CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761154Orig1s000

PRODUCT QUALITY REVIEW(S)

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	June 1, 2020
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Bruce Huang, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research II
Application:	BLA 761154
Applicant:	Mylan GmbH
Submission Date:	July 12, 2019
Product:	Hulio (adalimumab-fkjp)
Dosage form(s):	injection
Strength and Container-Closure:	40 mg/0.8 mL in a single-dose prefilled pen (HULIO Pen) 40 mg/0.8 mL in a single-dose prefilled syringe 20 mg/0.4 mL in a single-dose prefilled syringe
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The Prescribing Information, Medication Guide, Instructions for Use, Quick Reference Guide, container labels, and carton labeling submitted on May 28, 2020 are acceptable from an OBP labeling perspective.

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

(b) (4)

[redacted]

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A

[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.

Recommended labeling practices (placement of dosage form outside of parenthesis or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Labeling submitted on July 12, 2019 had the correct manufacturer's name, address, and US license number which corresponds to the manufacturer listed on FDA form 356h. Labeling submitted on March 26, 2020 was revised incorrectly to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No 2062". Revised to the licensed applicant (manufacturer) as provided on Form FDA 356h ("Manufactured by: Mylan GmbH, Turmstrasse 24, 6312 Steinhausen, Switzerland US license No 2062").
Applicant's response: Mylan acknowledges the Agency's comment…Mylan submitted an administrative update to the application on April 17, 2020 to transfer ownership/licensure of this application from Mylan GmbH to Mylan Pharmaceuticals Inc…Given the minor nature of the change in applicant name, it is our understanding that the currently assigned U.S. License Number 2062 will be reissued to Mylan Pharmaceuticals Inc. as part of the revocation and reissuance process. Accordingly, we wish to retain reference to Mylan Pharmaceuticals Inc. on all proposed labeling components so that this product will reflect the correct applicant at the time final regulatory action is taken.

OBP labeling's response: We acknowledge the transfer of ownership submission but also understand that the revocation and reissuance process is not yet complete. At this time, it is not certain that the process will assign the U.S. License Number 2062 to Mylan Pharmaceuticals Inc. as such, we ask that a placeholder be used for the US license number. The U.S license number is provided the approval letter and can be applied to the final labels and labeling. Please revise to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No XXXX".
The Applicant revised as requested

[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	☐ Yes ☐ No ☒ N/A

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located

Applicant's response: Mylan acknowledges the Agency's request and confirms that placement of the labels (once affixed) will allow for visual inspection by the patient. The syringe label is clear and allows full length and circumference visibility. See the 'Viewing Window' in Figure A.

(b) (4)

The Applicant's response is acceptable

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

***NDC numbers* (container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: space considerations

Misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☐ Yes ☐ No ☒ N/A

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Dispensing container (container label)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package[6] Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	Acceptable
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Labeling submitted on July 12, 2019 had the correct manufacturer's name, address, and US license number which corresponds to the manufacturer listed on FDA form 356h. Labeling submitted on March 26, 2020 was revised incorrectly to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No 2062". Revised to the licensed applicant (manufacturer) as provided on Form FDA 356h ("Manufactured by: Mylan GmbH, Turmstrasse 24, 6312 Steinhausen, Switzerland US license No 2062").
Applicant's response: Mylan acknowledges the Agency's comment…Mylan submitted an administrative update to the application on April 17, 2020 to transfer ownership/licensure of this application from Mylan GmbH to Mylan Pharmaceuticals Inc…Given the minor nature of the change in applicant name, it is our understanding that the currently assigned U.S. License Number 2062 will be reissued to Mylan Pharmaceuticals Inc. as part of the revocation and reissuance process. Accordingly, we wish to retain reference to Mylan Pharmaceuticals Inc. on all proposed labeling components so that this product will reflect the correct applicant at the time final regulatory action is taken.

OBP labeling's response: We acknowledge the transfer of ownership submission but also understand that the revocation and reissuance process is not yet complete. At this time, it is not certain that the process will assign the U.S. License Number 2062 to Mylan Pharmaceuticals Inc. as such, we ask that a placeholder be used for the US license number. The U.S license number

[6] 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.

is provided the approval letter and can be applied to the final labels and labeling. Please revise to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No XXXX". The Applicant revised as requested

Lot number or other lot identification (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the statement "No preservative" to all tray labeling per 21 CFR 610.61(e) *The Applicant revised as requested*

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the ingredient list appearing on all carton labeling to read as follows: "Each 0.8 mL [or 0.4 mL] single-dose prefilled syringe [or prefilled pen] contains 40 mg [or 20 mg] of adalimumab-xxxx, methionine (xx mg), monosodium glutamate (xx mg), polysorbate 80 (xx mg), sorbitol (xx mg) and Water for Injection, USP. Hydrochloric acid is added as necessary to adjust pH."
The Applicant revised as requested

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the statement "No U.S. Standard of potency" to all tray labeling per 21 CFR 610.61(r)
The Applicant revised as requested

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize	✓ Yes ☐ No

Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	✓ Yes ☐ No ☐ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Consider deleting the redundant statement "Prefilled pen [syringe] for Single Dose Only" appearing on all tray labeling or consider revising to read "Prefilled pen [syringe] is for one time use only".

We acknowledge that tray labeling submitted on March 26, 2020 revised from "Prefilled pen [syringe] for Single Dose Only" to read "Prefilled pen [syringe] is for one time use only", however, the carton labeling submitted on March 26, 2020 should also be revised for consistency. The Applicant revised as requested

Misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Consider revising the statement of dosage from "See package insert for full prescribing information" to read "Dosage: See Prescribing Information"
The Applicant revised as requested

Dispensing container (package labeling)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	✓ Yes ☐ No ☐ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: We combined the ingredient paragraphs into one paragraph to reduce clutter.
The Applicant revised as requested

Full Prescribing Information	
15 Cytotoxic Drug reference	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) xxxx is a cytotoxic drug. Follow applicable special handling and disposal procedures.1 1.OSHA Hazardous Drugs. OSHA. [Accessed on June 9, 2017, from http://www.osha.gov/SLTC/hazardousdrugs/index.html	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Per 21 CFR 201.1 and 21 CFR 201.100(e), the name and location of business listed here (street address, city, state, and zip code) is required in labeling and should be located after the Patient Counseling Information section, at the end of the PI. If the product has FDA-approved patient labeling that is not a separate document from the PI, the manufacturer information should be located at the end of labeling, after the FDA-approved patient labeling. If the FDA-approved patient labeling is a separate document, or is to be detached and distributed to patients, the manufacturer information should be located both after the Patient Counseling Information section and after the FDA-approved patient labeling.
The Applicant informed that the Medication Guide will not be a separate document and deleted the information appearing after the Patient Counseling Information.
This is acceptable.

Applicant's response: Mylan acknowledges the Agency's comment…Mylan submitted an administrative update to the application on April 17, 2020 to transfer ownership/licensure of

this application from Mylan GmbH to Mylan Pharmaceuticals Inc…Given the minor nature of the change in applicant name, it is our understanding that the currently assigned U.S. License Number 2062 will be reissued to Mylan Pharmaceuticals Inc. as part of the revocation and reissuance process. Accordingly, we wish to retain reference to Mylan Pharmaceuticals Inc. on all proposed labeling components so that this product will reflect the correct applicant at the time final regulatory action is taken. *OBP labeling's response: We acknowledge the transfer of ownership submission but also understand that the revocation and reissuance process is not yet complete. At this time, it is not certain that the process will assign the U.S. License Number 2062 to Mylan Pharmaceuticals Inc. as such, we ask that a placeholder be used for the US license number. The U.S license number is provided the approval letter and can be applied to the final labels and labeling. Please revise to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No XXXX". See Applicant's response for Medication guide.*

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
STORAGE AND HANDLING	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Labeling submitted on July 12, 2019 had the correct manufacturer's name, address, and US license number which corresponds to the manufacturer listed on FDA form 356h. Labeling submitted on March 26, 2020 was revised incorrectly to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No 2062". Revised to the licensed applicant (manufacturer) as provided on Form FDA 356h ("Manufactured by: Mylan GmbH, Turmstrasse 24, 6312 Steinhausen, Switzerland US license No 2062").

Applicant's response: Mylan acknowledges the Agency's comment…Mylan submitted an administrative update to the application on April 17, 2020 to transfer ownership/licensure of this application from Mylan GmbH to Mylan Pharmaceuticals Inc…Given the minor nature of the change in applicant name, it is our understanding that the currently assigned U.S. License Number 2062 will be reissued to Mylan Pharmaceuticals Inc. as part of the revocation and reissuance process. Accordingly, we wish to retain reference to Mylan Pharmaceuticals Inc. on all proposed labeling components so that this product will reflect the correct applicant at the time final regulatory action is taken.

OBP labeling's response: We acknowledge the transfer of ownership submission but also understand that the revocation and reissuance process is not yet complete. At this time, it is not certain that the process will assign the U.S. License Number 2062 to Mylan Pharmaceuticals Inc. as such, we ask that a placeholder be used for the US license number. The U.S license number is provided the approval letter and can be applied to the final labels and labeling. Please revise to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No XXXX".
The Applicant revised as requested

Patient Information Labeling Evaluation (N/A)

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
Recommended Labeling Practices references: Proprietary name in upper case letters on line 1, proper name (line 2) in lower case letters in parentheses, and dosage form followed by the route of administration (line 3) in lower case letters (see Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add in the dosage form (see Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019) *The Applicant revised as requested*

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for IFU: Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	✓ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	☐ Yes ☐ No ☒ N/A

INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019).	✓ Yes ☐ No

21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	☐ N/A

Comment/Recommendation: Add in the name and place of business of the manufacturer (see Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019)

Labeling submitted on July 12, 2019 had the correct manufacturer's name, address, and US license number which corresponds to the manufacturer listed on FDA form 356h. Labeling submitted on March 26, 2020 was revised incorrectly to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No 2062". Revised to the licensed applicant (manufacturer) as provided on Form FDA 356h ("Manufactured by: Mylan GmbH, Turmstrasse 24, 6312 Steinhausen, Switzerland US license No 2062").
Applicant's response: Mylan acknowledges the Agency's comment…Mylan submitted an administrative update to the application on April 17, 2020 to transfer ownership/licensure of this application from Mylan GmbH to Mylan Pharmaceuticals Inc…Given the minor nature of the change in applicant name, it is our understanding that the currently assigned U.S. License Number 2062 will be reissued to Mylan Pharmaceuticals Inc. as part of the revocation and reissuance process. Accordingly, we wish to retain reference to Mylan Pharmaceuticals Inc. on all proposed labeling components so that this product will reflect the correct applicant at the time final regulatory action is taken.

OBP labeling's response: We acknowledge the transfer of ownership submission but also understand that the revocation and reissuance process is not yet complete. At this time, it is not certain that the process will assign the U.S. License Number 2062 to Mylan Pharmaceuticals Inc. as such, we ask that a placeholder be used for the US license number. The U.S license number is provided the approval letter and can be applied to the final labels and labeling. Please revise to "Manufactured by and for: Mylan Pharmaceuticals Inc. Morgantown WV US license No XXXX".
The Applicant revised as requested

APPENDIX C. Acceptable Labels and Labeling
Prescribing Information/Medication Guide (submitted on May 28, 2020 \\cdsesub1\evsprod\bla761154\0048\m1\us\114-labeling\draft\labeling\draft-labeling-text-clean-pdf.pdf)

Instructions for Use (submitted on May 28, 2020 \\cdsesub1\evsprod\bla761154\0048\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-syringe-clean-pdf.pdf and \\cdsesub1\evsprod\bla761154\0048\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-pen-clean-pdf.pdf)

Quick reference guide (submitted on May 28, 2020 \\cdsesub1\evsprod\bla761154\0048\m1\us\114-labeling\draft\labeling\draft-labeling-text-quick-reference-guide-syringe-clean-pdf.pdf and \\cdsesub1\evsprod\bla761154\0048\m1\us\114-labeling\draft\labeling\draft-labeling-text-quick-reference-guide-pen-clean-pdf.pdf)

7 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: 6/01/2020 01:09:43PM
GUID: 50814c7000007a3d59329f660d8ddf02

Bruce Huang

Digitally signed by Bruce Huang
Date: 6/01/2020 05:06:29PM
GUID: 5621444a001ab2c406ce890a591799dd
Comments: Thanks very much Vicky!

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

Recommendation: BLA Approval

BLA Number: 761154
Review Number: 1
Review Date: 03/10/2020

Drug Name/Dosage Form	HULIO—adalimumab-fkjp; FKB327/ Injection
Strength/Potency	40 mg/0.8 mL, 20 mg/0.4 mL
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis
Applicant/Sponsor	Mylan GmbH
US agent, if applicable	n/a

Product Overview
HULIO (FKB327) is a fully human anti-TNF-α IgG1 monoclonal antibody proposed as a biosimilar to US-licensed Humira. HULIO is supplied as a prefilled syringe and an autoinjector as sterile liquid solution for subcutaneous injection.

Quality Review Team

Discipline	**Assessor**	**Branch/Division**
Drug Substance	Chen Sun	OPQ/OBP/DBRR II
Drug Product	Bruce Huang	OPQ/OBP/DBRR II
Immunogenicity	Bruce Huang	OPQ/OBP/DBRR II
Labeling	Vicky Borders-Hemphill	OPQ/OBP
Facility	Wayne Seifert	OPQ/OPMA/DBM
Microbiology Drug Substance	Madushini Dharmasena	OPQ/OPMA/DBM
Microbiology Drug Product	Virginia Carroll	OPQ/OPMA/DBM
Facility Secondary Assessor	Zhong Li	OPQ/OPMA/DBM
Microbiology Branch Chief	Patricia Hughes	OPQ/OPMA/DBM
Regulatory Business Project Manager	Kelly Ballard	OPQ/OPRO/DRBPMI/RBPMBI
Application Team Lead	Yanming An	OPQ/OBP/DBRR II
OBP Tertiary Assessor	Xianghong Jing	OPQ/OBP/DBRR II

Mutidisciplinary Review Team:

Discipline	**Assessor**	**Office/Division**
RPM	Elaine Sit	ODEII/DPARP

Cross-disciplinary Team Lead	Miya Paterniti	ODEII/DPARP
Signatory Authority	Nikolay Nikolov	ODEII/DPARP
Medical Officer	Natalie Pica / Miya Paterniti Denise Cook/Gordana Diglisic Sandhya Apparaju/Juli Tomaino	ODEII/DPARP ODEIII/DDDP ODEIII/DGIEP
Pharm/Tox	Lawrence Leshin / Carol Galvis	ODEII/DPARP
Clinical Pharmacology	Lei He / Ping Ji	OCP/DCPII
Statistics	Ginto Pottachal / Bechy Rothwell	OB/DB II
CMC Statistics	Chao Wang / Meiyu Shen	OB/DB IV

1. Names:
a. Proprietary Name: HULIO
b. Trade Name: HULIO
c. Non-Proprietary/USAN: adalimumab-fkjp
d. INN Name: adalimumab-fkjp
e. Company Code: FKB327
f. CAS Registry Number: 331731-18-1
g. OBP systematic name: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [FKB327]

Submissions Reviewed:

Submission(s) Reviewed	**Document Date**
761154/0001	07/12/2019
761154/0002 (response to OPMA IR on 07/31/2019)	08/06/2019
761154/0004 (response to OPMA IR on 08/05/2019)	08/12/2019
761154/0009 (response to OPMA IR on 09/06/2019)	09/19/2019
761154/0016 (response to OPMA IR on 11/06/2019)	11/20/2019
761154/0018 (response to CMC stat IR on 11/25/2019)	12/02/2019
761154/0019 (response to OBP IR on 11/20/2019)	12/09/2019
761154/0021 (response to OPMA IR on 12/18/2019)	12/30/2019
761154/0022 (response to OPMA IR on 01/07/2020)	01/17/2020
761154/0023 (response to OBP IR on 01/10/2020)	01/23/2020
761154/0030 (response to OBP IR on 02/13/2020)	02/25/2020
761154/0031 (response to OBP IR on 02/14/2020)	02/27/2020
761154/0033 (response to OBP IR on 02/19/2020)	02/28/2020
761154/0035 (response to OBP IR on 02/28/2020)	03/06/2020
761154/0037 (response to OPMA IR on 03/05/2020)	03/11/2020
761154/0038 (response to OBP IR on 03/09/2020)	03/11/2020

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
MAF (b) (4)	Device Master File	(b) (4)	(b) (4)	6	Adequate	Assessed by CDRH
	3			2	Adequate	N/A

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

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

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	116471	Fujifilm Kyowa Kirin Biologics Co.-sponsored IND under which FKB327 was developed and BPD meetings were held

3. Consults:

Discipline/Topic	Date Requested	Recommendation	Assessor
CDRH/ODE & OC	07/24/2020	Approval	Suzanne Hudak Rumi Young (TL)

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Product Quality (OPQ), CDER, recommends approval of BLA 761154 for Hulio manufactured by Mylan GmbH. The data submitted in this application, including the comparative analytical assessment, are adequate to support the conclusion that:

- The manufacture of Hulio is well-controlled and leads to a product that is pure and potent;
- Hulio is highly similar to US-licensed Humira notwithstanding minor differences in clinically inactive components.

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:
    Kyowa Hakko Kirin Co., Ltd.
    Takasaki Plant
    100-1 Hagiwara-machi, Takasaki,
    Gunma, 370-0013, Japan
    FEI: 3007588904

  - Drug Product:
    Terumo Yamaguchi D&D Corporation
    3-22 Azamurayama,
    Sayama, Yamaguchi,
    Yamaguchi,
    754-0894, Japan
    FEI: 3013611763

- Fill size and dosage form:
  40 mg/0.8 mL prefilled syringe and autoinjector
  20 mg/0.4 mL prefilled syringe

- Dating period:
  - Drug Product: 36 months: 2 to 8 °C
  - Drug Substance: (b) (4) months: (b) (4) °C
  - 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: Per FR notice 95-29960 well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products are exempt from 21 CFR 601.2a lot release requirement.

- Mylan claimed a categorical exclusion from the preparation of an environmental assessment for FKB327 in accordance with 21 CFR 25.31 (c). The claim is because FKB327 is considered "naturally occurring substance" and manufactured outside of the US, when exposed to the environment, is not expected to significantly alter the concentration or distribution of the substance or degradation products in the US environment.

  The claim of a categorical exclusion is accepted.

C. Assessment Summary:

Hulio is a proposed biosimilar to US-licensed Humira. Hulio has the same dosage form and route of administration as US-licensed Humira. Mylan seeks licensure for the following indications:

- Rheumatoid Arthritis (RA)
- Juvenile Idiopathic Arthritis
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)
- Adult Crohn's Disease (CD)
- Ulcerative Colitis (UC)
- Plaque Psoriasis (Ps)

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 that the drug substance and drug product manufacturing processes are well controlled and lead to a product with the expected quality attributes and free of adventitious agents.

The data support the demonstration that FKB327 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components (refer to Section II of this memo for further details and discussion of the differences observed).

Analytical similarity between FKB327 and US-licensed Humira was evaluated using a comprehensive array of analytical methods that were suitable to evaluate critical quality attributes of FKB327 and US-licensed Humira. The numbers of lots tested and the statistical analyses were appropriate to allow for a meaningful evaluation of the results of the analytical studies.

FKB327 has the same dosage form, strength, and route of administration as US-licensed Humira, but has a different formulation. Comparative protein concentration (mg/mL) was assessed as part of the comparative analytical assessment. The deliverable volume (mL) and fill weight data were assessed (b) (4). The proposed presentations of FKB327 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 U.S-licensed Humira (50 mg/mL). The strength of FKB327 prefilled syringe and autoinjector is the same as that of US-licensed Humira.

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

The facility assessor is recommending approval of Kyowa Hakko Kirin Co., Ltd., Takasaki Plant Gunma, Japan, FEI 3007588904, for commercial manufacture of FKB327 DS and Terumo Yamaguchi D&D Corporation, Yamaguchi, Japan, FEI 3013611763 for commercial manufacture of Hulio DP.

The OBP assessments including DS, DP, analytical similarity and validation of immunogenicity assays, DBM DS and DP microbiological assessments, and DBM facility technical assessment are located as separate documents in Panorama.

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

1. **Develop and implement tests in appropriate format (functional bioassay or the use of FcγRIIIa binding and C1q binding as surrogates) for the Fc-domain-mediated effector function of antibody-dependent cell mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) of FKB327 and add these tests to the drug substance release specification. The updated drug substance release specification, test methods and supporting validation data will be submitted (b) (4) by the end of third quarter of 2022, following 21 CFR 601.12 (b).**

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

A. Analytical Assessment Overview and Conclusions

The comparative analytical assessment between FKB327 and US-licensed Humira compared 29 lots of FKB327 and 39 lots of US-licensed Humira. The 29 FKB327 lots are from only 10 independent DS lots. Therefore, results from 10 FKB327 independent lots are considered in the comparative analytical assessment.

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

The expiry dates of the US-licensed Humira lots range from August 2012 to December 2017, which spans the shelf-life of US-licensed Humira and were adequate to capture potential reference product differences over time. The applicant also provided a comparison of stability under thermal forced degradation conditions of 40°C and accelerated conditions of 25°C.

Based on our assessment of the FKB327 and US-licensed Humira data, we determined that FKB327 has been demonstrated to be highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components. FKB327 has the same strength, dosage form, and route of administration as US-licensed Humira. The applicant used a comprehensive array of analytical methods that were suitable to evaluate critical quality attributes of FKB327 and US-licensed Humira to support the demonstration that the products are highly similar. Numbers of lots tested and statistical analyses were appropriate to allow for a meaningful evaluation of the results of the comparative analytical studies. Observed differences do not preclude a demonstration that FKB327 and US-licensed Humira are highly similar.

B. Results of Comparative Analytical Assessment

The results of these analytical comparisons support a demonstration that FKB327 is highly similar to US-licensed Humira and the results are summarized in Table A below:

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

Physico-chemical/Functional Characteristics	**Quality Attribute Assessed**	**Supports a Demonstration of Highly Similar**
Primary Structure	*Molecular weight (intact and deglycosylated molecule)*	*Yes*
	Amino acid sequence (Edman degradation, peptide mapping)	*Yes*
	Disulfide linkage	*Yes*
	N-glycosylation site	*Yes*
	Isoelectric point	*Yes*
	Extinction Coefficient	*Yes*
Amino Acid Modifications	*C-terminal variants*	*Yes**
	N-terminal variants	*Yes*
	Methionine oxidation	*Yes**
	Asparagine deamidation/isomerization	*Yes*
	Glycation	*Yes*
	Sulfhydryl content	*Yes*
	Trisulfide	*Yes**
	Thioether	*Yes*
	Cysteinylation	*Yes**
Glycosylation	*Afucosylation*	*Yes**
	High mannose	*Yes**
	Core-fucosylation	*Yes*
	Galactose/N-linked glycan	*Yes**
	Sialyation	*Yes**
	Glycosylation site occupancy	*Yes**
Higher Order Structure	*Secondary Structure (FTIR & Far-UV CD)*	*Yes*
	Tertiary Structure (near UV CD & Intrinsic fluorescence)	*Yes*

Physico-chemical/Functional Characteristics	**Quality Attribute Assessed**	**Supports a Demonstration of Highly Similar**
	DSC T_m1 and T_m2	*Yes*
Product-related substances and impurities	*HMW (SEC)*	*Yes*
	Monomer (SEC)	*Yes*
	LMW (SEC)	*Yes*
	Monomer, HMW, % LWM (FFF)	*Yes*
	Purity (HC + LC) (rCE-SDS)	*Yes*
	LMWS (rCE-SDS)	*Yes*
	MMWS (rCE-SDS)	*Yes*
	NGHC (rCE-SDS)	*Yes**
	HMWS (rCE-SDS)	*Yes*
	HMWS (nrCE-SDS)	*Yes*
	Purity (nrCE-SDS)	*Yes**
	LMWS (nrCE-SDS)	*Yes**
	Main species (CEX-HPLC)	*Yes**
	Acidic variants (CEX-HPLC)	*Yes**
	Basic variants (CEX-HPLC)	*Yes**
	Hydrophobic Heterogeneity	*Yes**
Bioactivity	*Tumor neutralizing factor (TNF)-alpha neutralization (cytotoxicity neutralization in L929 cells)*	*Yes*
	Binding to sTNFα by ELISA	*Yes*
	Binding to sTNFα by SPR	*Yes*
	Binding to tmTNFα by FACS	*Yes*
	Reverse signaling (apoptosis)	*Yes*
	Binding to FcγRIIIa (158V and 158F) by SPR	*Yes**
	Antibody-dependent cell-mediated cytotoxicity (ADCC)	*Yes*
	Binding to C1q by ELISA	*Yes*
	Complement dependent cytotoxicity (CDC) activity	*Yes*
	Binding to FcγRIIa & FcγRIIb by SPR	*Yes*
	Induction of regulatory macrophage assay	*Yes*
	Binding to FcγRI by SPR	*Yes*
	Binding to FcγRIIIb by SPR	*Yes**
	Binding to FcRn by SPR	*Yes*
Drug Product Attributes	*Protein content (UV absorbance)*	*Yes*

***** Differences between FKB327 and US-licensed Humira were noted. However, these differences do not preclude a demonstration of highly similar. See section D for additional information.

