0.1-0	0	
	16 hours			0	-0.1-0	0	
	1 hour	SEC	Monomer	-0.3	-0.1-0.2	-0.1	Similar/similar/comparable
			HMS	0	0-0.2	0	
			Fragments	0.3	-0.2-0	0	
	6 hours		Monomer	0	-0.7-0.6	0	
			HMS	0	-0.1-0.3	0	
			Fragments	0	-0.5-0.4	0	
	16 hours		Monomer	0	-0.1-0.1	0	
			HMS	0	0-0.1	0	
			Fragments	0	-0.2-0	0	
	1 hour	nrCE-SDS	IgG	-0.2	-0.1-0.5	0.3	Similar/similar/comparable
	6 hours		IgG	0	-0.3-0.5	0.2	
	16 hours		IgG	0.3	-1.0-0.3	0	
Drug product in 0.1 mM DTT at 40 °C	1 minute	UV spectrometry (mg/mL)		0.2	-0.1-0	0.1	Similar/similar/comparable
	5 minutes			0	-0.2-0.3	0.1	

Stress Conditions	Duration	Analytical methods	Quality Attributes	US-licensed Humira Batch #1017236	GP2017 DP min – max (4 batches)	EU-approved Humira Batch #34434XD11	GP vs. US-licensed Humira / GP vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
	20 minutes			0	-0.3-0	0	
	1 minute	nrCE-SDS	IgG	-10.1	-10.4- -8.6	-9.5	Similar/similar/comparable
	5 minutes		IgG	-35.2	-36.5- -33.9	-33.2	
	20 minutes		IgG	-69.3	-70.3- -70.8	-67.3	

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

The anti-drug antibody (ADA) responses in patients treated with adalimumab are well documented. The sponsor developed immunogenicity assays to detect the presence of ADA and to characterize the potential presence of neutralizing antibody (NAb) in the proposed clinical studies. The summary of immunogenicity assays used in the clinical studies is provided in Reviewer Table 1 below.

Reviewer Table 1. Summary of immunogenicity assays used in the clinical studies.

	GP17-101	GP17-102 GP17-103 GP17-104	GP17-301
ADA assay	BA-13009-R <ul style="list-style-type: none"> • Drug tolerance = 40 µg/mL • Sensitivity = 31 ng/mL 		BA-14014-R <ul style="list-style-type: none"> • Drug tolerance = 40 µg/mL • Sensitivity = 51 ng/mL
NAb assay	BA-13016-R <ul style="list-style-type: none"> • Drug tolerance = 3 – 6 µg/mL • Sensitivity = 320 ng/mL 	BA-15002-R <ul style="list-style-type: none"> • Drug tolerance = 40 µg/mL • Sensitivity = 107 ng/mL in HV serum = 152 ng/mL in psoriasis serum = 202 ng/mL in RA serum 	

ADA assay

The proposed ADA testing is established via a three-tiered approach including screening, confirmatory and titring. To detect the ADA in the serum samples, an electrochemiluminescence (ECL) bridging experiment is developed. To conduct the screening assay, serum samples are first subjected to an acid treatment to dissociate the pre-formed complexes. Samples are then added to GP2017-F(ab')₂-fragment coated plate for incubation. After removal of unbound molecules, ADAs are retrieved from the plate by a second acid treatment. With the addition of GP2017-biotin and GP2017-sulfotag, ADAs form a bridge between two labels. The complexes are then added to a streptavidin-coated MesoScale Discovery (MSD) plate. The signal readout is obtained from an ECL reaction and measured by a MSD plate reader.

If the resulting signal is higher than the screening cut-point (SCP), the sample will be further confirmed by a confirmatory assay. The confirmatory assay is a competitive inhibition test in which serum samples are spiked with excess amount of GP2017 and compared with unspiked samples. Specific ADAs will bind to the spiked GP2017, which will result in a signal reduction in comparison with the unspiked samples. If the % depletion meets the confirmatory cut-point (CCP), the sample is reported as confirmed positive for ADAs.

An ADA titer assay is performed by preparing a dilution series of test samples. The fold dilution of the most diluted sample that exhibits a signal above the SCP is defined as the ADA titer.