Soluble TNFα (sTNFα) binding and neutralization of sTNFα-induced cytotoxicity are generally regarded as the main mechanism of action for adalimumab products. Two assays were conducted to probe these activities and the results were analyzed by equivalence testing. For the cytotoxicity neutralization assay, the applicant provided data from 10 lots of FKB327 and 15 lots of US-licensed Humira. For the sTNF-α binding assay by ELISA, the applicant provided data from 10 lots of FKB327 and 15 lots of US-licensed Humira. OBP reviewed the justification of lots selection and concluded that the lots selection for each product adequately captured the lot-to-lot variability. The CMC Statistics assessor assessed statistical equivalence testing and determined that the data met the equivalence margins for both assays, supporting a demonstration that FKB327 is highly similar to US-licensed Humira.

Additional potential mechanisms of action have been proposed for adalimumab products, including antibody dependent cell-mediated cytotoxicity against cells expressing transmembrane TNF-α (tmTNF-α), complement dependent cytotoxicity against tmTNF-α positive cells, "reverse signaling" (signal transduction into cells by activation of tmTNF-α), and induction of regulatory macrophages. It is likely that the relative role for each of these mechanisms differs between indications approved for US-licensed Humira. Assays that are orthogonal to the sTNFα binding and the neutralization assays, assays that evaluate these additional potential mechanisms of action, and assays that evaluate purity, protein content, and other general properties of adalimumab products were assigned for quality range or visual comparison assessment.

The protein biochemistry and biological activity attributes tested in Table A met the pre-defined comparative analytical acceptance criteria in the comparison of FKB327 to US-licensed Humira with exceptions discussed in Section D of this memo. The testing results from the comparison of the stability under stressed and accelerated conditions indicated that the stability of FKB327 drug product and US-licensed Humira are similar and the differences noted do not preclude a demonstration that FKB327 is highly similar to US-licensed Humira.

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

Not applicable.

D. Assessment of Comparative Analytical Study Results

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

- Differences in glycosylation have been observed between FKB327 and US-licensed Humira:
    - Afucosylated complex glycans in FKB327 (4.0-5.0%) are above the quality range of US-licensed Humira (1.0-1.2%).
    - High-mannose glycans in FKB327 (3.9-4.6%) are below the quality range of US-licensed Humira (8.0-14.1%).
    - The non-glycosylated heavy chain (NGHC%) range (0.6-0.7%) in FKB327 measured by rCE-SDS is below the quality range of US-licensed Humira (1.4-2.5%). The glycosylation site occupancy for FKB327 ranged from 98.9-99.1%, higher than the quality range of US-licensed Humira (96.2-97.9%).

  The glycosylation differences observed between FKB327 and US-licensed Humira occur in the Fc region of the products. It is known that afucosylated complex glycans and high-mannose glycans may increase Fcγ receptor (FcγR) binding activities and that NGHC may have lower FcγR binding activity compared with intact molecules. To evaluate whether the observed differences in glycosylation impacted the interaction with FcγRs, the following has been considered:

  a. The total content in fucosylated complex glycans are similar between FKB327 and US-licensed Humira. The monosaccharide composition analysis results showed the fucose residues are similar between the two products. These data indicated that the total content in non-fucosylated glycans (afucosylated complex + high-mannose) are similar between the two products. The applicant proposed acceptable specifications of afucosylated + high-mannose glycans in DS release to ensure adequate control of this product attribute in commercial products.

b. The FcγR binding activities have been tested by SPR. The dissociation constants (K_Ds) for binding to FcγRIIIa (F & V) and FcγRIIIb-NA2 show differences between FKB327 and US-licensed Humira. FKB327 has slightly stronger binding affinity to the FcγRs:
   - FKB327 0.94-1.00 (x 10^{-6} M) vs. US-licensed Humira 0.97-1.06 (x 10^{-6} M) for FcγRIIIa(F)
   - FKB327 4.74-5.05 (x 10^{-6} M) vs. US-licensed Humira 4.81-5.22 (x 10^{-6} M) for FcγRIIIa(V)
   - FKB327 0.87-0.99 (x 10^{-5} M) vs. US-licensed Humira 0.93-1.05 (x 10^{-5} M) for FcγRIIIb-NA2

   The SPR binding differences between FKB327 and US-licensed Humira for the three FcγR binding affinities listed above are considered small (<3% for FcγRIIIa, and 6% for FcγIIIb-NA2). The inter-assay precision of the SPR testing is ≤20% RSD and the minor differences of K_Ds are relatively low compared to the assay variability. Binding to FcγRIIIa on effector cells is a critical step that can lead to ADCC activity. However, no differences were observed in ADCC activity between the two products.

In summary, the observed differences in afucosylation, high-mannose, glycosylation occupancy and FcγR binding activities do not preclude a determination that FKB327 and US-licensed Humira are highly similar.

- The ratio of terminal galactose per N-linked glycan for FKB327 ranges higher (0.24-0.35 mol/mol) than the quality range of US-licensed Humira (0.23-0.26 mol/mol). Increased galactosylation may increase Fc binding to C1q and result in CDC activity. However, no differences were observed for either C1q binding or CDC activity between two products. The terminal galactosyl glycans are adequately controlled in DS release for commercial products. Therefore, the differences noted in terminal galactose levels do not preclude a demonstration of highly similar.

- Sialylated glycans in FKB327 (2.7-3.9%) are above the quality range of US-licensed Humira (0-0.4%). Of the low levels of sialylated glycans detected, N-acetylneuraminic acid (Neu5Ac) is the predominant sialic acid form in both FKB327 and US-licensed Humira. While sialyation has a low potential to impact Fc effector functions, it has the potential to impact other antibody functional domains and could result in differences in bioactivity related to the Fab arm functionality. However, comparative analyses of FKB327 and US-licensed Humira showed that the difference in low-level sialylation had no observed effect on any receptor binding or functional assay activities, i.e., those indicative of Fab arm functionality. The sialylated glycans are adequately controlled in DS release. Therefore, the differences noted in glycosylation levels do not preclude a demonstration of highly similar.

- The percentage of acidic peak in all lots of FKB327 (22.9-30.5%) was above the quality range of US-licensed Humira (11.8-15.8%). The characterization study of the FKB327 acidic fractions showed that sialylated glycan is the major contributor to the relatively higher abundance of acidic variants in FKB327 than in US-licensed Humira. Glycation, deamidation/isomerization and oxidation were all observed to be higher in the acidic peaks of both products. However, the total amount of these variants was shown to be comparable and at low levels for both products. The percentages of main peak of three FKB327 lots (66.7%, 65.3% and 65.9%) were a little higher

than the quality range of US-licensed Humira (55.1-65.1%). The percentage of basic peak in all FKB327 lots (5.9-10.8%) was below the quality range of US-licensed Humira (20.3-31.9%).

To evaluate whether the difference in charge variants impacted bioactivity, the bioactivity of the purified acidic, basic and main species fractions from both products (FKB327 and US-licensed Humira) were tested using cytotoxicity neutralization, reverse signaling (apoptosis), FcRn binding, ADCC and CDC assays. The primary mechanism of action (MoA) of adalimumab across all indications is binding to soluble TNF-α and neutralizing its biological function by blocking its interaction with cell surface TNF-α receptors. An important outcome of TNF-α inhibition is neutralization of TNF-α receptor induced-cytotoxicity. Adalimumab binding to transmembrane TNF-α is also relevant to reverse signaling, ADCC and CDC activities and these activities are potential MoAs for certain indications for which US-licensed Humira is approved. Binding to FcRn is an important activity that impacts PK. All assays measure bioactivities that are clinically relevant and are suitably representative of the drug's MoAs for this analysis. The acidic fractions from both products show slightly lower activities for cytotoxicity neutralization, ADCC and CDC than the main peak fraction in a similar pattern. In addition, the combined activity of all charge variants is similar for both products. The applicant proposed to control the level of acidic variants for DS and DP release and stability to ensure the bioactivities of FKB327 remain similar to US-licensed Humira in commercial products and their control strategy was determined to be adequate.

The carboxypeptidase B treatment study indicated that the basic species are composed mainly of the variant with C-terminal lysine. Since the C-terminal lysine will be cleaved in vivo, it is not considered a critical quality attribute and bioactivity testing (cytotoxicity neutralization assay, ADCC, CDC, reverse signaling and FcRn binding assay) on the basic peak fraction did not show any impact on the biological functions representative of the product's MoA. The charge variants and post-translational modification differences observed between FKB327 and US-licensed Humira did not result in biological activity differences. Therefore, based on the charge variants characterization study and acceptable control strategy, the differences noted in acidic and basic species do not preclude a demonstration of highly similar.

- The percentages of LMWS (2.8-3.4%) and purity (96.4-97.1%) measured by nrCE-SDS are outside of the quality ranges of US-licensed Humira of ≤2.2% and ≥97.5%, respectively. The difference for each attribute compared to the quality range was approximately 1%. The levels of LMWS are low and the minor differences are not expected to cause any detectable difference in biological activities based on the results from bioactivity testing. Additionally, the levels of LMWS and purity have been adequately controlled at release and on stability and would prevent drift of further commercial lots. Therefore, the differences in the levels of purity and LMWS observed in the nrCE-SDS assays do not preclude a demonstration of highly similar.

- The heavy chain (HC) C-terminal variants include Gly^{450}, Lys^{451} and amidated Pro^{449}. C-terminal Gly^{450} is the major component of the C-terminal variants. FKB327 has higher Gly^{450} (95.9-98.9%) than the quality range of US-licensed Humira (88.9-95.6%). The C-terminal Lys in FKB327 is lower (0.3-0.5%) than the quality range of US-licensed Humira (3.9-10.3%). Amidated Pro^{449} in FKB327 is higher (0.7-3.7%) than the quality range of US-licensed Humira (0.4-1.0%). C-terminal lysine and amidated Pro are higher in basic variants compared to main or acidic peaks and are not considered CQAs. Lys^{451} is cleaved in serum. Amidated Pro^{449} has a similar charge profile as C-terminal Lys and is not expected to impact the Fc-mediated effector function. The bioactivity data from the basic variants showing similar results for the basic variants of FKB327 and US-

licensed Humira support that the difference of HC C-terminal variants does not preclude a determination of highly similar.

- The level of Met^{256} oxidation (2.5-3.8%) in FKB327 ranged slightly lower than the quality range of US-licensed Humira (3.2-5.5%). Met^{256} is located in the FcRn binding region and its oxidation might reduce thermal stability and decrease FcRn binding as well as in vivo serum half-life. Decreased Met^{256} oxidation in FKB327 may benefit product stability and FcRn binding. The FcRn binding assay and forced degradation studies show similar FcRn binding activity and similar degradation profile of FKB327 and US-licensed Humira. The observed differences in the level of Met^{256} oxidation do not preclude a determination of highly similar.

- The trisulfide formation level in the inter-chain disulfide linkage between HC and LC of FKB327 (5.6-9.7%) is above the quality range of US-licensed Humira (0.2-0.6%). IgG trisulfide modification is far from the CDR regions and would not be expected to significantly impact antigen-binding affinity. This was confirmed as there were no differences observed from the bioactivity testing. The observed differences in trisulfide do not preclude a determination of highly similar.

- The cysteinylation at the LC C-terminal cysteine residue of FKB327 (0.3-0.4%) is above the quality range of US-licensed Humira (0-0.3%). LC C-terminal cysteine variants have little impact on the biological activity of monoclonal antibodies in general, due to their distal location from the antigen-binding domain and from the sites involved in interactions with Fc receptors. Therefore, the slight difference in cysteinylation does not preclude a determination of highly similar.

- The hydrophobic heterogeneity of Fc fragment was evaluated by HI-HPLC. The Fc fragments with lower hydrophobicity eluted earlier than the Fc main peak. The peak area of lower hydrophobic Fc fragments of FKB327 (5.6-7.2%) are below the quality range of US-licensed Humira (18.6-30.6%). After carboxypeptidase B treatment, the peak area of lower hydrophobic fraction of FKB327 is similar to US-licensed Humira. These results indicated that the difference in the Fc hydrophobic heterogeneity between FKB327 and US-licensed Humira is due to C-terminal lysine variants. As discussed above, C-terminal lysine is not considered a critical quality attribute. The difference in hydrophobic Fc fragments does not preclude a determination of highly similar.

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

- FKB327 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components.
- For attributes where differences were observed between FKB327 and US-licensed Humira, the totality of the analytical data supports that the function, activity, and in vitro stability of FKB327 and US-licensed Humira are similar. Specifically, the differences noted in glycosylation and charge variants were not reflected in cell-based functional assays such as cytotoxicity neutralization, ADCC and CDC assays. Therefore, the analytical differences observed do not preclude a demonstration that FKB327 is highly similar to US-licensed Humira.

E. Same Strength:

FKB327 has the same dosage form and route of administration as US-licensed Humira. Mylan is seeking approval of 40 mg/0.8 mL FKB327 in a single-dose prefilled syringe and autoinjector and 20 mg/0.4 mL

in a single-dose prefilled syringe. US-licensed Humira is available at these strengths with these corresponding presentations. Comparative protein concentration (mg/mL), assessed as part of the comparative analytical assessment, and deliverable volume and fill weight data assessed (b) (4) were used to inform the assessment of whether each proposed presentation of FKB327 has the same strength as the corresponding presentation of US-licensed Humira. Based on the similarity and manufacturing data, the 40 mg/0.8 mL FKB327 prefilled syringe and autoinjector and the 20 mg/0.4 mL FKB327 prefilled syringe 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 corresponding presentations of US-licensed Humira. These presentations meet the statutory "same strength" requirement under section 351 (k)(2)(A)(i)(IV) of the PHS Act.

III. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and the associated control strategies for attributes that are relevant to both Drug Substance and Drug Product. For additional information, see the primary reviews, including the Drug Substance Quality Review and Drug Product Quality Review by OBP/DBRRII and the Drug Substance Microbiology Review and the Drug Product Microbiology Review by OPMA/DBM.

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

CQA (type)	Risk	Origin	Control Strategy	Other
TNF-α binding and neutralization (potency)	Efficacy	Intrinsic to molecule	(b) (4)	
High-molecular weight species HMWS; (product-related impurity)	Efficacy, pharmacokinetics, and immunogenicity	Manufacturing process and storage conditions. Can form due to agitation, temperature, or light exposure.		HWMS fraction has similar potency to monomer.
Low-molecular weight species LMWS (product-related impurities)	Efficacy, pharmacokinetics, and immunogenicity	Manufacturing process and storage conditions. Fragmentation may be caused by agitation, temperature, or light		

CQA (type)	Risk	Origin	Control Strategy	Other
Middle Molecular Weight Species MMWS (product-related impurities	Efficacy, pharmacokinetics, and immunogenicity	Manufacturing process and storage conditions. Fragmentation may be caused by agitation, temperature, or light m	(b) (4)	
Charge variants (product-related variants)	Efficacy, pharmacokinetics, and immunogenicity	Fermentation, purification, deamidation during storage		
Glycosylation (potency and product-related substance)	Efficacy and pharmacokinetics	Cell line, bioreactor conditions, and purification process		Non-glycosylated species (NGHC) has comparable bioactivities as the intact protein (b) (4)
Non-consensus glycosylated species, NCGS (product-related impurities)	Efficacy and pharmacokinetics	Manufacturing process		Glycosylation in the VH region at (b) (4).
Oxidation	Efficacy and safety	Manufacturing process and storage		Consistently low amount of Met^{256} oxidation (b) (4).
Protein Concentration	Efficacy, pharmacokinetics, safety	Manufacturing process		
ADCC	Efficacy	Intrinsic to molecule		PMC to add functional or binding assays to DS release specification
CDC	Efficacy	Intrinsic to molecule		

CQA (type)	Risk	Origin	Control Strategy	Other
Higher order structure (potency)	Efficacy and MoA	Intrinsic to molecule	(b) (4)	
Identity (identity)	Safety, efficacy	Intrinsic to molecule		

B. Drug Substance [adalimumab-fkjp] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2 below summarizes the critical quality attributes and their control strategy that are relevant specifically to the Drug Substance. For additional information, see the primary reviews, including the Drug Substance Quality Review and Drug Product Quality Review by OBP/DBRRII and the Drug Substance Microbiology Review and the Drug Product Microbiology Review by OPMA/DBM.

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

CQA (type)	Risk	Origin	Control Strategy
Appearance (color and clarity)	Safety	Manufacturing process	(b) (4)
Host Cell Proteins (process-related impurity)	Safety and immunogenicity	Derived from host cell line	
Host Cell DNA (process-related impurity)	Safety	Derived from host cell line	
(b) (4) (process-related impurity)	Safety and immunogenicity	Process-related (b) (4)	
(b) (4) (process-related impurity)	Safety	Added during fermentation	
(b) (4) (process-related impurity)	Safety	Added during fermentation	
(b) (4) (process-related impurity)	Safety	Added during fermentation	
(b) (4) (process-related impurity)	Safety	From raw materials	

CQA (type)	Risk	Origin	Control Strategy
Virus Contamination (contaminant)	Safety	Contamination during manufacture	(b) (4)
Mycoplasma	Safety	Contamination during manufacture	
Bacterial endotoxin	Safety, Purity	Endotoxin can be introduced through raw materials and throughout the manufacturing process	
Bioburden	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials and manufacturing process	

- Description: FKB327 is a recombinant human monoclonal antibody of the immunoglobulin G1 (IgG1) subclass consisting of 2 heavy chains and 2 light chains of the Kappa subclass. Each heavy chain contains 451 amino acids and each light chain contains 214 amino acids. Each heavy chain contains an N-linked glycan at a consensus glycosylation site on asparagine 301. FKB327 has a molecular weight of approximately 148 kDa. (b) (4)

- Mechanism of Action (MoA): FKB327 binds specifically to tumor necrosis factor alpha (TNF-α) and blocks its interaction with receptors (TNFR-1 and TNFR-2). TNF-α, expressed by immune cells and other cells in response to infection or inflammation, is expressed both as a soluble cytokine (sTNFα) and a membrane-bound (mbTNFα) form. Elevated levels of TNF-α are found in the synovial fluid of patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. TNF-α plays an important role in both the pathologic inflammation and the joint destruction that are characteristic of these diseases. FKB327 binds to mbTNFα on immune cells and induce apoptosis through "reverse signaling". FKB327 can induce multiple effector functions that depend on binding to mbTNFα, including antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). These activities have been suggested to contribute to inflammatory bowel disease indications, although the significance of the contribution of any of these individual mechanisms not well established (based on literature review).

- Potency Assay: The potency assay measures inhibition of soluble TNFα-induced apoptosis in a mouse fibroblast cell line that expresses TNF receptors (L929 cells). The assay counts viable cells by measuring ATP-dependent-luminescence emission using CellTiter-Glo

system. FKB327 causes a dose-dependent increase in luminescence signal. This activity is reported as a percentage of the activity of the reference standard.

- Reference Materials: (b) (4)

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

Raw materials used in commercial manufacture are of non-animal origin.

- Manufacturing process summary: (b) (4)

.

Three consecutive lots were executed at commercial scale to demonstrate that the manufacturing process is well-controlled and reproducibly yields a pure and potent product with the expected quality attributes.

- Overall, the process is under adequate microbial control. Microbial quality of the DS manufacturing process is controlled at every critical step (b) (4)

(b) (4) Adequate controls are in place to maintain microbiological product quality during maximum hold periods and throughout the manufacturing process.

(b) (4)

- Container closure: The drug substance container closure system is (b) (4) The stability containers are smaller but otherwise identical to the commercial container.

- Dating period and storage conditions: The applicant conducted real-time stability studies (b) (4) for 3 clinical lots manufactured with the proposed commercial process. These data are also supported by accelerated and stressed stability studies. These data support a dating period of (b) (4) months at (b) (4). The applicant committed to place one batch of FKB327 on stability 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 [Hulio] Quality Summary:

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

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

CQA (type)	Risk	Origin	Control Strategy
Appearance (color and clarity)	safety	Manufacturing process	(b) (4)
Appearance (visible particulates)	safety	Manufacturing process	
Sub-visible particles (general)	Safety	Manufacturing process, product degradation	
Polysorbate 80 content (excipient)	Safety, stability	Manufacturing process	
pH (general)	Safety, efficacy	Formulation	
Osmolality	Safety, stability	Formulation	

CQA (type)	Risk	Origin	Control Strategy (b) (4)
Filling volume (general)	Control of dosing	Manufacturing process	
Sterility (contaminant)	Safety (Infection), Purity and Efficacy (degradation or modification of products by contaminating microorganisms)	Contamination may be introduced throughout the manufacturing process or through failure of the container closure integrity	
Endotoxin (contaminant)	Safety, purity, and immunogenicity	Raw materials; contamination may be introduced throughout the DP manufacturing process	
Container closure integrity	Safety (loss of container closure integrity can lead to a loss in sterility during storage or evaporation/product leakage impacting concentration or content)	Container closure breaches during storage.	

- Potency and Strength: Potency of FKB327 is considered, for the purposes of this review, as the percent cytotoxicity neutralization activity relative to the current reference standard. The potency assay is the same as those described in the Drug Substance section of this review.

  FKB327 is supplied as 40 mg/0.8 mL and 20 mg/0.4 mL solution of adalimumab-fkjp.

- Summary of Product Design: FKB327 will be supplied in a safety prefilled syringe (PFS) and autoinjector (AI). The primary container of the Safety PFS and AI is PFS.

- List of Excipients: Excipients include Monosodium glutamate (10 mmol/L), Sorbitol (262 mmol/L), Methionine (5 mmol/L), polysorbate 80 (1.0 mg/mL) and diluted hydrochloric acid. Except for the antibody itself, all ingredients meet compendial requirements (USP/NF, Ph. Eur. and/or JP) and are commonly used for formulation of biopharmaceuticals. No excipients are of human or animal origin.

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

- Manufacturing process summary: (b) (4)

- Container closure: The primary packaging material for Hulio Drug Product consists of a single-use 1 mL plastic PLAJEX pre-filled syringe assembled into either safety-device, or autoinjector. Appropriate compatibility studies were performed for the container closure systems.

- Dating period and storage conditions: The sponsor conducted real-time, accelerated, and stressed stability studies on 3 commercial Drug Product lots and 8 clinical Drug Product lots. These data support a dating period of 36 months when stored at 2 to 8°C. The applicant committed to placing one lot of FKB327 on stability at 2-8°C each year that the product is manufactured. The stability testing program is adequate and consistent with ICH Q5C recommendations.

- List of co-package components: None.

D. Biopharmaceutics Considerations: None

E. Novel Approaches/Precedents: None

F. Any Special Product Quality Labeling Recommendations: None

G. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation

Drug substance manufacture Drug substance in-process, lot release, and stability testing Drug substance storage Master cell band and working cell bank manufacture and storage Drug product release test. Comparative analytical assessment.	Kyowa Hakko Kirin Co., Ltd. Takasaki Plant 100-1 Hagiwara-machi, Takasaki, Gunma, 370-0013, Japan	3007588904	VAI	A four-item FDA Form 483 was issued on October 4, 2019. Deficiencies were adequately addressed in the firm's responses to the FDA-483 Inspectional Observations.	Approve
Unprocessed bulk harvest testing	(b) (4)	-----	Waived	Approve	
DRUG PRODUCT					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug product manufacture, drug product in-process, release and stability testing Secondary packaging, device assembling, drug product storage,	Terumo Yamaguchi D&D Corporation 3-22 Azamurayama, Sayama, Yamaguchi, 754-0894, Japan	3013611763	VAI	A ten-item FDA Form 483 was issued on February 21, 2020. Deficiencies were adequately addressed in the firm's responses to the FDA-483 Inspectional Observations.	Approve
Drug product storage Drug product secondary packaging and labeling	(b) (4)	-----	Waived	Approve	

Finished product storage/distribution	(b) (4)			
Drug product storage Drug product secondary packaging and labeling Finished product storage/distribution	(b) (4)	-----	Waived	Approve

H. **Facilities:** A pre-license inspection for FKB327 drug substance manufacture was conducted on September 25-October 4, 2019 at Kyowa Hakko Kirin Co. A 4-item FDA Form 483 was issued and the initial recommendation is approval for the BLA. The final classification of the KHK pre-license inspection was acceptable.

The pre-license inspection of the drug product site Terumo Yamaguchi D&D Corp. was conducted on February 13-21, 2020. A 10-item FDA Form 483 was issued and the initial recommendation is withhold pending the firm's adequate response to objectionable conditions. The final classification of the TYD pre-license inspection was acceptable.

I. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
- Stability protocol for the extension of shelf life
- Annual stability protocol
- Qualification of new WCB
- Requalification of MCB and WCB
- Qualification of new reference standards
- Requalification of primary reference standards.
- Concurrent validation (b) (4) at commercial manufacturing scale
- Concurrent validation of reprocessing at commercial manufacturing scale (val-pv-ab-16-014)

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

b. Drug Product

i. Protocols approved:
- Stability protocol for the extension of shelf life
- Annual stability protocol.

ii. Outstanding review issues/residual risk: None
iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
Product Type					
1.	Recombinant Product		x		
2.	Naturally Derived Product			x	
3.	Botanical			x	
4.	Human Cell Substrate/source material			x	
5.	Non-Human Primate Cell Substrate/Source Material			x	
6.	Non-Primate Mammalian Cell Substrate/source material		x		
7.	Non-Mammalian Cell Substrate/Source Material			x	
8.	Transgenic Animal source			x	
9.	Transgenic Plant source			x	
10.	New Molecular Entity			x	
11.	PEPFAR drug			x	
12.	PET drug			x	
13.	Sterile Drug Product		x		
14.	Other: [fill in information]				
Regulatory Considerations					
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			x	
16.	Comparability Protocol(s)			x	
17.	End of Phase II/Pre-NDA Agreements 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	

Yanming An

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Xianghong Jing

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BLA MANUFACTURING FACILITY ASSESSMENT

Application ID	BLA 761154 Orig 1
Drug Product Name	FKB327, Adalimumab (Hulio)
Strengths	20 and 40 mg (PFS) and 40 mg (Pre-filled Pen)
Dosage Form	Injection solution
Administration Route	Subcutaneous
Indication	Rheumatoid Arthritis
Applicant Name	Mylan GmbH
US License Number	2062
Application Type	351 (k)

I. Manufacturing Summary

Facility Assessment Recommendation: Approval

Assessment Summary:

Adequate descriptions of equipment, facilities, utilities, environmental controls, and the cleaning and contamination control strategy were provided for FKB327 DS manufacture at Kyowa Hakko Kirin Co., Ltd., FEI: 3007588904, (b) (4) and DP at Terumo Yamaguchi D&D Corporation FEI: 3013611763, (b) (4). The final dosage form includes a 20 and 40 mg (PFS) and 40 mg (Pre-filled Pen).

FKB327 (adalimumab) has been developed as a biosimilar product to Humira® and is in the pharmacologic class of biologic anti-tumor necrosis factor-alpha (TNF-α) drugs. Adalimumab binds specifically to human TNF-α and neutralizes the biological function of TNF-α by blocking its interaction with TNFR1 and TNFR2 cell surface TNF receptors.

All proposed manufacturing and testing facilities are acceptable based on their acceptable compliance status.

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
BLA 761154 Orig 1	07/12/2019

Highlight Key Issues from Last Cycle and Their Resolution: 1st cycle, not applicable.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

None.

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No
Choose lifecycle consideration topic(s)	None

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Kyowa Hakko Kirin Co., Ltd. Takasaki Plant, 100-1 Hagiwara-machi, Takasaki-shi, Gunma, Japan 370 0013	3007588904	Manufacture of DS, IPC, stability and release testing for DS. Storage of DS, manufacture of MCB and WCB, and storage of MCB and WCB. Release testing for DP, with testing for identity, purity, potency, polysorbate 80 and protein concentration. CBI	Approve - Based on PAI/PLI
(b) (4)		Unprocessed bulk harvest testing. LBI	Approve - Based on Previous History
Terumo Yamaguchi D&D Corporation, 3-22 Azamurayama, Sayama, Yamaguchi, Japan 754-0894	3013611763	Manufacture of DP and release testing, and in-process and stability testing for DP. Secondary packaging, device assembly, and storage of DP. SVS IDD	Approve - Based on PAI/PLI
(b) (4)		Storage of DP, secondary packaging, labelling, and storage and/or distribution of finished product. SVS	Approve - Based on Previous History
		Storage of DP, secondary packaging, labelling, and storage and/or distribution of finished product. SVS	Approve - Based on Previous History
Fujifilm Kyowa Kirin Biologics 1-6-1 Ohtemachi Chiyoda-ku Tokyo, Japan 100-0004	3009727548	Biosimilarity testing and assessment. Note, this site was not inspected, but biosimilarity testing from the firm was assessed as part of the Kyowa Hakko Kirn Co. inspection.	Approve - Based on Previous History

II. Drug Product Manufacturing

1. Batch Formula

For 20mg PFS:

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

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Wayne Seifert	Zhong Li	3/14/2020	Adequate	Approve

Wayne Seifert

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GUID: 54947cf700352f7777a77d75519a2705

Zhong Li

Digitally signed by Zhong Li
Date: 3/14/2020 06:20:11PM
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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Pharmaceutical Manufacturing Assessment
Division of Biotechnology Manufacturing
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Primary Reviewer: Virginia Carroll, PhD
Secondary Reviewer: Jessica Hankins, PhD
Branch Chief: Patricia Hughes, PhD

BLA:	761154/0
Applicant:	Mylan GmbH
US License Number:	2062
Submission Reviewed:	351(k) BLA
Product:	HULIO (adalimumab-fkjp, FKB327)
Indications:	Same as HUMIRA (RA, Crohn's disease et al.)
Dosage Form:	Solution for subcutaneous injection, 20 mg/0.4 mL and 40 mg/0.8 mL (PFS) and 40 mg/0.8 mL (Pre-filled Pen)
Manufacturing Sites (DP):	Terumo Yamaguchi D&D Corporation (TYD), Yamaguchi, Japan (FEI 3013611763)
FDA Receipt Date:	7/12/2019
Action Date:	7/10/2020

Conclusion and Approvability Recommendation

The drug product part of the BLA, as amended, was reviewed from a sterility assurance and quality microbiology perspective and is recommended for approval.

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0001	7/12/2019	Original BLA
0004	8/12/2019	Response to IR
0022	1/17/2020	Response to IR
0037	3/11/2020	Response to IR

Module 3.2

P.1 Description and Composition of the Drug Product

FKB327 drug product is a sterile, single-use, preservative-free solution for subcutaneous injection. Three presentations at 50 mg/mL are proposed with the same primary container closure system (1 mL PLAJEX plastic syringe and (b) (4) rubber stopper with staked stainless-steel needle and needle shield)

- 20 mg/0.4 mL PFS with safety device
- 40 mg/0.8 mL PFS with safety device
- 40 mg/0.8 mL autoinjector (AI)

The composition of the 20 mg drug product is copied from the submission below. The composition of the 40 mg PFS and AI is the same as the 20 mg, with double the fill volume.

Table 1: Composition of FKB327 Drug Product

Component	Function	Quality Standard	Concentration	Quantity per DP Prefilled Syringe
FKB327	API	In-house[a]	50 mg/mL	20 mg
Monosodium Glutamate	(b) (4)	NF/JPC	10 mmol/L	0.75 mg
Sorbitol		NF/Ph. Eur./JP	262 mmol/L	19.1 mg
Methionine		USP/Ph. Eur./JP	5 mmol/L	0.30 mg
Polysorbate 80		NF/Ph. Eur./JP	1.0 mg/mL	0.40 mg
Diluted Hydrochloric Acid		NF/Ph. Eur./JP	Adjust to pH 5.2	As required
Water for Injection (distilled)		USP/Ph. Eur./JP	q.s. to 0.4 mL	q.s. to 0.4 mL

a: Meets the Drug Substance (DS) specification (see Section 3.2.S.4.1)
Abbreviations: API: Active Pharmaceutical Ingredient; JP: Japanese Pharmacopoeia; JPC: Japanese Pharmacopoeia Codex; NF: National Formulary; Ph. Eur. European Pharmacopoeia; q.s.: quantum sufficit; USP: United States Pharmacopeia.

Reviewer's Comment: Separate 3.2.P sections are submitted for 20 mg PFS, 40 mg PFS and 40 mg AI. When the information is the same between sections, the information is reviewed only once.

P.2 Pharmaceutical Development

(b) (4)

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Virginia Carroll

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Patricia Hughes Troost

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BLA STN 761154
Product FKB327
Manufacturer Mylan Inc.

OBP CMC Review Data Sheet

1. BLA#: 761154
2. Review Date: March 09, 2020
3. Primary Review Team:
    a. **Medical Officer**: Natalie Pica and Miya Paterniti (TL)
    b**. Pharm/Tox**: Leshin Lawrence and Carol Galvis (TL)
    c. **Product Quality Team**:
        OPQ/OBP: Chen Sun (DS, Similarity), Bruce Huang (DP, Immunogenicity), Yanming An (ATL) and Xianghong Jing (Review Chief)
        OPQ/OPMA/DBM: Madushini Dharmasena (DS), Virginia Carroll (DP), and Patricia Hughes (Branch Chief), Wayne Seifert, Zhong Li (Secondary facility assessor)
        OND/OTBB: Cristina Ausin and Stacey Ricci (TL)
        OPQ/OBP (labeling): Vicky Borders-Hemphill
    d. **Clinical Pharmacology**: Lei He and Ping Ji (TL)
    e. **Statistics**: Ginto Pottackal and Rebecca Rothwell (TL)
        Chao Wang (CMC Stat), Meiyu Shen (CMC Stat TL)
    f. **CDRH:** Suzanne Hudak and Rumi Young (TL)
    g. **RPM**: Elaine Sit (CDER/DPARP)
    h. **RBPM**: Kelly Ballard (OPQ)

4. Major GRMP Deadlines:
    a. Filing meeting: 08/08/2019
    b. Mid-cycle internal meeting: 11/21/2019
    c. Mid-cycle applicant meeting: 12/11/2019
    d. Internal Late-cycle meeting: 03/10/2020
    e. Late-cycle applicant meeting: 04/23/2020
    f. Primary review due: 03/12/2020
    g. Secondary review due: 03/19/2020
    h. Wrap-up meeting: 05/05/2020
    i. BsUFA action date: 07/12/2020

5. Communications with Applicant and OND:

Communication/Document:	Date:
Information Request (OPMA #1)	July 31, 2019
Information Request (OPMA #2)	August 02, 2019
Information Request (OPMA #3)	August 05, 2019
Filing and Planning Meeting	August 8, 2019
Information Request (OPMA #4)	September 06, 2019
OPQ filing Review	September 24, 2019
Information Request (OBP #1)	November 20, 2019
Internal Midcycle Meeting	November 21, 2019
Midcycle Meeting with Applicant	December 11, 2019
Information Request (OPMA #5)	January 07, 2020
Information Request (OBP #2)	January 10, 2020
Labeling Meeting	January 28, 2020
Information Request (OBP #3)	February 13, 2020
Information Request (OBP #4)	February 14, 2020
Information Request (OBP #5)	February 19, 2020

Information Request (OBP #6)	February 28, 2020
Information Request (OBP #7)	March 09, 2020

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
761154/0001	July 12, 2019	Yes
761154/0014 (OBP filing response)	November 13, 2019	Yes
761154/0018 (CMC Stats IR response)	December 02, 2019	Yes
761154/0019 (OBP IR#1 response)	December 09, 2019	Yes
761154/0023 (OBP IR#2 response)	January 23, 2020	Yes
761154/0030 (OBP IR#3 response)	February 25, 2020	Yes
761154/0031 (OBP IR#4 response)	February 27, 2020	Yes
761154/0033 (OBP IR#5 response)	February 28, 2020	Yes
761154/0035 (OBP IR#6 response)	March 06, 2020	Yes
761154/0036 (OBP IR#7 response)	March 11, 2020	Yes

7. Drug Product Name/Code/Type:
   a. Proprietary Name: Hulio
   b. Non-Proprietary Name/USAN: adalimumab-xxxx
   c. CAS Registry Number: 331731-18-1
   d. Chemical Name: Immunoglobulin G1 (human monoclonal D2E7 heavy chain anti-human tumor necrosis factor), disulfide with human monoclonal D2E7κ-chain, dimer
   e. INN Name: adalimumab
   f. OBP systematic name: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [FKB327]
   g. Other name(s): FKB327 (company code)

8. Pharmacological Category: Therapeutic recombinant human monoclonal antibody
9. Dosage Form: Solution for injection in pre-filled syringe and autoinjector
10. Strength/Potency:
   (i): The concentration/strength of the Drug Product: 20 mg/0.4 mL and 40 mg/0.8 mL
   (ii): Type of potency assay(s) Cell-based bioassay. Potency is defined as percent activity relative to reference standard.
11. Route of Administration: Subcutaneous injection
12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
		(b) (4)	Yes	Defer to the CDRH assessors
			Yes	No review was required as all information related to safety and compatibility with the product was provided in the BLA

13. Inspectional Activities: The pre-license inspection on the drug substance manufacturing site at Kyowa Kirin Co (100-1, Hagiwara-machi, Takasaki, Gunma, 3700013 Japan; FEI: 3007588904) was conducted from

September 25, 2019 to October 4, 2019 by Madushini Dharmasena (OPQ/OPMA/DBM) and Chen Sun (OPQ/OBP). The inspection was conducted to support the approval of Mylan's biosimilar BLA STN761154 for FKB327. The inspection covered the manufacture of drug substance with respect to Product Quality, Production, Laboratory Control, Materials, Comparative Analytical Assessment, Facilities and Equipment Systems. Form FDA 483 was issued to the firm with four observations for: (1) Testing of critical materials is not adequate; (2) There is no assurance that all the laboratory surfaces are cleaned; (3) Bioburden limit of (b) (4) is not appropriate for the (b) (4) validation study; and (4) The general procedure "Out of specification investigation" is inadequate.

Kyowa Kirin responded to Form 483 on October 25, 2019 and provided corrective actions for each of the observation. It was recommended that the inspection be classified as voluntary action indicated.

14. Consults Requested by OBP: The device components of the semi-finished syringe (SFS), prefilled syringe (PFS), and Autoinjector are reviewed by CDRH. Consult requests were processed by OND and OPQ.
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
X	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. Precedents: None

17. Administrative:

Name and Title	Signature and Date
Yanming An, Ph.D. Application Technical Lead, DBRRII/OBP/OPQ/CDER	See electronic signature and date
Chen Sun, Ph.D. Primary assessor, DBRRII/OBP/OPQ/CDER	See electronic signature and date
Bruce Huang, Ph.D. Primary assessor, DBRRII/OBP/OPQ/CDER	See electronic signature and date

Summary of Quality Assessments

I. Primary Assessor Summary Recommendation: The data submitted in this Biologics License Application (STN 761154) support the conclusion that the manufacture of HULIO is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents and meets the parameters recommended by FDA. The conditions used in the manufacturing process had been adequately validated, and the product had been consistently manufactured from multiple production runs. It is recommended that HULIO be approved for human use under conditions specified in the package insert.
The comparative analytical assessment performed supports that HULIO is highly similar to U.S.-licensed Humira notwithstanding minor differences in clinically inactive components

II. List of Deficiencies to be Communicated: None

III. List of Post-Marketing Commitments/Requirements: The applicant agrees a Post-Marketing Commitment to implement tests in drug substance release specification for effector functions of antibody-dependent cell mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC).

IV. Review of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion: Mylan claims a categorical exclusion from the requirements of environmental assessment (BLA section 1.12.14) based on 21 CFR §25.15(d) under the provisions of 21 CFR 25.31(b and c). Thus, no environmental assessment needs to be performed. Categorical Exclusion is appropriate for this product and should be granted.

V. Primary Container Labeling Review: The carton and container labels are reviewed by Vicky Borders-Hemphill with concurrence by Bruce Huang and Yanming An. The OBP carton and container labeling review will be uploaded as a separate file in Panorama.

VI. Review of Common Technical Document- Quality Module 3.2: The review of Modules 3.2 is included in this review memorandum. CTD Modules 3.2.S, 3.2.R, and 3.2.A were reviewed by Chen Sun and Yanming An. Modules 3.2.P, 3.2.S.4.2 and 3.2.S.4.3, were reviewed by Bruce Huang and Yanming An.

VII. Review of Immunogenicity Assays- Module 5.3.1.4: The immunogenicity assays were reviewed by Bruce Huang and Yanming An.

Description of Drug Substance and Drug Product

S. DRUG SUBSTANCE

3.2.S.1 General information

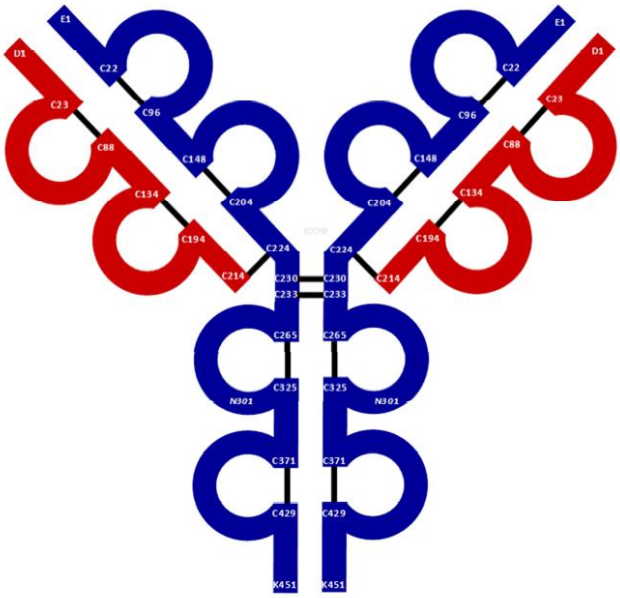
3.2.S.1.1 Structure

FKB327 is a human immunoglobulin G1 (IgG1 κ) isotype monoclonal antibody composed of two identical immunoglobulin kappa light chains (LC) and two identical immunoglobulin gamma heavy chains (HC). Each HC contains a single N-linked glycosylation site at Asn301. The main N-linked oligosaccharide structures of FKB327 are asialo, biantennary and fucosylated complex containing 0 and 1 galactose residues. FKB327 has the typical disulfide bond structure of a human IgG1 with the characteristic disulfide bond pattern. The molecular weight of FKB327 calculated by mass spectrometry is approximately 148,000 Da.

The higher order structure of FKB327 was characterized using orthogonal biophysical techniques. The secondary structure is predominantly β-sheet, the tertiary structure is consistent with a natively folded protein. Additional details are provided in Section 3.2.S.3.1 Elucidation of Structure and Other Characteristics.

The overall structure of FKB327 and the protein sequences for the LC and the HC are provided in figures below.

Figure 3.2.S.1.1-1 FKB327 Primary Structure



HCs are shown in blue and LCs are shown in red.
Black lines show the location of disulfide bonds.
N301 of HC: glycosylation site

Figure 3.2.S.1.1-2 Heavy Chain Amino Acid Sequence of FKB327

1	11	21	31	41
EVQLVESGGG	LVQPGRSLRL	SCAASGFTFD	DYAMHWVRQA	PGKGLEWVSA
51	61	71	81	91
ITWNSGHIDY	ADSVEGRFTI	SRDNAKNSLY	LQMNSLRAED	TAVYYCAKVS
101	111	121	131	141
YLSTASSLDY	WGQGTLVTVS	SASTKGPSVF	PLAPSSKSTS	GGTAALGCLV
151	161	171	181	191
KDYFPEPVTV	SWNSGALTSG	VHTFPAVLQS	SGLYSLSSVV	TVPSSSLGTQ
201	211	221	231	241
TYICNVNHKP	SNTKVDKKVE	PKSCDKTHTC	PPCPAPELLG	GPSVFLFPPK
251	261	271	281	291
PKDTLMISRT	PEVTCVVVDV	SHEDPEVKFN	WYVDGVEVHN	AKTKPREEQY
301	311	321	331	341
(N)STYRVVSVL	TVLHQDWLNG	KEYKCKVSNK	ALPAPIEKTI	SKAKGQPREP
351	361	371	381	391
QVYTLPPSRD	ELTKNQVSLT	CLVKGFYPSD	IAVEWESNGQ	PENNYKTTPP
401	411	421	431	441
VLDSDGSFFL	YSKLTVDKSR	WQQGNVFSCS	VMHEALHNHY	TQKSLSLSPG
451				
K				

Figure 3.2.S.1.1-3 Light Chain Amino Acid Sequence of FKB327

1	11	21	31	41
DIQMTQSPSS	LSASVGDRVT	ITCRASQGIR	NYLAWYQQKP	GKAPKLLIYA
51	61	71	81	91
ASTLQSGVPS	RFSGSGSGTD	FTLTISSLQP	EDVATYYCQR	YNRAPYTFGQ
101	111	121	131	141
GTKVEIKRTV	AAPSVFIFPP	SDEQLKSGTA	SVVCLLNNFY	PREAKVQWKV
151	161	171	181	191
DNALQSGNSQ	ESVTEQDSKD	STYSLSSTLT	LSKADYEKHK	VYACEVTHQG
201	211			
LSSPVTKSFN	RGEC			

3.2.S.1.3 General Properties

FKB327 is a human monoclonal IgG1 (κ) that specifically binds to human TNF-α and prevents its interaction with TNF-α receptor. The characteristics of FKB327 are outlined below:

- Description: Practically free from particles, clear to slightly opalescent, colorless to pale brownish-yellow liquid solution, free of visible particles.
- IgG Isotype: IgG subclass 1 kappa type (IgG1κ)
- Isoelectric point (pI): approximately 8.7.
- Extinction Coefficient (theoretical): 1.4 AU mL mg-1 cm-1.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Information on the manufacturing, storage, and control facilities for FKB327 drug substance (DS) are provided in the table below.

Table 3.2.S.2.1-1: Manufacturing and Control Testing Sites for FKB327 Drug Substance

Site Name and Address	Responsibility
Kyowa Hakko Kirin Co., Ltd. Takasaki Plant 100-1 Hagiwara-machi, Takasaki, Gunma, 370-0013, Japan FEI: 3007588904	• Manufacture of drug substance • In-Process testing, stability testing and release testing for drug substance • Storage of drug substance • Manufacture of Master Cell Bank and Working Cell Bank • Storage of Master Cell Bank and Working Cell Bank
(b) (4)	• Unprocessed bulk harvest testing

3.2.S.2.2 Description of Manufacturing Process and Process Controls & 3.2.S.2.4 Control of Critical Steps and Intermediates

(b) (4)

[redacted]

P: Drug Product

3.2.P - FKB327, solution for injection -Terumo

The applicant proposed three presentations of Hulio drug product: 40 mg/0.8 mL auto-injector (AI), 40 mg/0.8 mL pre-filled syringe (PFS), and 20 mg/0.4mL pre-filled syringe (PFS). The FKB327 DP compositions are the same for these presentations. The FKB327 drug product manufacturing process for the three presentations are

the same, except the filling volume and the AI assembly step. The review covered the common information shared among the three presentations and specific sections of each individual presentation.

3.2.P.1 Description and Composition of the Drug Product
FKB327 DP 50 mg/mL has the following characteristics:

- Sterile
- Preservative-free
- Practically free of particles
- Clear to slightly opalescent
- Colorless to pale brownish
- 50 mg/ml at pH 5.2
- (b) (4) l overfill is included to account for volume losses during administration of DP dose)

Quantitative composition of the FKB327 20 mg PFS DP, and FKB327 40 mg PFS/AI DP is shown in Table 3.2.P.1-1, reproduced below:

FKB327 20 mg PFS DP

Table 1: Composition of FKB327 Drug Product

Component	Function	Quality Standard	Concentration	Quantity per DP Prefilled Syringe
FKB327	API	In-house[a]	50 mg/mL	20 mg
Monosodium Glutamate	(b) (4)	NF/JPC	10 mmol/L	0.75 mg
Sorbitol		NF/Ph. Eur./JP	262 mmol/L	19.1 mg
Methionine		USP/Ph. Eur./JP	5 mmol/L	0.30 mg
Polysorbate 80		NF/Ph. Eur./JP	1.0 mg/mL	0.40 mg
Diluted Hydrochloric Acid		NF/Ph. Eur./JP	Adjust to pH 5.2	As required
Water for Injection (distilled)		USP/Ph. Eur./JP	q.s. to 0.4 mL	q.s. to 0.4 mL

a: Meets the Drug Substance (DS) specification (see Section 3.2.S.4.1)
Abbreviations: API: Active Pharmaceutical Ingredient; JP: Japanese Pharmacopoeia; JPC: Japanese Pharmacopoeia Codex; NF: National Formulary; Ph. Eur. European Pharmacopoeia; q.s.: quantum sufficit; USP: United States Pharmacopeia.

FKB327 40 mg PFS/AI DP

Table 1: Composition of FKB327 Drug Product

Table 1: Composition of FKB327 Drug Product

Component	Function	Quality Standard	Concentration	Quantity per DP Prefilled Pen
FKB327	(b) (4)	In-house[a]	50 mg/mL	40 mg
Monosodium Glutamate		NF/JPC	10 mmol/L	1.50 mg
Sorbitol		NF/Ph. Eur./JP	262 mmol/L	38.2 mg
Methionine		USP/Ph. Eur./JP	5 mmol/L	0.60 mg
Polysorbate 80		NF/Ph. Eur./JP	1.0 mg/mL	0.80 mg
Diluted Hydrochloric Acid		NF/Ph. Eur./JP	Adjust to pH 5.2	As required
Water for Injection (distilled)		USP/Ph. Eur./JP	q.s. to 0.8 mL	q.s. to 0.8 mL

a: Meets the Drug Substanc ee Section 3.2.S.4.1)
Abbreviations: API: Active Pharmaceutical Ingredient; JP: Japanese Pharmacopoeia; JPC: Japanese Pharmaceutical Codex; NF: National Formulary; Ph. Eur. European Pharmacopoeia; q.s.: quantum sufficit; USP: United States Pharmacopeia.