Two ADA assays, BA-13009-R and BA-14014-R, are developed for the clinical studies. The assay validation results are summarized in Reviewer Table 2 below. Of note, in BA-14016-R the sponsor reports the results of the ADA determination in serum samples from study GP17-3017. Because the percentage of ADA positive pre-dose samples is significantly higher than 5%, the sponsor established a GP17-3017 study specific screening cut point.

Reviewer Table 2. Validation results for BA-13009-R and BA-14014-R.

	BA-13009-R	BA-14014-R	Reviewer Comments
Positive control (PC) preparation	Rabbit anti- adalimumab F(ab') ₂ - polyclonal antibody. PC is prepared by hyperimmunization of rabbits with adalimumab F(ab') ₂ fragments and affinity purification of		PC is also used as the reference item to prepare quality control (QC) samples and calibration samples.

	the polyclonal antibody. The reagent is provided by (b) (4).		
Low positive control (LPC)	LPC (43 ng/mL) must be above both SCP and CCP	LPC (83 ng/mL) must be above both SCP and CCP	<i>The proposed criteria of passing both SCP and CCP correlates to 1% and 0.1% false-positive rates in BA-13009-R and BA-14014-R, respectively. This is sufficient to confirm the selection of LPC.</i>
Matrix and blank	Healthy human serum pool. The blank is prepared in 1:2 dilution.		<i>The signals of blank samples must be below SCP. The use of healthy human serum pool as the matrix control is acceptable.</i>
Selectivity	Matrix tolerance is evaluated using 10 individual human sera from healthy donors. The serum samples are spiked with 400 and 9600 ng/mL of PC. The spiked samples are compared to the calibration curve with 80 – 120% accuracy. The signals of spiked samples need to be above SCP.	Matrix tolerance is evaluated using 10 individual human sera of patients with psoriasis. The serum samples are spiked with LPC. The signals of spiked samples must be above SCP, matrix components appear not to interfere with the detection of ADAs.	<i>In study BA-13009-R, the sponsor reports that only four out of ten samples fulfill the accuracy criterion of 80 – 120%. From data provided in Appendix 2, these excursion results (125 – 140%) are marginally off the upper limit of 120%. It cannot be ruled out that these differences are related to inter-assay variability. As the ECL signals still meet the SCP, the study is adequate to support assay selectivity.</i>
Assay range	400 – 12800 ng/mL		<i>According to section 2.7.2 – Summary of Clinical Pharmacology Studies, I agree that this assay range is sufficient to detect ADA in patient serum samples</i>
Screening cut-point (SCP)	Floating: blank + 11.0	Floating: blank x 1.13	<i>The number of 50 serum samples is statistically sufficient to establish the SCP. Per Draft Guidance[†], a 5% false-positive rate is suitable to assess the screening positive results. Note that in BA-14016-R, the floating SCP is established as blank x 1.16 with the same statistical justification. With the assessments above, I agree that SCP is validated for both studies.</i>
	The SCP is established by using 50 individual patient serum samples measured in a 1:2 dilution three times by two analysts. In total, 300 individual results are obtained. As different mean values are often obtained from different runs, a floating CP is preferred. The floating SCP is then determined as the average signal of blank sample added or multiplied by a normalization factor. The normalization factor is calculated to reflect a statistical 5% false-positive rate.		
Confirmatory cut-point (CCP)	23% inhibition	21% inhibition	<i>The number of 50 serum samples is statistically sufficient to calculate the CCP. Per Draft Guidance[†], a 0.1% false-positive rate is well within the acceptable false-positive range to confirm the screening positive results.</i>
	The 50 individual patient serum samples used to establish SCP are spiked with excess (20 µg/mL) of GP2017 and compared with the respective unspiked samples. The analysis is performed three times by two analysts. The inhibition rate is defined as 100% x (1 – (GP2017 spiked samples/unspiked samples)). The CCP is statically established to include a 0.1% false-positive rate.		
Drug tolerance	40 µg/mL		<i>In section 2.7.2 – Summary of Clinical Pharmacology Studies, the detected GP2017 serum concentration range is 5 – 10 µg/mL. The validation range of 0.1 – 40 µg/mL GP2017 is sufficient to cover the drug concentration in the serum samples.</i>
	PC samples at 400, 1200, and 9600 ng/mL are prepared in 100% patient serum pool. These PC samples are mixed with serial dilutions of GP2017, ranging from 0.1 to 40 µg/mL. The drug tolerance limit is defined as the highest drug concentration at which the signal is ≥ SCP.		

Target tolerance	2000 pg/mL	1000 pg/mL	<i>The reported physiological level of TNF alpha is about 40 pg/mL in patients with psoriasis. The target tolerance limits are acceptable.</i>
Sensitivity	31 ng/mL	51 ng/mL	<i>The 5% false-positive rate is consistent with the same rate used to establish SCP and therefore, is acceptable. The numbers of six dilution series and six dilution steps are sufficient to perform a fitting to a regression model. The determined assay sensitivities are well within the recommended range in draft guidance[†].</i>
	Sensitivity is defined as the lowest PC concentration that consistently exhibits a signal \geq SCP. PC samples are prepared in six dilution series with more six dilution steps. The serial dilution concentration range includes the SCP. The results are fitted to a regression model to interpolate the concentration corresponding to the SCP. The sensitivity is determined with a 5% false-positive rate.		
Precision	CV \leq 20%		<i>Per draft guidance[†], the proposed acceptance criterion of CV \leq 20% for assay precision is acceptable. The validation results are well within the limit.</i>
	Intra-assay precision: five sets of validation samples are prepared and compared to the calibration curve. Inter-assay precision: one set of validation samples performed in six different runs in six different days.		
Accuracy	80 – 120% and total error \leq 30%		<i>Per draft guidance[†], the proposed acceptance criteria are acceptable. The validation results are well within the limit.</i>
Stability	<ul style="list-style-type: none"> • 5 freeze/thaw cycles with 80 – 120% accuracy • Stability at 2 – 8°C for 3 days with 80 – 120% accuracy • Stability at room temperature for 24 hours with 80 – 120% accuracy • Stability at -20°C for 3 months in BA-13009-R and for 12 months in BA-14014-R. Stability at -70°C for 10 months in BA-13009-R and for 12 months in BA-14014-R. Both are with 80 – 120% accuracy. 		<i>Three aliquots at two different concentrations are tested at the proposed storage conditions. The proposed 80 – 120% accuracy is suitable to validate the stability. In both methods, the proposed storage conditions are supported by the stability data.</i>

[†]Draft Guidance, Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (2016).

Additional reviewer comments:

- *The methodology of three-tiered ADA assay meets the general recommendation provided in the draft guidance for immunogenicity assay validation (2016). Based on the validation experiments, the established assay parameters including cut points and drug tolerance limits are sufficient and suitable for the intended clinical studies.*
- *The validation parameters reported in BA-14016-R are essentially the same as those established in BA-14014-R except the GP17-301 study specific assay cut point. In BA-14016-R, the floating SCP is blank x 1.16 while in BA-14014-R, the floating SCP is blank x 1.13. In both cases, the cut points are established via analyzing 50 drug-naïve serum samples of psoriasis patients in three independent runs on three days by two analysts. This validation approach is acceptable for both methods. During the original testing of samples from clinical study GP17-301, 29% of the first 296 pre-dose serum samples are found above the BA-14014-R SCP. This fraction is significantly higher than the 5% false-positive rate. To achieve the statistical 5% false-positive rate, a GP17-301 study specific SCP was established based on the available pre-dose serum samples (n = 296) at that time. The SCP is changed from blank x 1.13 to blank x 1.16. The confirmatory cut point remains unchanged as the one established in BA-14014-R. Because the number of pre-dose samples (n = 296) is sufficient and the 5% false-positive rate is sustained, I agree with the modified SCP used in the GP17-301 clinical study.*

Neutralizing antibody (NAb) assay

Serum samples confirmed as ADA positive are further tested for neutralizing ADAs. The method BA-13016-R is used to test samples from healthy volunteers (HV) and BA-15002-R is used to test samples from HV and patients with psoriasis or rheumatoid arthritis (RA).