The PLAJEX plastic syringe includes (b) (4) rubber stopper (b) (4), staked stainless-steel needle, and (b) (4) shield safety device.

Assessor comment: *The description of FKB327 DP composition provides adequate information on concentrations, quantities, functions, and quality standards of the DP constituents. All excipients are specified to meet quality standards of NF, Ph.Eur., JP, or USP. None of the proposed excipients are associated with increased risk to patient safety. The (b) (4) used for the rubber stopper is (b) (4) The veracity of the Applicant's claims are assessed in subsequent sections.*

3.2.P.2 Pharmaceutical Development (Refer to ICH Q8)
3.2.P.2.1 Components of the Drug Product
FKB327 DP has the same formulation as FKB327 DS, except for the addition of 5 mmol/L methionine (see Table 3.2.P.1-1, above), (b) (4) The listed excipients are commonly used for parenterally administered drugs, and none are derived from human or animal origin.
Assessor comment: *The nature of the DP components is acceptable for use in comprising the DP formulation; the listed excipients are reasonable for their specified purposes.*

3.2.P.2.1.1 Drug Substance
3.2.P.2.1.2 Excipients
3.2.P.2.2 Drug Product
3.2.P.2.2.1.1. – DP Formulation Development
The proposed Quality Target Product Profile (QTPP) elements of the DP formulation were generally targeted to be consistent with biosimilarity to U.S.-licensed Humira. In order to achieve the QTPP and control the consistency of DP quality, Critical Quality Attributes (CQA) were identified, and formulation development studies were performed with emphasis on those attributes with the potential for being most affected by storage and shipping.
Assessor comment: *The proposed QTPP elements, targets, and justifications are reasonable, being largely based on meeting or exceeding the targets set by the U.S.-licensed Humira.*

3.2.P.2.2.1 Formulation Development
(b) (4)

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(b) (4)

3.2.R Biosimilarity with Reference Product

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

- *FKB327 is highly similar to U.S.-licensed Humira.*
- *For attributes where minor potential differences between FKB327 and U.S.-licensed Humira are noted, the totality of the analytical data support that there are no impacts on product functional activity or stability in vitro. Specifically, the differences noted in N-linked glycan profile along with the differences in FcγRIII binding activities were not reflected in the functional assays, such as ADCC and CDC 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 comparative analytical assessment are adequate to support that the methods are scientifically sound and suitable to study the intended quality attributes.*
- *The applicant's proposed quality ranges based on a 3-standard deviation range are appropriate acceptance criteria for each attribute evaluated unless otherwise noted.*
- *The strength of U.S.-licensed Humira is labeled in mass per unit volume (50 mg/mL). U.S.-licensed Humira is filled into a single-dose pre-filled syringe or pen with a volume of 0.4 or 0.8 mL. FKB327 is seeking approval for the same strength as U.S.-licensed Humira. Comparative protein concentration (mg/mL), assessed as part of the comparative analytical assessment, and deliverable volume and fill*

weight data assessed (b) (4) *were used to inform the assessment of whether the proposed presentation of FKB327 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 and 20 mg/0.4 mL of FKB327 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.*

- *FKB327 has the same route of administration and dosage forms as U.S.-licensed Humira.*

3.2.R.1 Overall Strategy

The comparative analytical assessment consisted of comparison FKB327 DS/DP to U.S.-licensed Humira in the following studies:

1. Comparative physicochemical characterization studies of the following quality attributes (QA)
    - Primary structure, disulfide linkage, isoelectric point, and extinction coefficient
    - N-linked glycosylation
    - High order structure
    - Size, charge and hydrophobic heterogeneity
    - Amino acid modification
    - Strength
    - Visible and sub-visible particles
    - Process related impurities
2. Comparative functional characterization studies of the following quality attributes (QA)
    - Binding to recombinant human TNF-α (rhTNF-α)
    - Binding to trans-membrane TNF-α (tmTNF-α)
    - Binding to Fcγ receptors, C1q, and FcRn
    - Fab-associated functions
    - Fc-associated functions (effector functions)
3. Assessment of the similarity of the degradation profile under accelerated (25 °C) and stressed (40 °C) conditions
4. Assessment of the similarity of the long-term stability profile at the intended storage condition of 5 ± 3 °C (b) (4)

The applicant ranked the structural and functional attributes based on their potential impact and criticality on product efficacy, safety, PK and immunogenicity in the comparative analytical assessment. Two functional attributes, cytotoxicity neutralization and soluble TNF-α binding activities, are directly related to the adalimumab mechanism of action, and the results were evaluated using equivalence test. The rest of the assays testing functional activities, product purity and variants, protein concentration, glycosylation and amino acid modifications, which generate quantitative readouts were assessed using quality ranges approach. The results from assays such as, primary structure, high order structure, process-related impurities and particles were assessed by comparison of graphical/raw data. The data evaluation performed by the applicant relies on previous Agency recommendation on statistical methods. The Agency has since reevaluated its recommendations for data analysis, but this review will focus on the data assessment provide by the applicant. The Tiers and acceptance criteria for each Tier used in the analytical similarity assessment are summarized in Table 3.2.R.1-1 below.

Table 3.2.R.1-1 Acceptance Criteria for the Analytical Similarity Assessment

Tier	Similarity Testing	
	Analytical method	**Acceptance Criteria**
1	Equivalence test (Statistically more rigorous than quality range approach used for Tier 2)	90% confidence interval of the mean difference between the test and reference product is within ±1.5σ of the reference product, where σ is the estimate variability of the reference product.
2	Quality range	The individual values of 90% of test product lots fall within the quality range as mean±Xσ of the reference product data, where X, the standard deviation multiplier, is 3. This allows the analysis to provide the appropriate quality range.
3	Graphical / Raw data comparison	Not Applicable

Assessor Comment: *During the course of the development of FKB327, there were multiple discussions and communications between the applicant and the Agency regarding the comparative analytical assessment through regulatory meetings. The statistical methods and acceptance criteria, and the proposed structural and functional attribute testing, were consistent with FDA recommendations (refer to FDA BPD Type 2 meeting preliminary comments, June 13, 2016).*

A total of 25 FKB327 DP lots (from 6 DS lots) and 4 additional FKB327 DS lots were included in the comparative analytical assessment. The FKB327 DS lots were all produced at the commercial scale and commercial manufacturing site (Table 3.2.R.1-2). FKB327 DP lots include both the clinical lots manufactured at Terumo Corporation and the commercial lots produced at Terumo Yamaguchi D&D Corporation.
A total of 39 DP lots of U.S.-licensed Humira with labeled expiration dates between August 2012 and December 2017, which spans the shelf-life of US licensed-Humira to capture innovator product differences over time, was included as reference product in the comparative analytical assessment.

Table 3.2.R.1-2: FKB327 DP and DS lots used for comparative analytical assessment

DP Batch #	DS Batch #	DS Production Site	Production Date	Purpose of material
13201B	T1101VKA3	Kyowa Hakko Kirin Co., Ltd.	Feb 2013	Stability, establishment of specifications
13202B	1202VK	Kyowa Hakko Kirin Co., Ltd.	Feb 2013	Stability, establishment of specifications
13203B			Feb 2013	Stability, establishment of specifications
C14K1N	1301VK	Kyowa Hakko Kirin Co., Ltd.	Jun 2014	Clinical, establishment of specifications
C14K2N			Jul 2014	Clinical, establishment of specifications
C14K3S			Nov 2014	Stability, establishment of specifications
C14K3A			Nov 2014	Stability, establishment of specifications
C15K3N			Sep 2015	Clinical, establishment of specifications
C15K4N			Sep 2015	Clinical, establishment of specifications
C16K1N			Jan 2016	Clinical, establishment of specifications

C16K1S			Jan 2016	Clinical, establishment of specifications
C14K5S	1401VK	Kyowa Hakko Kirin Co., Ltd.	Dec 2014	Stability, establishment of specifications
C14K5A			Dec 2014	Stability, establishment of specifications
C15Y3S			Nov 2015	Stability, establishment of specifications
C15Y3A			Nov 2015	Stability, establishment of specifications
C16K2N			Jan 2016	Clinical, establishment of specifications
C16K2A			Jan 2016	Clinical, establishment of specifications
C14K8S	1402VK	Kyowa Hakko Kirin Co., Ltd.	Jan 2015	Stability, establishment of specifications
C14K8A			Jan 2015	Stability, establishment of specifications
C15Y4S				Stability, establishment of specifications
C15Y4A				Stability, establishment of specifications
C16K2N			Jan 2016	Clinical, establishment of specifications
C16K2A			Jan 2016	Clinical, establishment of specifications
C15Y5S	1501VK	Kyowa Hakko Kirin Co., Ltd.	Dec 2015	Stability, establishment of specifications Process performance qualification
C15Y5A			Dec 2015	Stability, establishment of specifications Process performance qualification
	1201VK	Kyowa Hakko Kirin Co., Ltd.	Aug 2012	Stability, establishment of specifications
	1502VK	Kyowa Hakko Kirin Co., Ltd.	Sep 2015	Stability, establishment of specifications Process performance qualification
	1503VK	Kyowa Hakko Kirin Co., Ltd.	Nov 2015	Stability, establishment of specifications Process performance qualification
	1601VK	Kyowa Hakko Kirin Co., Ltd.	Jul 2016	Stability, establishment of specifications Process performance qualification

Assessor Comment: *The 25 FKB327 DP lots assessed in the comparative analytical assessment were manufactured from six individual DS lots. For similarity assessment of each attribute, we consider an "independent" batch to be a single DP batch produced from a single DS batch, or a single DS batch where no subsequent DP batch is included in the analysis. It is noted that multiple DP lots from a single DS batch were included in the comparative analytical assessment for the functional assays, strength, visible and sub-visible particles, and are discussed in the section below.*

A summary of the comparative analytical assessment results is presented in the following Table 3.2.R.1-3.

Assessor Comment:

1. *Method validation or qualification was conducted for all methods used in the comparative analytical assessment. For methods proposed in DS and DP specifications, information regarding method*

validation is presented in section 3.2.S.4.3 and section 3.2.P.5.3. Method qualification of the functional assays, which were not included in the DS and DP specifications, were requested in an IR dated November 20, 2019 and Mylan responded on December 09, 2019. For general characterization tests (e.g., FTIR or peptide mapping) of certain attributes using graphical comparison assessment, the assay protocols and qualification reports were requested and reviewed during the pre-licensure inspection, and were found acceptable. Data provided are sufficient to allow meaningful evaluation of the results, and thus no product-specific method qualification was requested.

2. *Twenty-two FKB327 DP lots manufactured from six individual DS lots were tested by the cytotoxicity neutralization and soluble TNF-α binding assays. The FKB327 DP lots are not all independent. On November 25, 2019, CMC statistics assessors sent an IR requesting the re-evaluation of both assay results using independent DP or DS lots. In the response on December 02, 2019 (eCTD #0018), the applicant excluded all dependent DP data and included additional data from independent DS lots that were not used for manufacturing any FKB327 DP lots.*
   These independent DS lots are included in Table 3.2.R.1-2. The applicant performed the equivalence testing for both assessments. refer to section 3.2.R.2.1 below for the detailed assessment.
3. *Regarding the attributes assessed using quality range method, multiple FKB327 DP lots from six individual DS lots were tested in the comparative analytical assessment for ADCC and CDC activities, strength, visible and sub-visible particles. Given product strength and particles may be impacted by DP manufacture process, it is reasonable to consider all DP lots are independent in the assessment. For ADCC and CDC assays, nine FKB327 DP lots from 6 individual DS lots were tested. Results from 6 independent lots were considered in our evaluation. For assessment of the rest attributes, only independent FKB327 DS lots were tested. It is considered acceptable based on the following:*
   - *The FKB327 DS formulation* [redacted] (b) (4) *The minor difference is not expected to impact the performance of these assays.*
   - *The attributes, such as primary structure, high order structure, glycan profile, Fc receptor binding, and amino acid modifications, are intrinsic to the molecule and may be affected only by the FKB327 DS manufacturing process.*
   - *Batch analysis data for FKB327 DS and DP lots (refer to section 3.2.R.4 Comparison of Batch Data from FKB327 DS, FKB327 DP and Humira) indicate that FKB327 DS is comparable to FKB327 DP in terms of charge, size and hydrophobic heterogeneities, Fab and Fc mediated functions (i.e., cytotoxicity neutralization, apoptosis induction, ADCC and CDC), demonstrating that the DP manufacturing process has minimal effect on the quality of FKB327.*
4. *The number of lots of FKB327 and U.S.-licensed Humira tested for the analysis of each quality attribute was based on criticality, availability of material at the time of analysis, product batch variability and method variability, orthogonal approaches, and shelf-life coverage. Overall, the batch selection for the analysis of each quality attribute is considered adequate.*
5. *The applicant established quality ranges using the mean of the U.S.-licensed Humira ±3 standard deviations (SD) for comparisons to FKB327. We evaluated the 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. The ranges for FKB327 in the table represent the range of minimum and maximum results.*
6. *In response to FDA information request dated November 10, 2019, the applicant provided information regarding the reference standard lots used in each assay that reports a result relative to a reference standard on December 09, 2019 (eCTD #0019) with the requested data set. The reference standard lots used in the comparative analytical assessment are reviewed below in each method section.*

Table 3.2.R.1-3. FKB327 Comparative Analytical Assessment Results

Parameter	**Quality Attribute**	**Test Method**	**Statistical method**	**Number of lots (FKB:US-Humira)**	**US-Humira Range Or Quality range**	**FKB min-max Range**	**Supports a Demonstration of Highly Similar**
Primary Structure	Amino Acid Sequence	N-Terminal Amino Acid Sequencing	graphic/raw data comparison	1:1	Identical N-terminal sequences to FKB327 for both the HC and the LC	Identical N-terminal sequences to US-Humira for both the HC and the LC	Yes
		RP-HPLC-UV reduced peptide mapping	graphic/raw data comparison	1:1	Identical amino acid sequences to FKB327 for the HC and LC	Identical amino acid sequences to US-Humira for the HC and LC	Yes
		C-Terminal amino Acid sequencing by peptide mapping (LC/MS)	graphic/raw data comparison	1:1	Identical C-terminal amino acid sequences to FKB327 for the HC and LC	Identical C-terminal amino acid sequences to US-Humira for the HC and LC	Yes
	Disulfide Linkage	Reduced and non-reduced peptide mapping (LC/MS)	graphic/raw data comparison	1:1	Similar relative percentage of correctly linked disulfide bonds to FKB327	Similar relative percentage of correctly linked disulfide bonds to US-Humira	Yes

Parameter	Quality Attribute	Test Method	Statistical method	Number of lots (FKB:US-Humira)	US-Humira Range Or Quality range	FKB min-max Range	Supports a Demonstration of Highly Similar
	N-glycosylation Site	Reduced peptide mapping (LC/MS)	graphic/raw data comparison	1:1	N-glycosylation site consistent with FKB327	N-glycosylation site consistent with US-Humira	Yes
	Molecular Weight	ESI-TOF-MS	graphic/raw data comparison	1:1	Similar molecular mass and size to FKB327	Similar molecular mass and size to US-Humira	Yes
	Isoelectric Point	IEF	graphic/raw data comparison	1:1	Similar electrophoresis bands and pI range to FKB327	Similar electrophoresis bands and pI range to US-Humira	Yes
	Extinction Coefficient	UV 280	graphic/raw data comparison	1:1	1.37$(mg/mL)^{-1}cm^{-1}$	1.37$(mg/mL)^{-1}cm^{-1}$	Yes
Glycosylation	N-Linked Glycan Profile	MALDI-TOF-MS	Quality range	10 (independent):10	IP: 8.0-14.1%	3.9-4.6%	Yes
					SA: 0.0-0.4%	2.7-3.9%	Yes*
					M5: 2.7-6.2%	1.3-1.8%	Yes*
					G1F0: 0.0-0.4%	0.6-1.1%	Yes*
					G0F0: 0.7-1.2%	3.4-4.2%	Yes*
					F0: 1.0-1.2%	4.0-5.0%	Yes*
					G2F1: 1.8-2.2%	1.4-2.7%	Yes*
					G1F1: 16.2-19.2%	18.5-26.0%	Yes*
					G0F1: 66.0-70.1%	58.3-68.9%	Yes*
					F1: 84.5-90.9%	86.8-88.8%	Yes
					Gal/N: 0.23-0.26 mol/mol	0.24-0.35 mol/mol	Yes*
	Monosaccharide Composition	HILIC	Quality range	10 (independent):10	Man: 4.67-6.28 mol/mol	4.73-5.12 mol/mol	Yes
					Fuc: 1.38-1.73 mol/mol	1.55-1.66 mol/mol	Yes
					GlcNAc: 4.66-6.03 mol/mol	5.46-5.80 mol/mol	Yes
					Gal: 0.29-0.37 mol/mol	0.46-0.70 mol/mol	Yes*
					Neu5Ac: 0.0058-0.0083 mol/mol	0.0721-0.1032 mol/mol	Yes*
					Neu5Gc: 0.0002-0.0005 mol/mol	0.0018-0.0031 mol/mol	Yes*
	Glycosylation Site Occupancy	Reduced CE-SDS	Quality range	10 (independent):10	96.2-97.9%	98.9-99.1%	Yes*
	Non-consensus Glycosylation	Reduced CE-SDS	Quality range	10 (independent):10	0.1-1.3%	0.4-0.8%	Yes
Higher Order Structure	Secondary Structure	Far-UV CD	Graphic/raw data comparison	3 (independent):3	Visually similar secondary structure	Visually similar secondary structure	Yes

Parameter	Quality Attribute	Test Method	Statistical method	Number of lots (FKB:US-Humira)	US-Humira Range Or Quality range	FKB min-max Range	Supports a Demonstration of Highly Similar
					to FKB327	to US-Humira	
		FT-IR	Graphic/raw data comparison	3 (independent):3	Visually similar secondary structure to FKB327	Visually similar secondary structure to US-Humira	Yes
	Tertiary Structure	Near-UV CD	Graphic/raw data comparison	3 (independent):3	Visually similar structure to FKB327	Visually similar structure to US-Humira	Yes
		Intrinsic fluorescence	Graphic/raw data comparison	3 (independent):3	Similar maximum wavelength, minor difference in spectral intensity	Similar maximum wavelength, minor difference in spectral intensity	Yes*
	Thermo Transition	DSC	Graphic/raw data comparison	3 (independent):3	Similar profile, minor difference in Tm (Tm1: 72°C, Tm2: 83°C)	Similar profile, minor difference in Tm (Tm1: 75°C, Tm2: 84°C)	Yes*
Purity	Size Heterogeneity	Reduced CE-SDS	Quality range	10 (independent):10	HMW ≤ 2.1%	0.9-1.2%	Yes
					HC+LC ≥ 95.5%	97.7-98.1%	Yes
					NGHC 1.4-2.5%	0.6-0.7%	Yes*
					MMWs ≤ 0.7%	0.2-0.3%	Yes
					LMWs ≤ 0.2%	0.1-0.2%	Yes
		Non-reduced CE-SDS	Quality range	10 (independent):10	HMWs ≤ 0.5%	0.1-0.3%	Yes
					Monomer ≥ 97.5%	96.4-97.1%	Yes*
					LMWs ≤ 2.2%	2.8-3.4%	Yes*
		SEC	Quality range	10 (independent):10	HMWs ≤ 0.6%	0.3-0.5%	Yes
					Monomer ≥ 99.3%	99.4-99.7%	Yes
					LMWs ≤ 0.3%	0.0-0.1%	Yes
		FFF	Quality range	10 (independent):10	HMWs ≤ 0.3%	0.3-0.5%	Yes
					Monomer ≥ 99.5%	99.5-99.7%	Yes
					LMWs ≤ 0.1%	0.0%	Yes
	Charge Heterogeneity	CEX	Quality range	10 (independent):10	Acidic variants 11.8–15.8%	22.9–30.5%	Yes*
					Main species 55.1–65.1%	60.0–66.7%	
					Basic variants 20.3–31.9%	5.9–10.8%	
	Hydrophobic Heterogeneity		Quality range	10 (independent):10	18.6–30.6%	5.6–7.2%	Yes*
Amino acid Modifications	C-terminal variants	Peptide mapping (LC/MS)	Quality range	10 (independent):10	Lys^{451} 3.9–10.3%	0.3–0.5%	Yes*
					Gly^{450} 88.9–95.6%	95.9–98.9%	Yes*
					Amidated Pro^{449} 0.4–1.0%	0.7–3.7%	Yes*
	N-terminal variants	Peptide mapping (LC/MS)	Quality range	10 (independent):10	Glu 97.9–98.5%	97.7–98.3% (90% of lots fell within the quality range of	Yes

Parameter	Quality Attribute	Test Method	Statistical method	Number of lots (FKB:US-Humira)	US-Humira Range Or Quality range	FKB min-max Range	Supports a Demonstration of Highly Similar
						US-Humira)	
					pGlu 1.5-2.1%	1.7–2.3% (90% of lots fell within the quality range of US-Humira)	Yes
	Deamidation/ Isomerization	Peptide mapping (LC/MS)	Quality range	10 (independent):10	$Asn^{77 \text{ or } 84}$ 0.7–1.3%	0.9–1.2%	Yes
					Asn^{290} 0.2–0.2%	0.2-0.3% (90% of lots fell within the quality range of US-Humira)	Yes
					Asn^{319} 1.8–3.6%	2.1–2.9%	Yes
					Asn^{365} 0.2–0.6%	0.3–0.5%	Yes
					Asn^{388} 2.7–8.0%	4.3–7.0%	Yes
					Asn^{393} 0.0–3.7%	0.7–3.0%	Yes
					Asn^{438} 0.6–1.6%	0.9–1.3%	Yes
					Asn^{137} 0.2–0.4%	0.3–0.4%	Yes
					Asn^{158} 0.1–0.4%	≤0.3%	Yes
	Glycation	Peptide mapping (LC/MS)	Quality range	10 (independent):10	0.6–1.9%	1.2–1.9%	Yes
	Oxidation	Peptide mapping (LC/MS)	Quality range	10 (independent):10	Met^{34} 0.2–0.9%	0.4–0.7%	Yes
					Met^{83} 0.4–0.7%	≤0.3%	Yes*
					Met^{256} 3.2–5.5%	2.5–3.8%	Yes*
					Met^{432} 0.7–2.1%	0.8–1.5%	Yes
					Met^{4} 0.0–0.4%	0.2-0.3%	Yes
	Sulfhydryl Content	Ellman's assay	Quality range	10 (independent):10	0.29–0.39 mol/mol	0.28–0.34 mol/mol (90% of lots fell within the quality range of US-Humira)	Yes
	Trisulfide	Peptide mapping (LC/MS)	Quality range	10 (independent):10	0.2–0.6%	5.6–9.7%	Yes*
	Thioether	Reduced CE-SDS	Quality range	10 (independent):10	0.2–0.6%	0.3–0.5%	Yes
	Cysteinylation	Reduced CE-SDS	Quality range	10 (independent):10	0.0–0.3%	0.3-0.4%	Yes*
Process Related Impurities**	Residual DNA	Threshold method	Graphic/raw data comparison	10 (independent):10	< 1.2 pg/mg protein	< 2 pg/mg protein	Not applicable **
	HCP	ELISA	Graphic/raw data comparison	10 (independent):10	≤5.4 ng/mg protein	≤2.9 ng/mg protein	Not applicable **

Parameter	Quality Attribute	Test Method	Statistical method	Number of lots (FKB:US-Humira)	US-Humira Range Or Quality range	FKB min-max Range	Supports a Demonstration of Highly Similar
Visible and Sub-visible Particles**	Visible Particles	Visual inspection	Graphic/raw data comparison	22 (6 independent): 3	Practically free from particles	Practically free from particles	Not applicable **
	Sub-visible Particles	LO	Graphic/raw data comparison	22 (6 independent): 3	≥ 2µm, ≤18143 particles/syringe	≤ 607 particles/syringe	Not applicable **
					≥ 5µm, ≤8073 particles/syringe	≤ 153 particles/syringe	Not applicable **
					≥ 10µm, ≤2308 particles/syringe	≤ 37 particles/syringe	Not applicable **
					≥ 25µm, ≤91 particles/syringe	0 particles/syringe	Not applicable **
		MFI	Graphic/raw data comparison	9 (6 independent): 3	≥ 2µm, ≤56710 particles/syringe	≤ 7912 particles/syringe	Not applicable **
					≥ 5µm, ≤9622 particles/syringe	≤ 322 particles/syringe	Not applicable **
					≥ 10µm, ≤2163 particles/syringe	≤ 45 particles/syringe	Not applicable **
					≥ 25µm, ≤108 particles/syringe	≤1.64 particles/syringe	Not applicable **
Strength	Protein Concentration	UV 280	Quality range	22 (6 independent): 30	47.54–51.80 mg/mL	49.24–50.54 mg/mL	Yes
Biological Activities	Binding to soluble rhTNF-α	ELISA	Equivalence test	10 (independent): 15	±4.9% as mean difference	-3.7–1.1% as 90%CI	Yes
		SPR	Quality range	10 (independent):10	0.76–1.49×10^{-10} M	0.97–1.24×10^{-10} M	Yes
	Binding to tmTNF-α	Cell based FACS assay	Quality range	10 (independent):10	79.1–115.9%	88.6-107.0%	Yes
	Binding to Fc Receptors	FcγR I by SPR	Quality range	10 (independent):10	3.03–5.21×10^{-10} M	3.82–4.36×10^{-10} M	Yes
		FcγR IIa by SPR	Quality range	10 (independent):10	7.41–9.15×10^{-6} M	7.65–8.47×10^{-6} M	Yes
		FcγR IIb by SPR	Quality range	10 (independent):10	1.39–1.83×10^{-5} M	1.38–1.57×10^{-5} M 90% of lots met the quality range of US-Humira	Yes
		FcγR IIIa (F) by SPR	Quality range	10 (independent):10	0.97–1.06×10^{-6} M	0.94–1.00×10^{-6} M	Yes*
		FcγR IIIa (V) by SPR	Quality range	10 (independent):10	4.81–5.22×10^{-6} M	4.74–5.05×10^{-6} M	Yes*
		FcγR IIIb NA1 by SPR	Quality range	10 (independent):10	0.93–1.28×10^{-5} M	0.94–1.09×10^{-5} M	Yes
		FcγR IIIb NA2 by SPR	Quality range	10 (independent):10	0.93–1.05×10^{-5} M	0.87–0.99×10^{-5} M	Yes*
		FcRn by SPR	Quality range	10 (independent):10	5.84–8.81×10^{-8} M	6.64–7.59×10^{-8} M	Yes

Parameter	Quality Attribute	Test Method	Statistical method	Number of lots (FKB:US-Humira)	US-Humira Range Or Quality range	FKB min-max Range	Supports a Demonstration of Highly Similar
	Fab-associated Functions	Cytotoxicity neutralization assay	Equivalence test	10 (independent):15	±5% as mean difference	-4.0–0.3% as 90%CI	Yes
		Induction of apoptosis assay	Quality range	10 (independent):10	82.8–108.1%	95.6-113.5%	Yes
		Induction of regulatory macrophage assay	Graphic/raw data comparison	3 (independent):3	Visually similar inhibitory profile to FKB327	Visually similar inhibitory profile to US-Humira	Yes
	Fc-associated Functions	ADCC assay	Quality range	10(independent):10	88.3–129.5%	90.4–112.0%	Yes
		CDC assay	Quality range	9 (independent):14	89.1–108.1%	91.3–105.7%	Yes
	Binding to C1q	ELISA	Quality range	10(independent) :14	79.7–100.0%	93.1–101.5% 90% of lots met the quality range of US-Humira	Yes

* Differences between FKB327 and U.S.-licensed Humira were noted. However, these differences are considered minor and do not preclude a demonstration of highly similar. See section 3.2.R.2 Comparative Analytical Assessment Results for additional information and the detailed assessment.
** The applicant included assessment of process-related impurities, visible and sub-visible particles in the Comparative Analytical Assessment section. These data were assessed as part of the manufacturing and release control strategy and were not included for an evaluation for supporting a determination that FKB327 is highly similar to U.S.-licensed Humira.