The proposed NAb assay is based on competitive ligand binding to characterize the neutralizing ability to GP2017. Serum samples are first subjected to an acid treatment to dissociate the pre-formed antibody complexes. Subsequently, samples are added to GP2017-F(ab')₂ coated plate to anchor down ADAs. The second acid wash is performed to dissociate surface-bound ADAs from immobilized GP2017-F(ab')₂. ADAs then are incubated with GP2017-biotin and transferred to a TNF-alpha coated plate. If ADAs do not exhibit neutralizing ability, GP2017-biotin could bind to TNF-alpha and result in an ELISA signal, generated by horseradish-peroxidase (HRP) labeled streptavidin and trimethylbenzidine (TMB) as substrate. If NABs are present in the sample, a reduction of assay signal would be observed when compared to a negative control sample. The sample is reported as positive for neutralizing ADAs when the inhibition signal is equal to or greater than the assay cut-point.

The assay validation results are summarized in Reviewer Table 3 below.

Reviewer Table 3. Validation results for BA-13016-R and BA-15002-R.

	BA-13016-R	BA-15002-R	Reviewer Comments
Preparation of test item (positive control, PC)	Monoclonal human anti-adalimumab antibody is provided by (b) (4). Validation samples (VS) are prepared by adding defined concentrations of test item to serum samples obtained from HV or disease populations.		<i>Monoclonal human anti-adalimumab antibody is also used as the reference item to prepare quality control (QC) samples and calibration samples.</i>
Low positive control (LPC) in 100% serum	398 ng/mL LPC is selected close to and above the cut-point. This selection will allow a failure rate of 1%.	<ul style="list-style-type: none"> • HV: 156 ng/mL • Psoriasis: 190 ng/mL • RA: 260 ng/mL 	<i>The proposed criterion of passing assay cut point correlates to 1% false-positive rates. This is sufficient to confirm the selection of LPC.</i>
Matrix and blank	HV serum pool is provided by (b) (4). The matrix is prepared in 1:2 dilution.	<ul style="list-style-type: none"> • HV serum pool is provided by (b) (4). • Psoriasis serum pool is provided by (b) (4). • RA serum pool is provided by (b) (4). All three matrix components are prepared in 1:2 dilution.	<i>The signals of matrix samples (blanks) must be below the assay cut-point. The selection of the matrix control is acceptable.</i>
Selectivity	Matrix tolerance is evaluated using 10 individual human sera from healthy donors. The serum samples are spiked with two different concentrations of PC. The spiked samples are compared to the calibration curve with 80 – 120% accuracy. The signals of spiked samples need to be above the cut-point.	Matrix tolerance is evaluated using 10 serum samples from HV, patients with psoriasis and RA. The serum samples are spiked with LPC. To fulfill the acceptance criteria, the signals of LPC samples should be above cut-point while the matrix components should be below the cut-point.	<i>The number of test samples (n = 10) is statistically sufficient to conduct the validation experiment. In study BA-15002-R, all samples from HA and psoriasis patients meet the acceptance criteria. Only one sample from RA patients cannot pass the cut-point. This impact on matrix tolerance is minimal. In BA-13016-R, four out of ten serum samples cannot fulfill the accuracy criterion of 80 – 120%. These deviations (122 – 136%) could be interpreted as the experimental errors caused by the calibration curve preparation. Overall, both</i>

			<i>studies are adequate to support assay selectivity.</i>
Assay range	400 – 8000 ng/mL	106 – 800 ng/mL	<i>The assay linear range is established by six data points in BA-13016-R and seven data points in BA-15002-R, both with $R^2 \geq 0.999$. This is acceptable.</i>
Assay cut-point	<p>$\geq 23\%$ inhibition</p> <p>% inhibition is defined as = $100 [1 - ((OD_{\text{individual+biotin-GP2017}}) - (OD_{\text{individual}}) / (OD_{\text{human+biotin-GP2017}}) - (OD_{\text{human}})))]$</p>	<ul style="list-style-type: none"> • HV: floating, \leq control OD – 0.118 • Psoriasis: fixed, $\geq 13\%$ inhibition <p>% inhibition is defined as = $100 [1 - (OD_{\text{individual+biotin-GP2017}} / OD_{\text{human+biotin-GP2017}})]$</p> <ul style="list-style-type: none"> • RA: floating, \leq control OD x 0.83 	<i>The number of 50 serum samples is statistically sufficient to establish the assay cut-point. A 0.1 % false-positive rate is suitable to assess the positive results.</i>
	The cut-point is established by using 50 serum samples from HV (in BA-15002-R, 50 serum samples from HV, 50 from psoriasis patients and 50 from RA patients) in three runs on three different days. Each assay cut point is calculated to reflect a statistical 0.1 % false-positive rate.		
Drug tolerance	<ul style="list-style-type: none"> • 3 $\mu\text{g/mL}$ at VS1 • 0.5 $\mu\text{g/mL}$ at VS3 • 0.1 $\mu\text{g/mL}$ at LLOQ 	40 $\mu\text{g/mL}$	<i>In section 2.7.2 – Summary of Clinical Pharmacology Studies, the detected GP2017 serum concentration range is 5 – 10 $\mu\text{g/mL}$. The drug tolerance of 40 $\mu\text{g/mL}$ established in BA-15002-R is sufficient to cover the drug concentration in the serum samples. Thought the drug tolerance limit in BA-13016-R is lower than the detected drug concentration values, the intended clinical study GP17-101 (see above, Reviewer Table 1. Summary of immunogenicity assays used in the clinical studies) will not be used for PK similarity assessment. Therefore, the impact of low drug tolerance limit in BA-13016-R is minimized.</i>
	PC samples are prepared in 100% patient serum pool. These PC samples are mixed with serial dilutions of GP2017, ranging from 1 to 20 $\mu\text{g/mL}$ (in BA-15002-R, GP2017 ranging from 5 to 40 $\mu\text{g/mL}$). The drug tolerance limit is defined as the highest drug concentration that does not prevent the detection of PC samples \geq assay cut-point.		
Target tolerance	100 ng/mL	100 ng/mL	<i>The reported physiological level of TNF alpha is significantly lower than the target tolerance.</i>
Sensitivity	320 ng/mL	<ul style="list-style-type: none"> • HV: 107 ng/mL • Psoriasis: 152 ng/mL • RA: 202 ng/mL 	<i>The 5% false-positive rate is consistent with the same rate used to establish assay cut-point and therefore, is acceptable. The numbers of dilution series and validation runs are sufficient to perform the fitting to a regression model. Overall, I agree with the validation experiments.</i>
	Sensitivity is defined as the lowest PC concentration that consistently exhibits a positive signal. PC samples are prepared in seven dilution series (five dilution series in BA-15002-R) and performed in six runs. The dilution range includes the cut-point concentration. The results are fitted to a regression model to interpolate the concentration corresponding to the assay cut-point. The sensitivity is determined with a 5% false-positive rate.		
Precision	CV $\leq 20\%$		

	Intra-assay precision: five sets of validation samples are prepared and compared to the calibration curve. Inter-assay precision: one set of validation samples performed in six different runs in six different days.	<i>Per draft guidance[†], the proposed acceptance criterion of CV ≤ 20% is acceptable. In BA-15002-R, one set of data is reported as an outlier due to very low values. The validation results are adequate.</i>
Accuracy	80 – 120% and total error ≤ 30%	<i>Per draft guidance[†], the proposed acceptance criteria are acceptable. The validation results are well within the limit.</i>
Stability	<ul style="list-style-type: none"> • 5 freeze/thaw cycles with 80 – 120% accuracy • Stability at 2 – 8°C for 3 days with 80 – 120% accuracy • Stability at room temperature for 24 hours with 80 – 120% accuracy • Stability at -20°C for 3 months. Stability at -70°C for 10 months. Both are with 80 – 120% accuracy. 	<i>Three aliquots at two different concentrations are tested at the proposed storage conditions. The proposed 80 – 120% accuracy is suitable to validate the stability.</i>

[†]Draft Guidance, Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (2016).

Additional reviewer comments:

- *The validation of BA-15002-R is performed on 33 different days in 75 different runs. The QC samples do not exhibit any visually significant trends in these 75 runs (Figures 5-1 and 5-2 in BA-15002-R submission). This supports the assay robustness of BA-15002-R.*

When compared to BA-15002-R, BA-13016R exhibits a lower assay sensitivity and drug tolerance limit. While the validation results may not appear as sensitive as BA-15002-R, the intended GP17-101 clinical study is not used to support PK similarity assessment. The validation results of BA-13016-R would have little impact on the overall similarity assessment in the current BLA.