3.2.R.2 Comparative Analytical Assessment Results

3.2.R.2.1 Analytical Similarity Assessment for Assays evaluated by Equivalence Test

The blockade of TNF functionality by the binding of the Fab domain represents the primary MOA for FKB327 and U.S.-licensed Humira.

3.2.R.2.1.1 Cytotoxicity Neutralization

Soluble TNF-α specifically binds to its cell surface receptors and subsequently induces target cell cytotoxicity. The biological activity of adalimumab to neutralize soluble TNF-α is assessed by neutralization of TNF-α induced cytotoxicity. In the cell-based cytotoxicity neutralization assay, L929 cells are treated with TNF-α and with serial dilutions of adalimumab. The viable cells are determined using a luminometric cell viability reagent. The IC_{50} values that represent 50% of the maximal activity are determined for adalimumab samples and the reference standard. The relative activity of cytotoxicity neutralization is determined against the reference standard.
The analytical similarity assessment included the comparison of 10 independent FKB327 DS/DP lots to 15 U.S.-licensed Humira DP lots. An equivalence test was performed for the results between FKB327 and U.S.-licensed Humira and summarized in Table 3.2.R.2-1. The 90% confidence interval of the mean difference between FKB327 and U.S.-licensed Humira falls within the corresponding equivalence acceptance limits. Therefore, the applicant concluded that FKB327 is similar to U.S.-licensed Humira with respect to cytotoxicity neutralization activity.

Table 3.2.R.2-1 Equivalence Testing Results for Cytotoxicity Neutralization Assay (% Relative Potency)

Test Product	Number of Lots	Reference product	Number of Lots	Acceptance range	90% confidence interval	Result
FKB327 DP/DS	10	US-licensed Humira	15	-5.0–5.0	-4.0–0.3	Pass

Reference standard lot SVKA-01 and lot SVKA-03 were used in the assay. SVKA-03 was derived from the same DS batch (1402VK) with the same formulation and process, as SVKA-02. As described in Section 3.2.S.5, the relative potency of SVKA-02 was calculated as the geometric mean value of 16 measurements against SVKA-01. (b) (4) Because SVKA-02 and SVKA-03 are manufactured from the same drug substance, we concluded that the reference standards SVKA-01 and SVKA-03 have equivalent potency for cytotoxicity neutralization assay.

Assay qualification: The cytotoxicity neutralization assay is the current lot release potency assay for FKB327 and the assessment of the assay validation is detailed in section 3.2.S.4.1 Analytical Procedures and section 3.2.S.4.2 Validation of Analytical Procedures.

Assessor Comment: *Results from 22 FKB327 DP lots produced from 6 FKB327 DS lots, were initially analyzed by the equivalence test. On November 25, 2019, CMC statistics assessors sent an IR requesting the re-evaluation of both cytotoxicity neutralization and TNFα binding ELISA assays using data from at least 10 independent FKB327 DS or DP lots. In the response on December 02, 2019 (amendment #0018), the applicant excluded all dependent DP data for the equivalence test. Results from 4 independent DS lots, which were not used for manufacturing any FKB327 DP lots, were added to the statistical evaluation. The data in Table 3.2.R.2-1 reflect the updated equivalence testing results. Review of the suitability of the statistical evaluation of equivalency for the cytotoxicity neutralization activity is conducted by the CMC statistical review team in the Office of Biostatistics. Contingent on final recommendation from the Office of Biostatistics, these data support a determination that FKB327 is highly similar to U.S.-licensed Humira.*

3.2.R.2.1.2 TNF-α Target Binding by ELISA
The binding affinities of FKB327 and U.S.-licensed Humira to soluble TNF-α were assessed by ELISA. The same FKB327 DP and U.S.-licensed Humira lots assessed for cytotoxicity neutralization were tested for similarity assessment. Briefly, test samples and the reference standard were added to soluble TNF-α coated microplate and were detected by an HRP labelled anti-human IgG antibody. An HRP substrate was used to generate the signal. The absorbance was measured at 450 nm. EC_{50} values that represent 50% of the maximal binding activity were determined for both the reference standard and test samples. The relative binding activity for each sample was calculated against the activity of the reference standard. An equivalence test was performed and the results are summarized in Table 3.2.R.2-2. The 90% confidence interval of the mean difference between FKB327 and U.S.-licensed Humira falls within the corresponding equivalence acceptance limits. The applicant concluded that FKB327 is similar to U.S.-licensed for soluble TNF-α binding.

Table 3.2.R.2-2 Equivalence Testing Results for Antigen Binding Activity (% Relative Potency)

Test Product	Number of Lots	Reference product	Number of Lots	Acceptance range	90% confidence interval	Result
FKB327 DP/DS	10	US-licensed Humira	15	-4.9–4.9	-3.7–1.1	Pass

Reference standard lot SVKA-01 and lot SVKA-03 were used in the ELISA binding assay for comparative analytical assessment. In response to FDA information request, the applicant provided the results of bridging measurement demonstrating that reference standard lot SVKA-01 and lot SVKA-03 are equivalent in potency of the TNF-α binding assay. Additionally, considering that the cytotoxicity neutralization assay monitors FKB327 binding to TNF-α, the reference standard bridging data from the cytotoxicity neutralization assay also support the equivalency of lot SVKA-01 and lot SVKA-03 in potency of the TNF-α binding.

Assay qualification: The assay validation report is included in the BLA submission. The linear range of 50-200% relative potency was demonstrated with a correlation coefficient of 0.997. The assay showed a recovery rate of 87.8 -109.5% and a precision of 3.5 – 5.2% relative standard deviation. Assay specificity was demonstrated by lack of reaction to human IgG1 and assay matrix. All the validation characteristics met the acceptance criteria.

Assessor Comment: *Results from 22 FKB327 DP lots produced from 6 FKB327 DS lots, were initially analyzed by the equivalence test. On November 25, 2019, CMC statistics assessors sent an IR requesting the re-evaluation of this attribute using data from at least 10 independent FKB327 DS or DP lots. In the response on December 02, 2019 (amendment #0018), the applicant excluded all data from the dependent DP lots for the equivalence test. Results from 4 independent DS lots, which were not used for manufacturing any FKB327 DP lots, were added to the statistical evaluation. The data in Table 3.2.R.2-1 reflect the updated equivalence testing results. Review of the suitability of the statistical evaluation of equivalency for the TNF-α binding activity is conducted by the CMC statistical review team in the Office of Biostatistics. Contingent on final recommendation from the Office of Biostatistics, the equivalence test results support that FKB327 and U.S.-licensed Humira are similar in potency in TNF-α target binding.*

3.2.R.2.2 Analytical Similarity Assessment with Quality Range Approach

Quality range approach was used to assess the analytical similarity study results from assays testing attributes with moderate risk to product quality and clinical outcomes. The quality ranges are established as Mean ± 3×SD from the results of U.S.-licensed Humira lots. Analytical similarity would be established for the quality attribute if at least 90% of the lots of FKB327 are within the quality range of U.S.-licensed Humira.

3.2.R.2.2.1 Binding to TNF-α by SPR

The binding affinities of FKB327 and U.S.-licensed Humira to recombinant human TNF-α (rh TNF-α) were evaluated using surface plasmon resonance (SPR) technology. In the SPR assay, adalimumab was captured on a biosensor chip surface using an anti-human IgG1 Fc antibody, and then the rhTNF-α was titrated over the chip at different concentrations. Binding of rhTNF-α to immobilized antibody was measured. The dissociation equilibrium constant for each sample was calculated by non-linear regression of the binding curves. The similarity assessment included the comparison of 10 independent lots of FKB327 DS to 10 U.S.-licensed Humira DP lots. The dissociation rate constants (K_D) values for FKB327 and U.S.-licensed Humira are provided in the BLA submission (not re-produced here). The applicant established the quality range of 0.76 - 1.49 from 10 U.S.-licensed Humira DP lots (Mean ± 3×SD). The dissociation rate constant values for the 10 lots of FKB327 DS range from 0.97 to 1.24, which are within the quality range of U.S.-licensed Humira DP lots.

Table 3.2.R.2-3 Similarity Assessment for Antigen Binding Affinity by SPR for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Dissociation constant (K_D) ($\times 10^{-10}$ M)
Test product	FKB327 DS	10	Average	1.14
			SD	0.09
			Maximum	1.24
			Minimum	0.97
Reference product	US-licensed Humira	10	Acceptance range	0.76–1.49
Results				Pass

Assay qualification: The SPR assay was qualified for assessment of binding ability of FKB327 to human TNF-α. The binding of a concentration range of TNFα (0.35 - 12 nM) to FKB327 was measured. For each assay run, kinetic analysis was performed and association rate constant (ka), dissociation rate constant (kd) and equilibrium dissociation constant (KD) were calculated. The relative standard deviations (CV%) of ka, kd and KD calculated from the results of 4 repeated analyses were less than 15.0%. The intra- and inter-assay precisions were 3.4% and 12% respectively. Specificity was assessed by demonstrating a lack of interference from assay matrix.

Assessor Comment: *All FKB327 DS lots tested were within the established quality range of U.S.-licensed Humira. Data provided support that FKB327 is similar to U.S.-licensed Humira with respect to antigen binding affinity.*

3.2.R.2.2.2 Binding to Trans-membrane (tmTNF-α)
The binding affinity to tmTNF-α was evaluated for FKB327 DS and U.S.-licensed Humira by FACS analysis. EL-4 cells expressing tmTNF-α are used for the FACS analysis. Adalimumab or reference standard bound to tmTNF-α is detected with fluorescein-labeled anti-human IgG by flow cytometry. The relative potency of each sample is calculated against the reference standard. Ten independent lots of FKB327 DS to 10 U.S.-licensed Humira DP lots were tested and included in the similarity assessment. The statistical quality range of U.S.-licensed Humira lots is 79.1% - 115.9% (Mean ± 3×SD). The relative potency of FKB327 DS lots, ranging from 88.6% to 107%, are within the quality range of U.S.-licensed Humira (Table 3.2.R.2-4). Only one reference standard lot (lot SVKA-01) was used for generating analytical similarity assessment data for tmTNF-α binding activity.

Table 3.2.R.2-4 Similarity Assessment for tmTNF-α Binding Activity for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Relative Activity to Reference Standard (%)
Test product	FKB327 DS	10	Average	97.6
			SD	6.3
			Maximum	107.0
			Minimum	88.6
Reference product	US-licensed Humira	10	Acceptance range	79.1–115.9
Results				Pass

Assay qualification: The mTNF binding assay was qualified with respect to specificity, precision, and linearity. FKB327 binding increased with concentration increment specifically (0.03 to 3000 ng/mL), demonstrating assay specificity. The linear range was 50-150% relative potency. The intra- and inter-assay precision were determined to be 1.6% and 18.8%, respectively.

Assessor Comment: *All FKB327 DS lots tested were within the established quality range for tmTNF-α Binding activity and support that FKB327 is similar to U.S.-licensed Humira.*

3.2.R.2.2.3 Binding to Fcγ Receptors and FcRn

The binding affinities of FKB327 and U.S.-licensed Humira to the human Fcγ receptors, including FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa-F158 (FcγRIIIa(F)), FcγRIIIa-V158 (FcγRIIIa(V)), FcγRIIIb-NA1 (FcγRIIIbNA1), FcγRIIIb-NA2 (FcγRIIIbNA2) and human FcRn, were evaluated by SPR assays. The Fc receptors were immobilized on a biosensor chip respectively. The FKB327 or U.S.-licensed Humira samples were injected over the surface of the biosensor at various concentrations to measure the Fc receptor binding. The dissociation constant K_D for each sample was calculated by non-linear regression of the binding curves. The same 10 independent FKB327 DS lots and 10 lots of U.S.-licensed Humira were tested for each of the Fc receptors. The SPR assay data were analyzed using quality ranges and summarized in Table 3.2.R.2-5, Table 3.2.R.2-6, and Table 3.2.R.2-7. The statistical quality range of K_D for binding to each Fc receptor was derived from the 10 U.S.-licensed Humira lots. As indicated in Table 3.2.R.2-5 and Table 3.2.R.2-7, all FKB327 DS lots tested were within the quality ranges with respect to FcγRI, FcγRIIa, FcγRIIb, and FcRn binding.

The quality range of 0.97-1.06 for FcγRIIIa-F158 binding was established from the 10 U.S.-licensed Humira lots, while the quality range of FcγRIIIa-V158 is 4.81-5.22. The RIIIa-F158 K_D of FKB327 DS lots ranged from 0.94-1.00 and eight lots were out of the lower limit of quality range by 0.01-0.03. For FcγRIIIa-V158 binding, FKB327 DS lots ranged from 4.74-5.05 and three lots were below the lower limit of quality range by 0.01-0.07.
The quality range of 0.93-1.28 for FcγRIIIb-NA1 binding was established from the 10 U.S.-licensed Humira lots, while the quality range of FcγRIIIb-NA2 is 0.93-1.05. The FcγRIIIb-NA1 K_D of FKB327 DS lots ranged from 0.94-1.09. All the lots were within the quality ranges of U.S.-licensed Humira. For FcγRIIIb-NA2 binding, FKB327 DS lots ranged from 0.87-0.99 and five lots were below the lower limit of quality range by 0.04-0.06.

Table 3.2.R.2-5 Similarity Assessment for Binding Affinity to FcγRI, FcγRIIa and FcγRIIb Receptors of FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Dissociation constant (K_D)		
				FcγRI ($\times 10^{-10}$ M)	FcγRIIa ($\times 10^{-6}$ M)	FcγRIIb ($\times 10^{-5}$ M)
Test product	FKB327 DS	10	Average	4.05	7.99	1.48
			SD	0.20	0.30	0.07
			Maximum	4.36	8.47	1.57
			Minimum	3.82	7.65	1.38
Reference product	US-licensed Humira	10	Acceptance range	3.03–5.21	7.41–9.15	1.39–1.83
Results				Pass	Pass	Pass

Table 3.2.R.2-6 Similarity Assessment for Binding Affinity to FcγRIIIa(F), FcγRIIIa(V), FcγRIIIb-NA1 and FcγRIIIb-NA2 Receptors of FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Dissociation constant (K_D)			
				FcγRIIIa (F) ($\times 10^{-6}$ M)	FcγRIIIa (V) ($\times 10^{-6}$ M)	FcγRIIIb-NA1 ($\times 10^{-5}$ M)	FcγRIIIb-NA2 ($\times 10^{-5}$ M)
Test product	FKB327 DS	10	Average	0.96	4.90	0.98	0.92
			SD	0.02	0.11	0.05	0.05
			Maximum	1.00	5.05	1.09	0.99
			Minimum	0.94	4.74	0.94	0.87
Reference product	US-licensed Humira	10	Acceptance range	0.97–1.06	4.81–5.22	0.93–1.28	0.93–1.05
Results				Not Pass	Not Pass	Pass	Not Pass

Table 3.2.R.2-6 Similarity Assessment for Binding Affinity to FcRn of FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Dissociation constant (K_D) ($\times 10^{-8}$ M)
Test product	FKB327 DS	10	Average	7.08
			SD	0.34
			Maximum	7.59
			Minimum	6.64
Reference product	US-licensed Humira	10	Acceptance range	5.84–8.81
Results				Pass

Assay qualification: The SPR assay was qualified to assess FKB327 binding to human Fcγ receptors and FcRn. The equilibrium dissociation constants (KD) of FKB327 binding to each of Fc receptors (FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa (F), FcγRIIIa (V), FcγRIIIb NA1, FcγRIIIb NA2, and FcRn) were calculated respectively based on the association rate constants and dissociation rate constants measured. The results showed an intra-precision of 0.6 - 6.4% and an inter-precision of 2.0 -20% geometric relative standard deviation (RSD). There was no interference from assay matrix.

Assessor Comment: *All FKB327 DS lots tested were within the established quality range for FcγRI, FcγRIIa, FcγRIIb, FcγRIIIb-NA1, and FcRn binding and, supporting similarity of FKB327 and U.S.-licensed Humira. N-linked glycans in the Fc region of IgG1 monoclonal antibodies modulate FcγRIII binding and Fc-mediated effector functions (e.g., ADCC and CDC). It is well-established that the absence of core fucose leads to enhanced FcγRIII binding and subsequently promotes ADCC activity, while sialylation, galactosylation and high mannose may also play a role. Data from assessment of N-linked glycan profile showed that FKB327 had slightly higher levels of sialylation, afucosylation, and galactosylation; and a slightly lower level of high mannose when compared to Humira (refer to section 3.2.R.2.2.8 below).*
The slightly lower dissociation constants observed for FKB327 compared to Humira in the assays for FcγRIIIa(F), FcγRIIIa(V), and FcγRIIIb-NA2, are consistent with the differences observed in the glycan profiles. However, the results of effector functions (i.e., ADCC and CDC) were similar for FKB327 and U.S.-licensed Humira (refer to section 3.2.R.2.2.6 below), indicating that the differences in glycan profiles and the resulting differences in FcγRIII binding observed can be mitigated and have minimal effect on effector functions. Therefore, the differences in glycan profiles and FcγRIII binding between FKB327 and U.S.-licensed Humira would not preclude determination of similarity of FKB327 and U.S.-licensed Humira.

3.2.R.2.2.4 Induction of Apoptosis (Reverse Signaling)

Direct apoptosis induced by Fab region of adalimumab against tmTNF-α expressing cells is a likely mechanism of action for adalimumab. The apoptosis-inducing activity was evaluated by a cell-based assay using tmTNF-α expressing EL-4 cell line. The EL-4 cells were incubated with varying concentrations of FKB327 or Humira to induce apoptosis. Cell apoptosis was determined by flow cytometry with Annexin V-FITC. EC_{50} was determined for both the reference standard and samples and then the relative potency was calculated for each sample against the reference standard.

The similarity assessment included the comparison of 10 independent FKB327 DS lots to 13 U.S.-licensed Humira DP lots. The applicant derived the statistical quality range of 82.8-108.1% relative activity from the 11 U.S.-licensed Humira lots. All FKB327 DP lots tested were within quality range for apoptosis induction. Only one reference standard lot (lot SVKA-01) was used for generating comparative analytical assessment data for reverse signaling activity.

Table 3.2.R.2-7 Similarity Assessment of Apoptosis Induction for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Relative Activity to Reference Standard (%)
Test product	FKB327 DS	10	Average	102.2
			SD	5.8
			Maximum	113.5
			Minimum	95.6
Reference product	US-licensed Humira	13	Acceptance range	82.8–108.1
Results				Pass

Assay qualification: The cell-based apoptosis assay was qualified. The linear range was 50-150% relative potency, and the assay accuracy in the linear range was 6.2%. Linearity (0.995) was demonstrated by calculating the coefficient of determination. The intra- and inter-assay precision were 8.1% and 8.3% respectively. No interference from assay matrix observed.

Assessor Comment: *90% of FKB327 DS lots tested were within the established quality range for apoptosis induction and supported similarity of FKB327 and U.S.-licensed Humira.*

3.2.R.2.2.5 Antibody-dependent Cellular Cytotoxicity (ADCC) Activity

ADCC occurs when IgG binds to antigens expressed on target cells and the IgG Fc domains engage Fc receptors (e.g., FcγRIIIa) on the surface of NK cells, leading to the activation of the NK cells, with concomitant granule exocytosis and target cell death. It is known that U.S.-licensed Humira has moderate ADCC activity. The ADCC activity was assessed using the tmTNF-α expressing EL-4 cell line for FKB327 and U.S.-licensed Humira. In this assay, the natural killer cell line NK-92 was used as the effector cells and tmTNF-α expressing EL-4 as the target cells. The EL-4 cells were first labeled with fluorescent calcein, and then mixed with NK-92 cells and serial dilutions of the reference standard or samples. The degree of EL-4 cell death was quantified by measurement of fluorescence released. EC_{50} was determined for both the reference standard and samples. The relative potency was calculated for each sample against the reference standard.

The similarity assessment included the comparison of 10 independent FKB327 DS lots to 10 U.S.-licensed Humira DP lots. The statistical quality range of 88.3-129.5% was established from the 10 U.S.-licensed Humira lots. The FKB327 DP lots tested ranged from 90.4-122%, which were within the quality range for ADCC activity. The reference standard lot SVKA-01 was used for generating comparative analytical assessment data for ADCC activity.

Table 3.2.R.2-8 Similarity Assessment of ADCC activity for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Relative Activity to Reference Standard (%)
Test product	FKB327 DS	10	Average	105.9
			SD	5.01
			Maximum	112.2
			Minimum	95.2
Reference product	US-licensed Humira	10	Acceptance range	88.3–129.5
Results				Pass

Assay qualification: The ADCC assay was qualified with a linear range of 50-150% relative potency, while the correlation coefficient of the regression line was 0.970 in the range. The intra- and inter-assay precision were 10.2% and 10.9% relative standard deviation. Specificity was demonstrated by lack of interference from assay matrix

Assessor Comment: *All FKB327 DP lots tested were within the established quality range for ADCC activity and support similar ADCC activity for FKB327 and U.S.-licensed Humira.*

3.2.R.2.2.6 Complement-dependent Cytotoxicity (CDC) Assay
CDC is an immune mechanism associated with the interaction of IgG Fc domains and complement system. Adalimumab mediated CDC leads to the lytic death of the tmTNF-α expressing target cells. The CDC activity was assessed using the tmTNF-α expressing EL-4 cell line for FKB327 and U.S.-licensed Humira. The EL-4 cells labeled with fluorescent calcein were first incubated with serial dilutions of the reference standard or samples; and then rat complement was added. The degree of EL-4 cell death was quantified by measurement of fluorescence released. EC_{50} was determined for both the reference standard and samples. The relative potency was calculated for each sample against the reference standard.