- *From Table 4-2 and Table 4-3 (data provided in section 2.7.2 – Summary of Clinical Pharmacology Studies, pages 84 and 85, respectively), no significant differences are found in ADA positive rates and NAb rates in five clinical studies. A statistical analysis of the comparisons is deferred to the clinical pharmacology reviewer.*



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From: Michael Shanks, Biologist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Biologic License Application for GP2017 (Adalimumab) that is a biosimilar* to Humira® (adalimumab) injection
US License: 2003
Applicant: Sandoz Inc.
Mfg Facility: Drug Substance:
Sandoz GmbH Schaftenau, Biochemiestrasse 10, Langkampfen, Austria FEI
3004828473

(b) (4)

Drug Product:
(b) (4)

Proposed Trade Name: To be determined
Nonproprietary Name: To be determined. Referred to as “GP2017 (Adalimumab)” by the applicant*)
Dosage: GP2017 is presented in pre-filled syringe of 40 mg/0.8 mL to be administered via subcutaneous injection.
Indication: GP2017 is indicated for the treatment of Rheumatoid Arthritis; Juvenile Idiopathic Arthritis; Psoriatic Arthritis; Ankylosing Spondylitis; Adult Crohn's Disease; Ulcerative Colitis; Plaque Psoriasis.
Due Date: 10/30/2018

RECOMMENDATION: This application is recommended as APPROVE from a facility review perspective.

SUMMARY

The subject BLA proposes the manufacture of GP2017 (Adalimumab) that is a biosimilar to Humira® (adalimumab) injection. Sandoz Inc.'s GP2017 Drug Substance (DS) and Drug Product (DP) is a recombinant human immunoglobulin IgG1 type monoclonal antibody specific for TNFα. The starting material, is a Chinese Hamster Ovary (CHO)

(b) (4)
(b) (4)

(b) (4)
(b) (4)
(b) (4)
The DS manufacturing process is performed at Sandoz GmbH (Langkampfen, Austria).

The GP2017 DP manufacturing process involves (b) (4)
(b) (4)

A pre-license inspection for GP2017 Drug Substance was conducted on 02/15-20/2018 at Sandoz GmbH (Langkampfen, Austria). A four-item FDA Form 483 was issued, and the initial recommendation is approve for this BLA. A final classification of the Sandoz GmbH pre-license inspection was acceptable. Additionally, a pre-license inspection for GP2017 Drug Substance was also conducted on (b) (4) at (b) (4). A five-item FDA Form 483 was issued, and the initial recommendation is approve for this BLA. A final classification of the (b) (4) pre-license inspection was acceptable.

Regarding the GP2017 drug product manufacturing at (b) (4) (b) (4) a four-item FDA Form 483 was issued at the conclusion of a surveillance inspection that occurred on (b) (4). A final classification of the (b) (4) inspection was VAI and found acceptable. The pre-approval inspection for Drug Product site was waived because of the sites compliance status and its recent inspection.

The Drug Substance and Drug Product manufacturing sites, Sandoz GmbH, (b) (4), and (b) (4), were approved based on their inspections and/or compliance status. All other related manufacturing and testing facilities have an acceptable compliance status.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

3.2.S Drug Substance [Substance – Manufacturer]

3.2.S.2. Manufacture

3.2.S.2.1 DS Manufacturers.

The sites proposed for GP2017 Drug Substance manufacture and testing activities are presented below in Table 1.

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CONCLUSION

Descriptions provided for the Sandoz GmbH Langkampfen (FEI 3004828473) and (b) (4) for the manufacture of GP2017 Drug Substance and the (b) (4) for the manufacture of Drug Product facilities as proposed in BLA 761071 were reviewed. All other related manufacturing and testing facilities have an acceptable compliance status. The current compliance status for the proposed DS and DP manufacturing is **acceptable** and a recommended of **approve** is made from a facilities assessment standpoint.

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