Nine lots of FKB327 DP and 14 lots of U.S.-licensed Humira were assessed for CDC activity. As indicated in table 3.2.R.2-9, the statistical quality range of 89.1-108.1% relative potency for the CDC assay were derived from 14 U.S.-licensed Humira lots. The relative CDC activity of FKB327 DP ranges from 91.3 to 101.4% and all lots assessed fall within the quality range. The reference standard lot SVKA-01 was used for generating comparative analytical assessment data for CDC activity.

Table 3.2.R.2-9 Similarity Assessment of CDC activity for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Relative Activity to Reference Standard (%)
Test product	FKB327 DS/DP	9	Average	99.0
			SD	4.2
			Maximum	105.7
			Minimum	91.3
Reference product	US-licensed Humira	14	Acceptance range	89.1–108.1
Results				Pass

Assay qualification: The cell-based assay was qualified for assessment of FKB327 CDC activity. The linear range of 60-140% relative potency and a linearity of 0.992 were demonstrated. The assay accuracy in the range was demonstrated with a precision of 3.5-5.8% relative standard deviation.

Assessor Comment: *All FKB327 DP lots tested were within the established quality range for CDC activity, supporting similarity of FKB327 and U.S.-licensed Humira.*

3.2.R.2.2.7 Binding to C1q

C1q is the first sub-component of the classical complement pathway. Binding of C1q to IgG Fc domain is the first step in the CDC mechanism. The binding activity to C1q was evaluated for FKB327 DS and U.S.-licensed Humira by ELISA, where bound C1q is detected using an anti-C1q horseradish peroxidase conjugated antibody. The relative binding potency was calculated for each sample against the reference standard.

Ten independent lots of FKB327 DS and 14 lots of U.S.-licensed Humira were assessed. Table 3.2.R.2-10 shows the quality range of 79.7-100% relative binding potency, which were derived from the 14 U.S.-licensed Humira lots. The range of FKB327 DS lots is 93.1-101.5%, which were within the quality range. Only one reference standard lot (lot SVKA-01) was used for generating data for analytical similarity assessment of C1q binding.

Table 3.2.R.2-10 Similarity Assessment of C1q Binding for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Relative Activity to Reference Standard (%)
Test product	FKB327 DS	10	Average	97.3
			SD	2.4
			Maximum	101.5
			Minimum	93.1
Reference product	US-licensed Humira	14	Acceptance range	79.7–100.0
Results				Pass

Assay qualification: The ELISA was qualified for assessment of FKB327 binding to C1q. The linear range was demonstrated as 50-200% relative potency. The correlation coefficient was 0.9966 and sufficient linearity was obtained. The assay recovery rate (%) in this range were 85.7 to 102.5%. The intra-assay precision of 2,2% and inter-assay precision of 17.6% were demonstrated.

Assessor Comment: *90% FKB327 DS lots tested were within the established quality range for C1q Binding. Data provided support similar C1q binding activity for FKB327 and U.S.-licensed Humira.*

3.2.R.2.2.8 Heterogeneity due to N-linked glycosylation

It is known that IgG1 effector functions (e.g., ADCC, CDC), which are mediated by Fc domain or complement receptor binding, are indirectly impacted by the levels of N-linked glycosylation, such as afucosylation, high mannose, galactosylation, and sialylation. In general, higher levels of afucosylation, galactosylation, and high mannose glycan increase binding affinity of IgG1 to FcγRIIIa, resulting in enhanced ADCC activity. High mannose content and sialylated species are relevant to product serum half-life through differential clearance (e.g., FcRn binding) and subsequently affect product PK. Additionally, the level of galactosylation could impact CDC activity through C1q binding.

The similarity assessment included the comparison of 10 FKB327 DS lots to 10 U.S.-licensed Humira DP lots. N-linked glycan profiling along with monosaccharide content, glycosylation site occupancy and non-consensus glycosylation were assessed. The statistical quality ranges were derived from the 10 U.S.-licensed Humira lots.

N-linked glycan profile

The N-linked glycan profile of FKB327 and U.S.-licensed Humira was evaluated by RP-HPLC after the glycans were hydrolyzed with N-glycosidase F and labelled with o-aminobenzamide. The eluted peaks were monitored by fluorescence detection. The structure of each peak from both FKB327 and U.S.-licensed Humira samples were analyzed by MALDI-TOF-MS. Each peak from the N-linked glycan profile was assigned to following groups based on their structures

- Sialylated glycans (SA)
- Incompletely processed-species (IP), including hybrid and high-mannose (M5) glycans
- Afucosylated glycans (F0), including G1F0 and G0F0
- Core-fucosylated glycans (F1), including G2F1, G1F1 and G0F1

Comparison of the major N-linked glycans for FKB327 DS and U.S.-licensed Humira lots are presented in table 3.2.R.2-11 and 3.2.R.2-12 below.

The level of core-fucosylated glycans (F1, total of G2F1, G1F1 and G0F1) in FKB327 DS lots ranged from 86.8 to 88.8% and was within the quality range of U.S.-licensed Humira (84.5-90.9%), while the amount of afucosylated glycans (F0, total of G1F0 and G0F0) of FKB327 DS lots (4-5%) was above the quality range of U.S.-licensed Humira (1.0-1.2%).

The level of incompletely processed-species (IP, 3.9-4.6%) in FKB327 lots, including hybrid type glycans and high-mannose glycans (M5, 1.3-1.8%) were below the quality ranges of U.S.-licensed Humira (IP: 8.0-14.1%; M5: 2.7-6.2%), whereas the amount of sialylated glycans of all FKB327 lots (2.7-3.9%) exceeded the quality range of U.S.-licensed Humira (0.0-0.4%).

A relatively higher molar ratio of galactose (Gal/N) was observed in FKB327 DS lots (0.24-0.35 mol/mol) compared to the quality range of U.S.-licensed Humira (0.23-.026 mol/mol), indicating a higher level of galactosylation in FKB327 DS lots.

Table 3.2.R.2-11 Similarity Assessment of **N-Linked Glycan Profile for FKB327 Compared with U.S.-licensed Humira**

Product		**Number of Lots**	**Item for Assessment**	**SA (%)**	**IP (%)**	**M5 (%)**	**G1F0 (%)**	**G0F0 (%)**	**F0 (%)**
Test product	FKB327 DS	10	Average	3.3	4.2	1.5	0.8	3.9	4.7
			SD	0.4	0.2	0.2	0.2	0.2	0.3
			Maximum	3.9	4.6	1.8	1.1	4.2	5.0
			Minimum	2.7	3.9	1.3	0.6	3.4	4.0
Reference product	US-licensed Humira	10	Acceptance range	0.0–0.4	8.0–14.1	2.7–6.2	0.0–0.4	0.7–1.2	1.0–1.2
Results				Not Pass	Not Pass	Not Pass	Not Pass	Not Pass	Not Pass

F0: Total of G0F0 and G1F0

Table 3.2.R.2-12 Similarity Assessment of **N-Linked Glycan Profile for FKB327 Compared with U.S.-licensed Humira**

Product		Number of Lots	Item for Assessment	G2F1 (%)	G1F1 (%)	G0F1 (%)	F1 (%)	Gal/N (mol/mol)
Test product	FKB327 DS	10	Average	1.8	21.3	64.7	87.8	0.28
			SD	0.5	2.6	3.7	0.7	0.04
			Maximum	2.7	26.0	68.9	88.8	0.35
			Minimum	1.4	18.5	58.3	86.8	0.24
Reference product	US-licensed Humira	10	Acceptance range	1.8–2.2	16.2–19.2	66.0–70.1	84.5–90.9	0.23–0.26
Results				Not Pass	Not Pass	Not Pass	Pass	Not Pass

F1: Total of G0F1, G1F1 and G2F1; Gal/N: Molar ratio of galactose per N-linked glycan calculated from G0F0, G1F0, G0F1, G1F1 and G2F1

Monosaccharide Composition

The N-glycans of FKB327 DS and U.S.-licensed Humira were released by heat treatment followed by labelling with fluorescence tags, separated by RP-HPLC and quantified by fluorescence detection. The levels of neutral sugar (Man, Fuc, and Gal), amino sugar, and sialic acid in 10 independent lots of FKB327 DS were compared to the quality ranges of 10 U.S.-licensed Humira lots (Table 3.2.R.2-13 and Table 3.2.R.2-14).

As indicated in table 3.2.R.2-13, the amount of Man, Fuc and GlcNAc residues in FKB327 DS were similar to those in Humira and the results met the quality ranges of U.S.-licensed Humira. However, the amount of Gal residue in FKB327 DS lots (0.46-0.70 mol/mol) was above the quality range of U.S.-licensed Humira (0.29-0.37). In addition, the levels of sialic acids in FKB327 lots exceeded the quality ranges of U.S.-licensed Humira (Table 3.2.R.2-14). The results for sialic acids and Gal residue correlated with the results for N-linked glycan profiling.

Table 3.2.R.2-13 Similarity Assessment for Monosaccharide Composition (Neutral and Amino Sugar) for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Neutral Sugar (mol/mol)			Amino Sugar (mol/mol)
				Gal	Man	Fuc	GlcNAc
Test product	FKB327 DS	10	Average	0.55	4.93	1.61	5.60
			SD	0.09	0.13	0.04	0.14
			Maximum	0.70	5.12	1.66	5.80
			Minimum	0.46	4.73	1.55	5.46
Reference product	US-licensed Humira	10	Acceptance range	0.29–0.37	4.67–6.28	1.38–1.73	4.66–6.03
Results				Not Pass	Pass	Pass	Pass

Table 3.2.R.2-14 Similarity Assessment for Monosaccharide Composition (Sialic Acid) for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Sialic Acid (mol/mol)	
				Neu5Ac	Neu5Gc
Test product	FKB327 DS	10	Average	0.0873	0.0023
			SD	0.0113	0.0004
			Maximum	0.1032	0.0031
			Minimum	0.0721	0.0018
Reference product	US-licensed Humira	10	Acceptance range	0.0058–0.0083	0.0002–0.0005
Results				Not Pass	Not Pass

Assay qualification: The RP-HPLC method is proposed as a release test for FKB327. Information regarding the assay procedure and assay validation are described in section 3.2.S.4.2 Analytical Procedures and section 3.2.S.4.3 Validation of Analytical Procedures.

Assessor Comment: *The results of N-linked glycan profile and monosaccharide composition showed that FKB327 had slightly higher levels of sialylation, afucosylation and galactosylation and a lower level of high mannose when compared to Humira. These results are consistent with the data derived from FcγRIII binding assays, showing the increased binding affinity of FKB327 to FcγRIII. The levels of these glycosylation variants are known to have a potential effect on the ADCC and CDC activities and on the PK profile. However, these minor differences are mitigated by the fact that no significant differences in ADCC and CDC activities were observed between FKB327 and U.S.-licensed Humira. In addition, a RP-HPLC assay is included in the release testing for FKB327 DS to control the N-linked glycan variants. This will mitigate the risk that N-linked glycans drift from the levels observed in the comparative analytical assessment. Overall, the differences observed in N-linked glycan profiles do not preclude a determination that FKB327 is highly similar to U.S.-licensed Humira.*

Glycosylation Site Occupancy

The glycosylation site occupancy was assessed by reduced CE-SDS for FKB327 DS and U.S.-licensed Humira. Glycosylation was shown to occur at the Asn^{301} residue of the HC of FKB327 and U.S.-licensed Humira. As shown in Table 3.2.R.2-15, the glycosylation site occupancy of ten lots of FKB327 DS was consistent at a value of approximately 99%, which is slightly higher than the quality range of U.S.-licensed Humira (96.2-97.9%).

Table 3.2.R.2-15 Similarity Assessment of Glycosylation Site Occupancy for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Glycosylation Site Occupancy (%)
Test product	FKB327 DS	10	Average	99.0
			SD	0.1
			Maximum	99.1
			Minimum	98.9
Reference product	US-licensed Humira	10	Acceptance range	96.2–97.9
Results				Not Pass

Assay qualification: The reduced CE-SDS method is proposed as a release test for FKB327. Information regarding the assay procedure and assay validation are described in section 3.2.S.4.2 Analytical Procedures and section 3.2.S.4.3 Validation of Analytical Procedures.

Assessor Comment: *The minor difference observed regarding glycosylation site occupancy will not preclude a determination of similarity between FKB327 and U.S.-licensed Humira, taking into account the results of ADCC and CDC assays.*

Non-consensus Glycosylation

The level of non-consensus glycosylation was assessed by reduced CE-SDS for FKB327 DS and U.S.-licensed Humira. The amount of non-consensus glycosylated species (NCGS) was estimated as a percentage of non-consensus glycosylated HC per total HC. The results, as presented in Table 3.2.R.2-16, showed that the NCGS content for ten lots of FKB327 DS was 0.4-0.8%, which is within the quality range of U.S.-licensed Humira (0.1-1.3%).

Table 3.2.R.2-16 Similarity Assessment for Non-consensus Glycosylation Content for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Non-consensus glycosylation content (%)
Test product	FKB327 DS	10	Average	0.6
			SD	0.1
			Maximum	0.8
			Minimum	0.4
Reference product	US-licensed Humira	10	Acceptance range	0.1–1.3
Results				Pass

Assessor Comment: *All FKB327 DS lots tested were within the established quality range of U.S.-licensed Humira, supporting similarity of FKB327 and U.S.-licensed Humira.*

3.2.R.2.2.9 Charge Variants by CEX-HPLC

It is known that IgG monoclonal antibodies commonly display charge heterogeneity arising from post-translational modifications, which may impact product efficacy, safety, and immunogenicity. Typical modifications that contribute to a complex charge profile may include, but are not limited to, C-terminal heterogeneity, N-terminal pyroglutamate, glycoforms, deamidation, sialic acid, and oxidation. Ten lots of FKB327 DS and 10 lots of U.S.-licensed Humira were assessed for charge heterogeneity by CEX-HPLC method. The CEX-HPLC method is currently used as a release assay for FKB327 DS and DP.

The charge variants profile of FKB327 and U.S.-licensed Humira contains 3 distinct regions: acidic, main, and basic peaks. The percentage content of each peak area is calculated to evaluate the overall charge heterogeneity. Table 3.2.R.2-17 shows the statistical quality ranges for acidic species (11.8-15.8%), main peak (55.1-65.1%), and basic species (20.3-31.9%) derived from the 10 lots of U.S.-licensed Humira. All FKB327 DS lots have acidic variants (22.5-30.9%) above the upper limit of U.S.-licensed Humira quality range and basic variants (5.9-10.8%) below the lower limit of quality range. For the main peak, three FKB327 lots were above the upper limit of the quality range.

Table 3.2.R.2-17 Similarity Assessment for CEX-HPLC Results of FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Acidic Peak (%)	Main Peak (%)	Basic Peak (%)
Test product	FKB327 DS	10	Average	27.4	63.7	8.9
			SD	2.0	2.0	1.6
			Maximum	30.5	66.7	10.8
			Minimum	22.9	60.0	5.9
Reference product	US-licensed Humira	10	Acceptance range	11.8–15.8	55.1–65.1	20.3–31.9
Results				Not Pass	Not Pass	Not Pass

CEX-HPLC analysis indicated a higher level of the basic species in U.S.-licensed Humira lots when compared with the results for FKB327. After carboxypeptidase B treatment, the majority of basic peaks in U.S.-licensed Humira shift towards the main peak, while the basic peaks slightly decreased for FKB327, demonstrating that the principal factor contributing to the difference of basic species between FKB327 DS and U.S.-licensed Humira is the C-terminal lysine on the IgG heavy chains.
To further characterize the charge variants, CEX-HPLC fractions were collected from FKB327 and U.S.-licensed Humira. The contents of N- and C-terminal variant of the HC, size variants, sialylated glycan, glycated form, oxidized form and deamidated/isomerized form were also investigated for each fraction. The following biological functions were also assessed for each fraction.

- FcRn binding affinity,
- Cytotoxicity neutralizing activity,
- Apoptosis activity
- ADCC activity
- CDC activity

The results showed that the biological activities of each fraction collected from FKB327 and U.S.-licensed Humira were similar.

Assay Qualification: The CEX-HPLC method is currently included in the release and stability testing for FKB327. Refer to section 3.2.S.4.2 Analytical Procedures and section 3.2.S.4.3 Validation of Analytical Procedures for review details regarding the assay procedure and assay validation.

Assessor comment: *CEX-HPLC analysis indicated a higher level of the acidic species and lower amount of the basic species in FKB327 lots when compared with the results for U.S.-licensed Humira. Carboxypeptidase B treatment results indicated that C-terminal lysine is the major contributor to the higher level of basic species in Humira (~80%), while only 10% in FKB327. Since c-terminal lysine will be cleaved in vivo, the relatively lower basic species in FKB327 did not show any impact on the biological functions of the product. C-terminal amidated proline and HMWS were observed to be higher in the basic fractions of FKB327 than in Humira. However, due to the relative low abundance of these variants, the difference did not show significant impact on the biological activities of the products.*

The acidic variants in both FKB327 and Humira were characterized to contain sialylation of N-glycan, LMWS, glycation, and deamidation/isomerization. Sialylated glycans is the major contributor to the relatively higher abundant of acidic variants in FKB327. Glycation and deamidation/isomerization were observed to be higher in acidic peaks for both products. But the total amount of these variants was at low levels and was not expected to impact the biological activity of the products. Oxidations of Met^{256} *and* Met^{432} *were observed to be higher in both acidic and basic peaks and the total amount of the variants was shown to be comparable between FKB327 and Humira.*

The bioassay results for each CEX-HPLC fraction indicated that the main peak, acidic and basic species from FKB327 and U.S.-licensed Humira are comparable with respect to biological activities of cytotoxicity neutralization, apoptosis, FcRn binding, ADCC and CDC. The acidic fractions from both products show relatively lower activities for cytotoxicity neutralization, ADCC and CDC than the main peak fraction in a similar pattern. Since the percentage of acidic variants is higher in FKB327 than U.S.-licensed Humira, the specification of acidic variants of CEX-HPLC was tightened to ensure the bioactivities of FKB327 remain similar to Humira in future commercial lots. The differences in charge variants between FKB327 and U.S.-licensed Humira would not preclude a determination that FKB327 is highly similar to U.S.-licensed Humira.

3.2.R.2.2.10 Size Heterogeneity

Size heterogeneity is an intrinsic property of IgG monoclonal antibodies and may impact product efficacy, safety, immunogenicity or PK. The potential size variants include high molecular weight (HMW) species (e.g., dimers or higher order oligomeric species), middle and low molecular weight (MMW and LMW) species formed through truncation of the polypeptide backbone and/or incomplete assembly of IgG subunits, and NGHC. Ten lots of FKB327 DS and 10 lots of U.S.-licensed Humira was evaluated for size heterogeneity by Capillary Gel Electrophoresis with sodium dodecyl sulfate (CE-SDS), SEC-HPLC and field flow fractionation (FFF). The statistical quality ranges were derived from the 10 lots of U.S.-licensed Humira. The CE-SDS and SEC-HPLC methods are currently used as release assays for FKB327 DS and DP.

Size Exclusion Chromatography (SEC)

Table 3.2.R.2-18 shows the statistical quality ranges derived from the 10 U.S.-licensed Humira lots for main peak (≥ 99.3%), HMWs (≤ 0.6%) and LMWs (≤ 0.3%), respectively. The 10 FKB327 DS lots were tested and the ranges for main peak, HMWs and LMWs are 99.4-99.7%, 0.3-0.5% and 0-0.1%, respectively. All lots were within the US quality range, meeting the acceptance criteria for similarity.

The HMW species present in FKB327 DS and U.S.-licensed Humira were characterized with respect to molecular size, higher-order structure and biological activities. Each HMW fraction isolated by SEC-HPLC was assessed. The results showed that the HMWs in both FKB327 DS and US-Humira were mainly dimer species. The secondary and tertiary structure of the HMWS in FKB327 DS and U.S.-licensed Humira were similar. Regarding the biological activities, the FcRn binding and cytotoxicity neutralizing activities of HMWS were similar for FKB327 DS and U.S.-licensed Humira. Minor differences were observed in the apoptosis, ADCC and CDC assays between the HMWS from FKB327 and U.S.-licensed Humira lots. Considering that the HMWs are present at very low levels (≤ 0.5%) for both FKB327 DS and U.S.-licensed Humira and both products currently show similar biological activities as shown in Sections above, we do not anticipate that the differences observed would affect the efficacy and safety of the product.

Table 3.2.R.2-18 Similarity Assessment of the SE-HPLC Results for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Purity (%) (Main Peak)	HMWS (%)	LMWS (%)
Test product	FKB327 DS	10	Average	99.6	0.4	0.1
			SD	0.1	0.1	0.0
			Maximum	99.7	0.5	0.1
			Minimum	99.4	0.3	0.0
Reference product	US-licensed Humira	10	Acceptance range	≥ 99.3	≤ 0.6	≤ 0.3
Results				Pass	Pass	Pass

Assay Qualification: The SEC-HPLC method is currently included in the release and stability testing for FKB327. Refer to section 3.2.S.4.2 Analytical Procedures and section 3.2.S.4.3 Validation of Analytical Procedures for review details regarding the assay procedure and assay validation.

Assessor comment: *All FKB327 DS lots tested were within the established quality range for size variants, supporting similarity of FKB327 and U.S.-licensed Humira. For the minor differences observed from the extended characterization studies for the HMWs of FKB327 and U.S.-licensed Humira lots, considering that the HMWs of 0.5% are very low and FKB327 and U.S.-licensed Humira lots are comparable for all biological activities. The differences in ADCC and CDC activities of HMWs do not preclude a determination that FKB327 is highly similar to U.S.-licensed Humira.*

Capillary Gel Electrophoresis with sodium dodecyl sulfate (CE-SDS)

Size heterogeneity was assessed for FKB327 DS and U.S.-licensed Humira lots by CE-SDS under non-reducing and reducing conditions.

The reduced CE-SDS (rCE-SDS) detects the main peaks corresponding to the HC and LC, along with fragments (e.g., LMW and MMW species), non-reducible HMW species, and the peaks lacking consensus glycosylation (NGHC). In comparison to U.S.-licensed Humira, no novel peaks were observed in the electropherograms for FKB327 DS. Table 3.2.R.2-19 shows the statistical quality ranges derived from the 10 U.S.-licensed Humira lots for purity (HC+LC, ≥ 95.8%), HMWs (≤ 1.9%), LMWs (≤ 0.2%), MMWs (≤ 0.7%), and NGHC (1.4-2.5%). The 10 FKB327 DS lots were tested and the ranges for main purity, HMWs, LMWs, MMWs, and NGHC are 97.7-98.1%, 0.9-1.2%, 0.1-0.2%, 0.2-0.3%, and 0.6-0.7%, respectively. All lots were within the US quality ranges with the exception of NGHC. The amounts of the NGHC in FKB327 DS lots were slightly lower than those of U.S.-licensed Humira, which were consistent with the results from the analysis of glycosylation site occupancy.

Table 3.2.R.2-19 Similarity Assessment of the CE-SDS (R) Results for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Purity[a] (%)	LMWS (%)	MMWS (%)	NGHC (%)	HMWS (%)
Test product	FKB327 DS	10	Average	97.9	0.2	0.3	0.7	1.1
			SD	0.1	0.1	0.0	0.0	0.1
			Maximum	98.1	0.2	0.3	0.7	1.2
			Minimum	97.7	0.1	0.2	0.6	0.9
Reference product	US-licensed Humira	10	Acceptance range	≥ 95.8	≤ 0.2	≤ 0.7	1.4–2.5	≤ 1.9
Results				Pass	Pass	Pass	Not Pass	Pass

[a] Purity was calculated by the sum of the HC and the LC

Assay Qualification: The reduced and non-reduced CE-SDS methods are currently included in the release and stability testing for FKB327. Refer to section 3.2.S.4.2 Analytical Procedures and section 3.2.S.4.3 Validation of Analytical Procedures for review details regarding the assay procedure and assay validation.

Assessor comment: *All FKB327 lots tested were within the quality ranges for purity, HMW, LMW, and MMW. The amounts of the NGHC in U.S.-licensed Humira is higher when compared to FKB327, which is consistent with the results of glycosylation site occupancy for FKB327 and U.S.-licensed Humira. However, the relative abundance of NGHC is very low and is not expected to cause any detectable difference in biological activities. These minor differences between FKB327 and US-Humira with respect to N-linked glycosylation would not preclude the conclusion of analytical similarity.*

Non-reduced CE-SDS (nrCE-SDS) was performed under denaturing conditions to unfold the protein and disrupt non-covalent associations. The levels of intact IgG and product-related fragment species present in FKB327 and U.S.-licensed Humira were analyzed. Both nrCE-SDS electropherograms of FKB327 and U.S.-licensed Humira consist of one main peak, which is the intact IgG, along with low levels of LMW pre-peaks (e.g., HHL and HL)

and trace level of post-peaks as HMW species. No missing peak or novel peaks observed in the electropherograms of FKB327 DS lots. Table 3.2.R.2-20 shows the statistical quality ranges derived from the 10 U.S.-licensed Humira lots for intact IgG (≥ 97.5%), LMW fragments (≤ 2.2%) and HMW species (≤ 0.5%), respectively. In comparison to U.S.-licensed Humira, higher levels of LMWs (2.8-3.4%) with a slightly lower percentage of the main peak (96.4-97.1%) in FKB327 DS lots were observed. The percentage of HMWs (0.1-0.3%) in FKB327 DS was comparable to that in Humira. The main peak and the LMWS were outside of the quality ranges.

Table 3.2.R.2-20 Similarity Assessment of the CE-SDS (NR) Results for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Purity (%)	LMWS (%)	HMWS (%)
Test product	FKB327 DS	10	Average	96.8	3.1	0.1
			SD	0.2	0.2	0.1
			Maximum	97.1	3.4	0.3
			Minimum	96.4	2.8	0.1
Reference product	US-licensed Humira	10	Acceptance range	≥ 97.5	≤ 2.2	≤ 0.5
Results				Not Pass	Not Pass	Pass

Assessor Comment: *Increased levels of LMW fragments and corresponding lower percentage of main peak were observed in the FKB327 DS lots tested. However, the levels of LMW fragments in FKB327 DS and U.S.-licensed Humira were low and the difference between FKB327 DS and U.S.-licensed Humira was small (≤ 1.2%). Additionally, all the FKB327 DS lots and FKB327 DP lots from these FKB327 DS lots showed comparable biological activities when compared to U.S.-licensed Humira (refer to section 3.2.R.2.1 and section 3.2.R.2.2). Therefore, the difference in LMW fragments does not preclude a determination that FKB327 is highly similar to U.S.-licensed Humira.*

Field Flow Fractionation (FFF)

Field flow fractionation was conducted to assess the size heterogeneity of FKB327 DS and U.S.-licensed Humira as an orthogonal test to the SE-HPLC analysis. FFF analysis was conducted using a mobile phase of PBS. Detection was conducted by monitoring UV absorbance at 215 nm. Ten FKB327 DS lots and 10 U.S.-licensed Humira lots were tested for purity, LMWs and HMWs, and quality range analysis was performed on the data set. Table 3.2.R.2-21 shows the statistical quality ranges derived from the 10 U.S.-licensed Humira lots for purity (≥ 99.5%), HMWs (≤ 0.3%), and LMWs (≤ 0.1%). For the FKB327 DS lots tested, the ranges for main purity and HMWs were 99.5-99.7% and 0.3-0.5%, respectively; while the LMWs was not detectable. All lots were within the quality ranges of US-Humira for purity and LMWs. However, FKB327 DS lots contained a slightly higher amount of HMWs that was above the US-Humira quality range.

Table 3.2.R.2-21 Similarity Assessment for FFF Results of FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	LMWS (%)	Main Peak (%)	HMWS (%)
Test product	FKB327 DS	10	Average	0.0	99.6	0.4
			SD	0.0	0.1	0.1
			Maximum	0.0	99.7	0.5
			Minimum	0.0	99.5	0.3
Reference product	US-licensed Humira	10	Acceptance range	≤0.1	≥99.5	≤0.3
Results				Pass	Pass	Not Pass

Assessor Comment: *All FKB327 DS lots tested were within the established quality range for purity and LMWs. Even though a slightly higher amount of HMWs were detected by FFF in FKB327 lots. The levels of HMWs (≤ 0.5%) is very low and the difference (≤ 0.2%) between FKB327 lots and U.S.-licensed Humira is small. Taking account of the SEC-HPLC results, the difference in HMWs does not preclude the conclusion of analytical similarity between FKB327 and U.S.-licensed Humira.*

3.2.R.2.2.11 Concentration of active ingredient

Protein concentration is assessed using the quality range analysis. The similarity assessment included the comparison of 22 FKB327 DP lots, which were produced from 6 independent FKB327 DS lots, to 30 U.S.-licensed Humira DP lots. The protein concentration of FKB327 DP and U.S.-licensed Humira was determined by ultraviolet spectroscopy at 280 nm. The applicant states that an experimentally determined extinction coefficient of 1.4 $mg^{-1}cm^{-1}mL$ was used for determination of protein concentration of FKB327 DP and U.S.-licensed Humira. As shown in Table 3.2.R.2-22, the statistical quality range of 47.54-51.8 mg/mL was derived from the 30 U.S.-licensed Humira lots. The results indicate that all 22 FKB327 DP lots (49.24-50.54 mg/mL) were within the quality range.

Table 3.2.R.2-22 Similarity Assessment for Protein Concentration for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Protein Concentration (mg/mL)
Test product	FKB327 DP	22	Average	50.09
			SD	0.32
			Maximum	50.54
			Minimum	49.24
Reference product	US-licensed Humira	30	Acceptance range	47.54–51.80
Results				Pass

Assay qualification: The ultraviolet (UV) spectroscopy procedure is validated as a quantitative method for the determination of the protein concentration of FKB327 drug substance and drug product. Refer to section 3.2.S.4.2 Analytical Procedures and section 3.2.S.4.3 Validation of Analytical Procedures for review details regarding the assay procedure and assay validation.

Assessor Comment: *The protein concentrations for all FKB327 DP lots were within the quality range of the U.S.-licensed Humira. The results support the conclusion that FKB327 DP protein concentration is similar with U.S.-licensed Humira.*

On November 20, 2019, an IR was sent to the applicant regarding how the extinction coefficient of FKB327 (1.4 $mg^{-1}\cdot cm^{-1}\cdot mL$) used for calculation of FKB327 protein concentration was determined. The applicant responded (amendment eCTD 0019) on December 09, 2019 with the requested information. The extinction coefficient of FKB327 was calculated from the absorbance of FKB327 samples at UV 280 nm divided by FKB327 protein concentration. The FKB327 protein concentration was calculated based on the leucine concentration measured, the theoretical leucine composition of FKB327 and the theoretical molecular weight of FKB327. The method used for determination of extinction coefficient of FKB327 is a common approach that is described in the literature and is acceptable.

3.2.R.2.2.12 Hydrophobic Heterogeneity

The hydrophobic heterogeneity of Fc fragment of FKB327 and U.S.-licensed Humira was evaluated by hydrophobic interaction chromatography (HI-HPLC). Samples were digested using papain, separated by HI-HPLC. Eluted peaks were detected at 215 nm. Ten independent lots of FKB327 DS and 10 lots of U.S.-licensed Humira were tested for similarity assessment. The chromatograms for FKB327 and U.S.-licensed Humira consist of the typical Fab peak, Fc main peak, and lower hydrophobic Fc pre-peaks. Quality range analysis was performed on this data set for the lower hydrophobic Fc pre-peaks. Table 3.2.R.2-23 shows the statistical quality range of 18.6-30.6% for Fc pre-peaks derived from the 10 U.S.-licensed Humira lots. All FKB327 DS lots tested have consistent levels of the Fc pre-peaks at 5.6-7.2%, which are below the lower limit of U.S.-licensed Humira quality range.

The applicant performed HI-HPLC on the same lots of FKB327 DS and U.S.-licensed Humira after CpB treatment. The Fc pre-peak areas in U.S.-licensed Humira lots significantly decreased due to CpB treatment, while no change was observed in FKB327 DS, indicating that the C-terminal lysine contributes to the difference in the Fc pre-peak profile between FKB327 DS and U.S.-licensed Humira. As shown in Table 3.2.R.2-24, the statistical quality range of Fc pre-peaks from the 10 U.S.-licensed Humira lots after CpB treatment were 4.6-8.9%. All FKB327 lots were within the quality range for the Fc pre-peaks (4.5-5.4%), supporting similarity.

Table 3.2.R.2-23 Similarity Assessment for HI-HPLC Results from FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Fc pre peak (%)
Test product	FKB327 DS	10	Average	6.4
			SD	0.4
			Maximum	7.2
			Minimum	5.6
Reference product	US-licensed Humira	10	Acceptance range	18.6–30.6
Results				Not Pass

Table 3.2.R.2-24 Similarity Assessment for HI-HPLC (CpB Treated) Result from FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Fc pre peak (%)
Test product	FKB327 DS	10	Average	4.9
			SD	0.2
			Maximum	5.4
			Minimum	4.5
Reference product	US-licensed Humira	10	Acceptance range	4.6–8.9
Results				Pass

Assessor Comment: *The results of HI-HPLC for FKB327 and U.S.-licensed Humira with or without CpB treatment demonstrated that there was no significant difference in hydrophobic variants between FKB327 DS and Humira other than the C-terminal lysine variants of the HC. Given C-terminal Lysine of monoclonal antibodies is enzymatically cleaved in vivo, the difference in the hydrophobic profile between FKB327 and U.S.-licensed Humira due to C-terminal Lysine variants are not expected to affect the safety and efficacy of the product, and would not preclude a determination that FKB327 is highly similar to U.S.-licensed Humira.*

3.2.R.2.2.13 Amino Acid Modifications

The amino acid modifications and sequence variants in FKB327 and U.S.-licensed Humira were determined in terms of C- and N-terminal variants, deamidation/isomerization, glycation, oxidation, sulfhydryl, thioether, trisulfide and cysteinylation. Peptide mapping with HPLC-UV/MS was used to identify and quantify the amino acid modifications and sequence variants unless another method was specified. Samples were denatured, alkylated and digested with Lys-C. The resulting peptides samples were separated, analyzed, and quantified by HPLC-UV/MS. Ten independent lots of FKB327 DS and 10 lots of U.S.-licensed Humira DP were tested for similarity assessment. Quality range analysis was performed on the data set for each of the amino acid modifications and sequence variants.

C-terminal Variants

As shown in table Table 3.2.R.2-25, the same three HC C-terminal variants (Lys^{451}, Gly^{450}, and Amidated Pro^{449}) were seen for FKB327 DS and U.S.-licensed Humira. However, the content of each variant was different between FKB327 DS and U.S.-licensed Humira. The quality ranges derived from the 10 U.S.-licensed Humira lots for Lys^{451}, Gly^{450}, and Amidated Pro^{449} were 3.9-10.3%, 88.9-95.6, and 0.4-1.0%, respectively. The sequence variant ranges in FKB327 DS lots for Lys^{451}, Gly^{450}, and Amidated Pro^{449} were 0.3-0.5%, 95.9-98.9%, and 0.7-3.7%, respectively. The results were outside of the similarity acceptance criteria.

Table 3.2.R.2-25 Similarity Assessment for C-terminal Variant Content of FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Content of C-terminal Variants (%)		
				Lys^{451}	Gly^{450}	Amidated Pro^{449}
Test product	FKB327 DS	10	Average	0.4	97.1	2.5
			SD	0.1	1.0	1.0
			Maximum	0.5	98.9	3.7
			Minimum	0.3	95.9	0.7
Reference product	US-licensed Humira	10	Acceptance range	3.9–10.3	88.9–95.6	0.4–1.0
Results				Not Pass	Not Pass	Not Pass

Assessor Comment: *FKB327 DS lots contain relatively higher levels of Gly^{450} and amidated Pro^{449}, and lower level of Lys^{451}when compared to these in U.S.-licensed Humira. The Gly^{450} is the major variant in both FKB327 and U.S.-licensed Humira. Literature reported that C-terminal lysine of monoclonal antibodies is enzymatically cleaved in vivo. The differences in C-terminal lysine variant does not affect product performance in vivo. The amidated Pro^{449} variant is at low level and the difference between FKB327 and U.S.-licensed Humira is minor, representing low risk on product quality. In addition, the C-terminal variants do not affect antigen binding and FcR binding. Taking together, the differences in C-terminal variants between FKB327 lots and US-Humira do not preclude a determination of analytical similarity.*

N-terminal Variants

Both FKB327 DS and U.S.-licensed DP were denatured, reduced, alkylated and digested with Lys-C. The resulting peptides were analyzed and quantified by HPLC-UV/MS with respect to N-terminal variants of the HC. As shown in Table 3.2.R.2-26, the same two kinds of N-terminal variants (Glu^{1} and pGlu^{1}) were observed in FKB327 DS and U.S.-licensed Humira. The level of each variant was similar between FKB327 DS and U.S.-licensed Humira, meeting the acceptance criteria for similarity.

Table 3.2.R.2-26 Similarity Assessment for N-terminal Variant Content of FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Content of N-terminal Variants (%)	
				Glu^{1}	pGlu^{1} [a]
Test product	FKB327 DS	10	Average	98.0	2.0
			SD	0.2	0.2
			Maximum	98.3	2.3
			Minimum	97.7	1.7
Reference product	US-licensed Humira	10	Acceptance range	97.9–98.5	1.5–2.1
Results				Pass	Pass

a: pyro-glutamic acid residue

Assessor Comment: *The levels of N-terminal variants of the HC in 90% FKB327 DP lots were within the quality range of the U.S.-licensed Humira. The results support the conclusion that FKB327 is similar with U.S.-licensed Humira in the levels of N-terminal variants.*

Deamidation/Isomerization

Deamidation is a common amino acid modification of IgG antibody that occurs on asparagine residues, generally resulting in isomerization of asparagine residues. The levels of deamidation and isomerization of the asparagine residues were evaluated for FKB327 and U.S.-licensed Humira by peptide mapping with mass spectrometric detection. The results indicated that the aspartic acid residues were deamidated and isomerized at consistent levels between FKB327 and US-Humira. The range of deamidation and isomerization for each asparagine residue in FKB327 DS lots were within the Humira quality range, meeting similarity criterion.

Table 3.2.R.2-27 Similarity Assessment for Deamidated/Isomerized Variant Content for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Content of Deamidated/Isomerized Variants (%)											
				HC									LC		
				Asn^{77} or Asn^{84}	Asn^{290}	Asn^{319} [a]		Asn^{365}	Asn^{388}	Asn^{393}	Asn^{388}, Asn^{393} or Asn^{394}	Asn^{438}	Asn^{137} [a]		Asn^{158}
Test product	FKB327 DS	10	Average	1.1	0.2	2.7	2.0	0.4	5.4	2.1	1.4	1.1	0.7	0.3	NA
			SD	0.1	0.0	0.3	0.2	0.1	1.0	0.8	0.2	0.2	0.1	0.0	NA
			Maximum	1.2	0.3	2.9	2.2	0.5	7.0	3.0	1.7	1.3	0.8	0.4	0.3
			Minimum	0.9	0.2	2.1	1.6	0.3	4.3	0.7	1.1	0.9	0.6	0.3	NA
Reference product	US-licensed Humira	10	Acceptance range	0.7–1.3	0.2–0.2	1.8–3.6	1.4–2.5	0.2–0.6	2.7–8.0	0.0–3.7	0.8–2.0	0.6–1.6	0.4–0.9	0.2–0.4	0.1–0.4
Results				Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass

a: Each content measured is expected to be either deamidated or isomerized species.

Assessor Comment: *Data provided support analytical similarity of FKB327 and U.S.-licensed Humira in terms of Asparagine residues deamidation and isomerization.*

Glycation

Glycation is a non-enzymatic reaction which generally occurs on the ε-amino group of lysine residues. Glycation of IgG mostly occurs during manufacture of products due to presence of glucose. The glycation of lysine imposes a spatial restriction such that it becomes resistant to trypsin digestion. The glycated species in FKB327 and U.S.-licensed Humira were separated after digestion using a column with a sorbitol gradient buffer and detected at 280 nm. Table 3.2.R.2-28 shows the statistical quality range from the 10 U.S.-licensed Humira lots for glycated species (0.6-1.9%). All FKB327 DS lots were within the quality range (1.2-1.9%), meeting the acceptance criterion for similarity.

Table 3.2.R.2-28 Similarity Assessment for Glycated Species Content for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Glycated Species (%)
Test product	FKB327 DS	10	Average	1.6
			SD	0.3
			Maximum	1.9
			Minimum	1.2
Reference product	US-licensed Humira	10	Acceptance range	0.6–1.9
Results				Pass

Assessor Comment: *Data provided support that FKB327 and U.S.-licensed Humira are similar in the level of glycation.*

Oxidation

Oxidation of methionine residues is a common post-translational modification or degradation pathway of IgG product that potentially results from exposure to oxygen, chemical oxidizing agents, and light exposure. The oxidation level of methionine residues was assessed for FKB327 and U.S.-licensed Humira. The peptides containing oxidized methionine residues are separated from non-oxidized peptides and quantified by HPLC-UV/MS. The same oxidized species (Met^{34} and Met^{432} on HC, and Met^{4} on LC) were observed for both FKB327 and U.S.-licensed Humira and Met^{256} HC was the main site of oxidation. Table 3.2.R.2-29 shows the statistical quality range of oxidation from the 10 U.S.-licensed Humira lots for Met^{34} (0.2-0.9%), Met^{432} (3.2-5.5%), and Met^{4} (≤ 0.4%). The FKB327 DS lots have similar oxidation levels for Met^{34} (0.2-0.9%), Met^{432} (0.8-1.5%) and Met^{4} (0.2-0.3%) compared to U.S.-licensed Humira, meeting the similarity criterion. However, a lower oxidation

level at Met^{256} was seen in FKB327 DS lots (2.5-3.8%) than that in Humira. The results of Met^{256} oxidation for 7 FKB327 DS lots were below the lower limit of Humira range.

Table 3.2.R.2-29 Similarity Assessment for Oxidized Variant Content for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Content of Oxidized Variants (%)			
				HC			LC
				Met^{34}	Met^{256}	Met^{432}	Met^{4}
Test product	FKB327 DS	10	Average	0.6	3.0	1.1	0.3
			SD	0.1	0.4	0.3	0.1
			Maximum	0.7	3.8	1.5	0.3
			Minimum	0.4	2.5	0.8	0.2
Reference product	US-licensed Humira	10	Acceptance range	0.2–0.9	3.2–5.5	0.7–2.1	0.0–0.4
Results				Pass	Not Pass	Pass	Pass

Assessor Comment: *All FKB327 DS lots are within the quality range derived from 10 lots of U.S.-licensed Humira for Met^{432}, $Met^{34}$and Met^{4} oxidation, meeting the acceptance criterion. The level of Met^{256} oxidation in FKB327 ranged slightly lower than the quality ranges. Decreased Met^{256} oxidation in FKB327 may benefit product stability and FcRn binding. Literature reported that Met^{256} oxidation might reduce thermal stability and decrease Protein A and FcRn binding as well as in vivo serum half-life. Taking together, the difference in Met^{256} oxidation between FKB327 lots and US-Humira does not preclude a determination of analytical similarity.*

Sulfhydryl Content

The free sulfhydryl content of FKB327 and U.S.-licensed Humira was measured using Ellman's assay, in which 5,5'-dithio-bis(2-nitrobenzoic acid) (DTNB) is employed to react with free sulfhydryls. The intensity of the resulting color is proportional to the quantity of free sulfhydryl, and quantitation is performed by comparison with a linear standard curve constructed from serial dilutions of N-acetyl-cysteine reacted with DTNB. As shown in Table 3.2.R.2-30 below, the free sulfhydryl levels are very low and similar in all FKB327 DS lots and U.S.-licensed Humira DP lots. The results met the acceptance criterion for similarity.

Table 3.2.R.2-30 Similarity Assessment for Sulfhydryl Content for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Sulfhydryl Content (mol/mol)
Test product	FKB327 DS	10	Average	0.31
			SD	0.02
			Maximum	0.34
			Minimum	0.28
Reference product	US-licensed Humira	10	Acceptance range	0.29–0.39
Results				Pass

Assessor Comment: *The free sulfhydryl content in 90% FKB327 DP lots tested were within the quality range of the U.S.-licensed Humira. Data provided support that FKB327 and U.S.-licensed Humira are similar in the level of free sulfhydryl content.*

Trisulfide

The trisulfide formation level in the inter-chain disulfide linkage between HC and LC was evaluated by peptide mapping with HPLC-UV/MS for FKB327 and U.S.-licensed Humira. The level of the trisulfide variants were calculated as the percentage of the MS intensity of the fragment against the total intensity of the corresponding fragments. Table 3.2.R.2-31 shows the statistical quality range from the 10 U.S.-licensed Humira lots for trisulfide (0.2-0.6%). The FKB327 DS lots have higher amount of trisulfide variants (5.6-9.7%) compared to U.S.-licensed Humira, which is out of the upper limit of the Humira quality range.

Table 3.2.R.2-31 Similarity Assessment for Trisulfide Variants Content for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Content of Trisulfide Variants (%)
Test product	FKB327 DS	10	Average	7.7
			SD	1.4
			Maximum	9.7
			Minimum	5.6
Reference product	US-licensed Humira	10	Acceptance range	0.2–0.6
Results				Not Pass

Assessor Comment: *The range of trisulfide variants in FKB327 DS lots (5.6-9.7%) is higher than the quality ranges of U.S.-licensed Humira. However, literature reported that IgG trisulfide variants do not significant impact antigen-binding affinity. Additionally, trisulfide variants could be converted to disulfide form after administration. Therefore, trisulfide variants would not affect in vivo performance of the product. Overall, the difference in the content of the trisulfide between FKB327 and U.S.-licensed Humira is considered not to have an impact on the biological activities of the product, taking into account the results of the functional similarity assessment.*

Thioether

The thioether level in the inter-chain disulfide linkage between the HC and LC was evaluated by CE-SDS under reduced conditions. The thioether level was measured as a content of covalently-linked HC and LC species that was eluted as a peak after the HC peak. As shown in Table 3.2.R.2-32, the thioether species in FKB327 DS lots were consistent with a range of 0.3- 0.5%, that was within the Humira quality range (0.2-0.6%). The results met the acceptance criterion for similarity.

Table 3.2.R.2-32 Similarity Assessment for Thioether Variants Content for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Content of Thioether Variants (%)
Test product	FKB327 DS	10	Average	0.4
			SD	0.1
			Maximum	0.5
			Minimum	0.3
Reference product	US-licensed Humira	10	Acceptance range	0.2–0.6
Results				Pass

Assessor Comment: *Data provided support analytical similarity of FKB327 and U.S.-licensed Humira.*

Cysteinylation

The cysteinylation level, which occurs at the C-terminal cysteine residue of the LC, was evaluated for FKB327 DS and U.S.-licensed Humira by CE-SDS under non-reducing conditions. The cysteinylation level was measured as a content of the LC peak that include both the normal LC and the cysteinylated LC. Table 3.2.R.2-33 shows the statistical quality range from the 10 U.S.-licensed Humira lots for cysteinylation (0.0-0.3%). The FKB327 DS lots have higher cysteinylated content (0.3-0.4%) compared to U.S.-licensed Humira, which is out of the Humira quality range.

Table 3.2.R.2-33 Similarity Assessment for Cysteinylation Variants Content for FKB327 Compared with U.S.-licensed Humira

Product		Number of Lots	Item for Assessment	Content of Cysteinylation Variants (%)
Test product	FKB327 DS	10	Average	0.4
			SD	0.1
			Maximum	0.4
			Minimum	0.3
Reference product	US-licensed Humira	10	Acceptance range	0.0–0.3
Results				Not Pass

Assessor Comment: *The cysteinylated contents were at very low level in both FKB327 and U.S.-licensed Humira. Cysteinylation at the C-terminal cysteine residue of the LC would not affect product antigen binding and Fc receptor binding. The slight difference in cysteinylation (≤ 0.1%) between FKB327 and U.S.-licensed Humira is not considered to have an impact on biological activities of the product. Therefore, the difference in cysteinylation observed does not preclude a determination of analytical similarity.*

3.2.R.2.3 Similarity Assessment for Attributes using Raw Data/Graphical Comparison

Product high order structure, process related impurities, and additional biological activities were assessed for FKB327 and U.S.-licensed Humira, as well as the primary structure attributes, including amino acid sequence, MW, disulfide bond, pI, extinction coefficient, N-glycosylation site. These attributes were assessed using side-by-side graphical comparisons of the raw data. Visible and sub-visible particles were evaluated based on compendial requirements.

Assessor Comment: *Primary structural properties, such as C-terminal variants, post-translational modifications on specific amino acid residues within the protein (e.g., oxidation, deamidation, glycation, free sulfhydryl and thioether), were discussed in the section 3.2.R.2.2 Similarity Assessment with Quality Range Approach.*

3.2.R.2.3.1 Primary Structure

The primary structure of FKB327 and U.S.-licensed Humira was analyzed by the following characterization tests:

- Amino acid sequence by Edman sequencing and LC/MS peptide mapping
- Molecular weight determination by mass spectrometry (ESI-TOF-MS)
- Identification of disulfide bonds using non-reduced and reduced LC/MS peptide mapping
- Identification of N-glycosylation site by peptide mapping with or without deglycosylation
- Isoelectric point determination (pI) by IEF
- Extinction coefficient determination by amino acid analysis and UV absorbance at 280 nm

The results demonstrated that the primary structure and amino acid sequence are same for FKB327 and U.S.-licensed Humira. The molecular weight of the polypeptide chain of FKB327 was identical to the theoretical mass of adalimumab. The similarity of disulfide linkages and N-glycosylation site of FKB327 with U.S.-licensed Humira were verified. The pI values and the extinction coefficient determined for FKB327 were comparable to those of U.S.-licensed Humira.

Assessor comment: *Data provided support analytical similarity of FKB327 and U.S.-licensed Humira in terms of primary structure, taking into consideration the results of primary structural properties assessed in the section 3.2.R.2.2 Similarity Assessment with Quality Range Approach.*

3.2.R.2.3.2 High Order Structure
The similarity of the higher order structure of FKB327 and U.S.-licensed Humira was assessed by the following characterization assays:

- Far and near-UV circular dichroism (CD)
- Fourier transform infrared spectroscopy (FTIR)
- Intrinsic fluorescence spectroscopy
- Differential scanning calorimetry (DSC)

Three independent lots of FKB327 DS and 3 lots of U.S.-licensed Humira were included in similarity assessment for high order structure.

Far-UV CD spectra for FKB327 and U.S.-licensed Humira are consistent with protein folded into a predominantly β-sheet secondary structure. Near-UV CD spectra of FKB327 and U.S.-licensed Humira are typical of IgG antibodies with defined tertiary and disulfide structures. Both the far- and near-UV CD spectra for FKB327 were identical to those for U.S.-licensed Humira. FTIR spectroscopy also revealed similar β-sheet bands for FKB327 and U.S.-licensed Humira, which are consistent with the results of Far-UV CD. The intrinsic fluorescence spectra exhibited that the tryptophans are unexposed for both FKB327 and U.S.-licensed Humira. The spectrum of FKB327 was similar in the shape to that of Humira, while the fluorescence intensity of FKB327 DS was slightly higher than that of U.S.-licensed Humira. DSC, used to evaluate thermal stability, showed two thermal transitions for both FKB327 and U.S.-licensed Humira, corresponding to unfolding of the C_H2, Fab, and C_H3 domains. However, the temperatures at which endothermic transitions occur were slightly different between FKB327 and U.S.-licensed Humira. The applicant performed extended studies and demonstrated that the slight differences in the intrinsic fluorescence intensity and thermal stability between FKB327 and U.S.-licensed Humira were caused by differences in the formulation buffers.

Assessor comment: *The results of characterization studies demonstrate that FKB327 has a similar secondary and tertiary structure to U.S.-licensed Humira. The minor difference observed in the intrinsic fluorescence intensity and thermal stability are not expected to have any significance based on the results of functional activity assays.*

3.2.R.2.3.3 Visible and Sub-visible Particles
Visible and sub-visible particles may increase product immunogenicity and impact product quality and safety. The visible particles were analyzed by visual inspection at the same illuminance conditions for FKB327 and U.S.-licensed Humira. Twenty-two lots of FKB327 DP and three lots of U.S.-licensed Humira were inspected for similarity. All lots of FKB327 and U.S.-licensed Humira were practically free from particles. Sub-visible particles (≥ 2 µm, ≥ 5 µm, ≥ 10 µm, and ≥ 25 µm) were measured by light obscuration assay according to USP <788>. Twenty-two lots of FKB327 DP and six lots of U.S.-licensed Humira were assessed for sub-visible particles. Lower numbers were observed for all size of sub-visible particles in FKB327 DP lots as compared to U.S.-licensed Humira. Additionally, the applicant used micro-flow imaging (MFI) to detect particles over a range of 1µm to 25 µm. Consistent with the results of light obscuration assay, FKB327 DP lots showed lower particle levels than U.S.-licensed Humira.

3.2.R.2.3.4 Induction of Regulatory Macrophages-Mixed Lymphocyte Reaction (MLR) Assay
Induction of regulatory macrophage is considered a part of mechanism of action for adalimumab in inflammatory bowel disease. A mixed lymphocyte reaction (MLR) assay was employed to evaluate the inhibitory effects of FKB327 and Humira on cell proliferation by induction of regulatory macrophage. In the MLR assay, three concentrations (0.08, 0.4, 2.0 μg/mL) of FKB327 or Humira were added into a mixed culture of human peripheral blood mononuclear cells (PBMC). After incubation for 6 days, the cellular proliferation was measured by incorporation of tritium-thymidine. Each sample was tested by five assay runs. Similarity was assessed with mean counts per minute (CPM) at each concentration by raw data comparison. The similarity assessment included the comparison of 3 FKB327 DP lots to 3 U.S.-licensed Humira DP lots. The inhibition of cell proliferation in MLR by FKB327 was comparable to that by U.S.-licensed Humira by raw data comparison.

3.2.R.2.3.5 Process-related Impurities
Residual DNA and HCP are potential impurities derived from the manufacturing process of DS and may impact product quality and safety. For similarity assessment, the level of residual DNA was monitored using the threshold method for FKB327 and U.S.-licensed Humira, while the content of HCP was measured by a commercial ELISA kit. Ten lots for each of FKB327 DS and Humira DP were tested. The results of HCP and residual DNA were consistent across ten lots of FKB327 DS (DNA < 1.7 pg/mg protein, HCP < 2.9 ng/mg protein) and were similar to those for U.S.-licensed Humira (DNA < 1.2 pg/mg protein, HCP ≤ 5.4 ng/mg protein).

3.2.R.3 Comparison of Stability Profile
3.2.R.3.1 Comparison of Degradation Profile
Stability study was conducted under accelerated (25°C) and stressed (40°C) conditions to compare the degradation profiles between FKB327 DP and U.S.-licensed Humira. Fifteen lots of FKB327 DP (from 6 independent DS lots) and 6 lots of U.S.-licensed Humira were tested for similarity assessment. Table 3.2.R.3-1 presents the testing schedule and analytical assays performed in the stability study. The applicant states that stability time points for U.S.-licensed Humira were determined based on the age of each batch at the initiation of the stability. Data obtained at earliest time point was used as the initial time point data. The stability results to compare the degradation profiles between FKB327 and U.S.-licensed Humira are discussed below.

Table 3.2.R.3-1 Stability Study Protocol for Comparison of Degradation Profile of FKB327 DP with U.S.-licensed Humira

Test item	Initial	Accelerated conditions (25°C)			Stressed conditions (40°C)		
		1 m	3 m	6 m	1 m	2 m	3 m
Appearance	X	–	–	X	–	–	X
pH	X	–	X	X	–	–	X
Protein concentration	X	X	X	X	X	X	X
SE-HPLC	X	X	X	X	X	X	X
CE-SDS (R)	X	X	X	X	X	X	X
CE-SDS (NR)	X	X	X	X	X	X	X
CEX-HPLC	X	X	X	X	X	X	X
Cytotoxicity neutralizing assay	X	X	X	X	X	X	X
Visible particles	X	–	X	X	X	–	X
Particulate matter in injections	X	–	X	X	X	–	X
HI-HPLC	X	X	X	X	X	X	X

m=months, X=Tested, –=not tested
Abbreviations: CE-SDS (NR): capillary electrophoresis-sodium dodecyl sulfate (non-reduced); CE-SDS (R): capillary electrophoresis-sodium dodecyl sulfate (reduced); CEX-HPLC: cation exchange-high performance liquid chromatography; HI-HPLC: hydrophobic interaction-high performance liquid chromatography; SE-HPLC: size exclusion-high performance liquid chromatography.

Under the accelerated conditions of 25°C, the results of CEX-HPLC showed increases in the acidic peaks with a corresponding decrease in the main peak for both FKB327 DP and U.S.-licensed Humira over time. Similar trends with accelerated rates of change were noted in the 40°C data. Overall, the rates of the changes for each peak at 25°C and 40°C were similar for FKB327 DP and Humira.

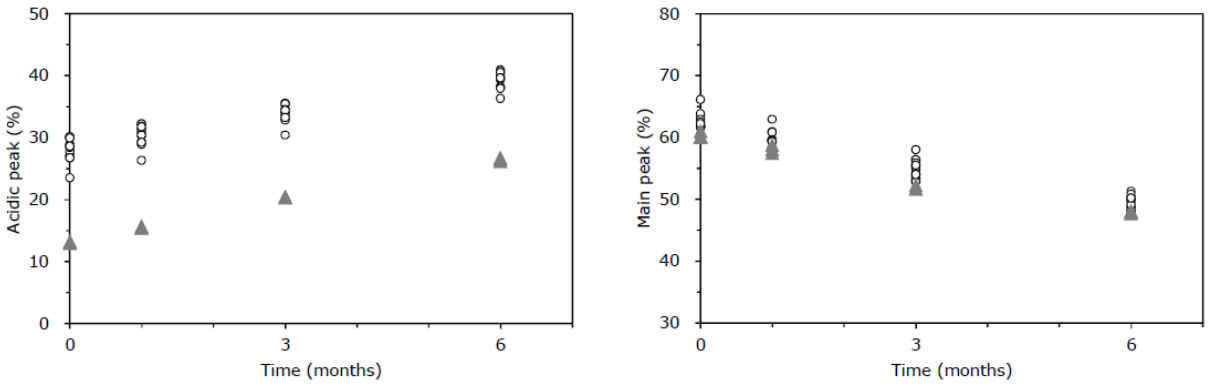

Figure 3.2.R.3-1 CEX-HPLC Results for FKB327 DP and Humira Stored at 25°C

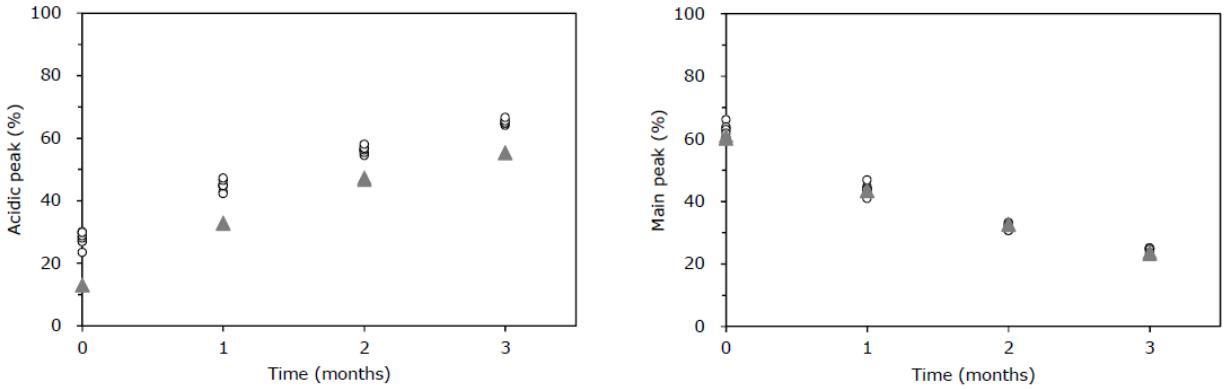

Figure 3.2.R.3-2 CEX-HPLC Results for FKB327 DP and Humira Stored at 40°C

Assessor comment: *As discussed in 3.2.R.2.2.9 Charge Variants by CEX-HPLC, a higher level of the acidic species and lower amount of the basic species were observed in FKB327 lots when compared with U.S.-licensed Humira. However, the differences in charge variants between FKB327 and U.S.-licensed Humira are considered to have no impact on the biological activities of the product based on the results of functional assays. During the degradation study, similar degradation trends were observed for acidic and main peaks at 25°C and 40°C for FKB327 DP and Humira. No change was seen in the basic peaks for both FKB327 DP and Humira at 25°C, while a decrease (≤ 6%) in the content of the basic peaks was detected for Humira at 40°C over three months.*

SE-HPLC results for both FKB327 DP and Humira showed a slight increase in the LMWs (≤ 0.6%) and HMWs (≤ 0.3%) with a corresponding decrease in the main peak during storage at 25°C. Both products degrade faster at 40°C than at 25°C. The rates of degradation seen in FKB327 DP was similar or slower than seen in Humira at 40°C and 25°C, demonstrating that the stability of FKB327 DP is comparable to U.S.-licensed Humira.

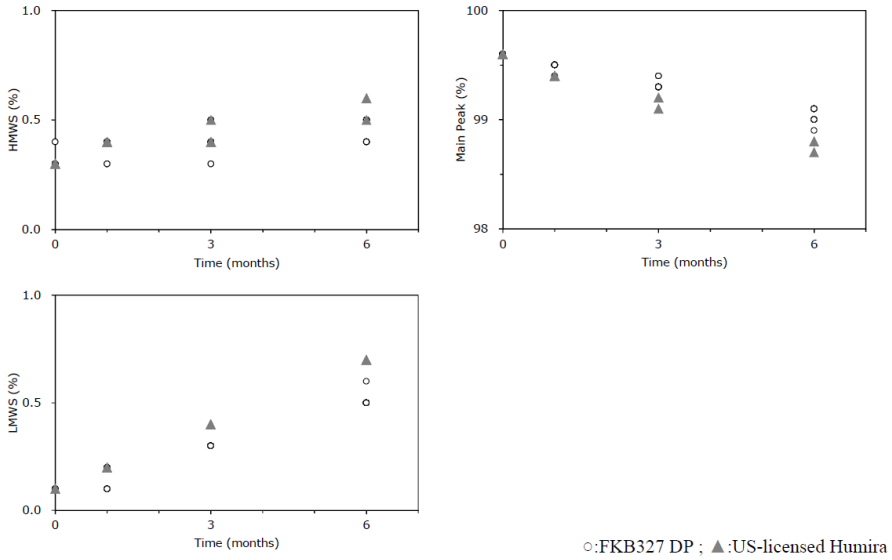

Figure 3.2.R.3-3 SE-HPLC Results for FKB327 DP and Humira Stored at 25°C

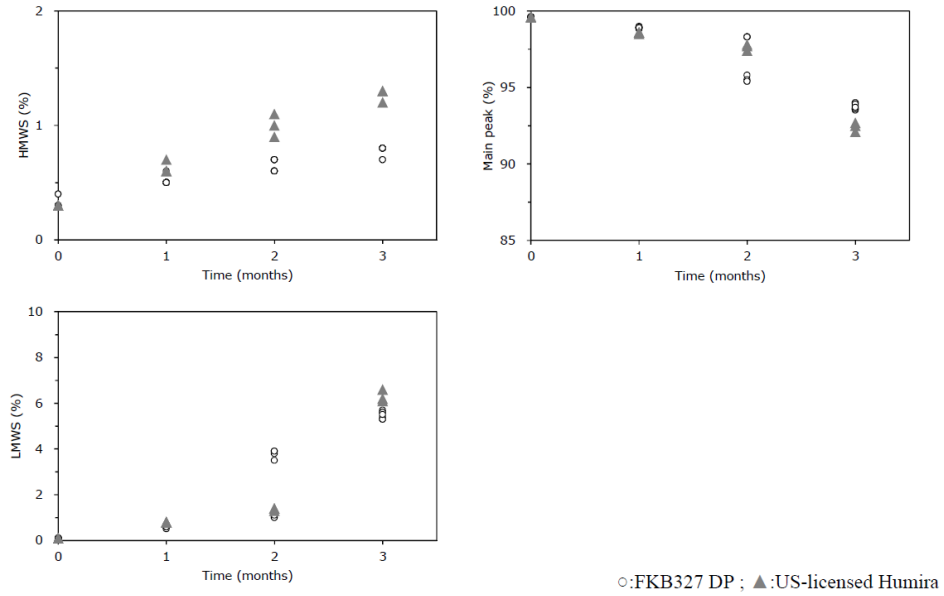

Figure 3.2.R.3-4 SE-HPLC Results for FKB327 DP and Humira Stored at 40°C

Consistent with the results of CEX-HPLC and SE-HPLC, product purity, size variants, and hydrophobic variants assessed by CE-SDS (reduced and non-reduced) and HI-HPLC showed similar trends for FKB327 DP and U.S.-licensed Humira at accelerated and stressed conditions. The protein content, pH, visible and subvisible particles, and bioactivity remained unchanged for FKB327 DP and U.S.-licensed Humira at accelerated and stressed conditions through the stability study.

Assessor comment: *The applicant compared the stability profile of FKB327 and U.S.-licensed Humira under accelerated condition of 25°C and stress condition of 40°C. FKB327 DP and U.S.-licensed Humira DP were tested with the same analytical methods as those in the FKB327 stability protocol. The analytical testing results indicated that the stability profile under forced degradation conditions of FKB327 DP is similar to U.S.-licensed Humira.*

3.2.R.3.2 Stability Profile of U.S.-licensed Humira at Long-term Storage Conditions

The applicant performed a long-term stability study (2−8°C) for three lots of U.S.-licensed Humira to assess the stability profile of U.S.-licensed Humira across the shelf-life of the product. The same analytical tests as those for FKB327 DP stability study were used. Stability time points were determined based on the age of each lot of Humira available at the initiation of the stability study. Data obtained at the earliest time point was used as the initial time point data.

Protein concentration, potency, sub-visible particles, pH and appearance remain constant during the storage. Minor changes in purity (≤ 0.7%) were detected by CE-SDS and SEC over time up to 36 months. The results for charge variants showed a slight decrease in main peak (≤ 3.2%) and corresponding increase in the acidic species.

Assessor Comment: *Similar trends of charge and size variants were observed for FKB327 DP under the long-term storage condition (2−8°C) (refer to section 3.2.P.8 Stability), indicating that the long-term stability of FKB327 and U.S.-licensed Humira are similar.*

3.2.R.4 Comparison of Comparative Analytical Data from Lots of FKB327 DP vial and U.S.-licensed Humira

Assessor Comment: *FKB327 DP were manufactured in three presentations (vial, PFS, and AI) during development. Of note, the PFS and AI presentations are the proposed commercial presentations. The applicant performed PK similarity and comparative clinical studies using the DP lots of FKB327 vial, PFS, and AI. However, FKB327 DP vials were not included in the comparative analytical assessment in the original BLA submission. After internal discussion within the review team and additional data review, we consider that lack of DP vial lots in the comparative analytical assessment would not impact review of the BLA based on the following:*

- *Two DS lots used for making DP vial lots are included in the comparative analytical assessment in the BLA, which were subject to a full panel of comparative analytical tests against U.S.-licensed Humira (e.g., Fab activities, Fc activities, glycosylation, and purity tests). And these two DS lots were also used to produce DP PFS and AI lots.*
- (b) (4).
- *The FKB327 DP manufacturing process mainly encompasses* (b) (4). *The product quality attributes are primarily determined by the DS manufacturing process.*
- *Comparability of FKB327 DP vial, PFS, and AI presentations are demonstrated by data from analytical comparability, stability, comparative stress stability studies included in the BLA.*
- *During the early IND stage, three DP vial lots (VK001, VK002, and TVK120117) were included in the comparative analytical assessment for certain tests, including purity and potency assays. The data was provided in the original IND 116471 and support similarity of FKB327 DP vials and U.S.-licensed Humira.*

On September 24, 2019, the following comment in the 74-day letter was sent to the applicant.

It is noted that comparative analytical data from FKB327 drug product vial lots (VK001, VK002, and TVK120117) and U.S.-licensed Humira lots (092852E, 092872E, 081492E, 200632E, 201292E, 201362E, 231602E, 240462E, 240472E, 1004009, 260972E, 261512E) were provided in the original IND 116471 submission. Update your BLA section 3.2.R.1 Similarity Assessment: FKB327 vs U.S.-licensed Humira to include the comparative analytical data from these FKB327 drug product vial lots and U.S.-licensed Humira lots.

The applicant responded on November 13, 2019 (eCTD 0014) with data from lots of FKB327 DP vial and U.S.-licensed Humira, which are summarized in below.

3.2.R.4.1 Comparison of Analytical Data between FKB327 DP Vial and U.S.-licensed Humira

Information for the lots of FKB327 DP vial and U.S.-licensed Humira tested is presented in Table 3.2.R.4-1 and Table 3.2.R.4-2. The U.S.-licensed Humira lots, FKB327 DP vial lots along with the corresponding FKB327 DS lots were measured by CEX-HPLC, SE-HPLC, CE-SDS for purity, cytotoxicity neutralizing assay for potency, and compendial assays for the sub-visible particles.

Table 3.2.R.4-1 Lot Information of FKB327 Vial DP

Lot No.	Manufacturing Date	DS Lot No.	Manufacturer
TVK120117	Jan 2012	T1101VKA3	Kyowa Hakko Kirin Co., Ltd.
VK001	Jan 2013	1202VK	
VK002	Jan 2013	1202VK	

Table 3.2.R.4-2 Lot Information of U.S.-licensed Humira

Lot No.	Expiration Date	Manufacturer
092852E	May 2013	Abbvie Inc.
092872E	Jun 2013	
081492E	Jun 2013	
200632E	Apr 2014	
201292E	Apr 2014	
201362E	May 2014	
231602E	Jun 2014	
240462E	Jul 2014	
240472E	Aug 2014	
1004009	Aug 2014	
260972E	Sep 2014	
261512E	Oct 2014	

Potency, as measured using the cell cytotoxicity neutralizing assay, is comparable among lots of FKB327 and U.S.-licensed Humira. SE-HPLC results show comparable levels of main peak, HMW species, and LMW species.

The lots of FKB327 DP vial and DS contain increased levels of CEX-HPLC acidic peak (22.9-27.1% versus 12.6-14.6%) compared to U.S.-licensed Humira and lesser amounts of later eluting basic peaks. These differences are similar to the differences seen between U.S.-licensed Humira and FKB327 DS as discussed in section 3.2.R.2. The differences in charge variants are expected to not impact product biological activities.

The reduced CE-SDS profiles are comparable among all lots tested. Consistent with the results of reduced CE-SDS for FKB327 and U.S.-licensed Humira described in section 3.2.R.2, the amounts of the NGHC in U.S.-licensed Humira is slightly higher when compared to FKB327 (1.6-2.1% versus 0.6-0.7%), which is attributed to the difference in glycosylation site occupancy. As discussed in section 3.2.R.2.2.8 Heterogeneity, these minor differences between FKB327 and US-Humira would not preclude the conclusion of analytical similarity.

Non-reducing CE-SDS was used to analyze disulfide bonding isoforms. Increased levels of LMW fragments (2.9-3.2% versus 1.4-1.8%) and corresponding lower percentage of main peak were observed in the FKB327 lots tested, which are also consistent with the non-reducing CE-SDS results for FKB327 DS and U.S.-licensed Humira presented in section 3.2.R.2. The levels of LMW fragments in FKB327 DS and U.S.-licensed Humira are very low and the minor difference in LMW fragments have no effect on the biological activities of the product.

Sub-visible particulates with size of ≥ 2 µm, ≥ 5 µm, ≥ 10 µm and ≥ 25 µm were measured by a compendial assay (light obscuration) and MFI. Significantly greater numbers were observed for all size of particulates in U.S.-licensed Humira as compared to those in FKB327 DP vial lots.

Assessor Comment: *The differences in charge and size variants by CEX-HPLC, reduced and non-reduced CE-SDS between FKB327 DP vials and U.S.-licensed Humira are consistent with those observed between lots of FKB327 DS and U.S.-licensed Humira discussed in section 3.2.R.2. These differences would not preclude the conclusion of analytical similarity.*

3.2.R.4.2 Comparison of Degradation Profile between FKB327 DP Vial and U.S.-licensed Humira

The applicant conducted stability studies under accelerated (25°C) and stressed (40°C) conditions and photostability testing to assess the degradation profile of FKB327 DP vials and U.S.-licensed Humira. Three lots for each of FKB327 DP vial and U.S.-licensed Humira were tested. The quality attributes assessed include appearance, protein concentration, pH, purity (SE-HPLC, HIC, CEX-HPLC, and reduced and non-reduced CE-SDS) and potency.

Overall, both FKB327 DP vial and U.S.-licensed Humira remained stable with respect to appearance, protein concentration, pH, and potency up to 6 months at 25°C and over 3 months at 40°C. The charge variant results from CEX-HPLC showed similar trend and comparable rates of degradation for FKB327 DP vial and U.S.-licensed Humira under accelerated and stressed conditions. The results of SE-HPLC, HIC, and CE-SDS indicated decreased purity for both FKB327 DP vial and U.S.-licensed Humira over time. The levels of LMWs, HMWs, and hydrophobic variants increased, while the intact IgG decreased. The rates of changes in the size and hydrophobic variants of FKB327 DP were similar or lower to the rates seen in the U.S.-licensed Humira.
The photostability testing was conducted with light exposure conditions that comply with ICH guideline Q1B. For CEX-HPLC, CE-SDS, SE-HPLC and the neutralizing cytotoxicity assay, changes with respect to size and charge variants, hydrophobic variants, and potency were seen in both FKB327 DP vial and U.S.-licensed Humira, but the changes and the rate of each change in FKB327 DP were similar to or lower than those observed for U.S.-licensed Humira. There was no significant change in pH and protein concentration.

Assessor Comment: *Data provided support similarity of FKB327 DP vial presentation and U.S.-licensed Humira.*

Immunogenicity Assessment

1. Summary Basis of Recommendation/Executive Summary

1.1 Immunogenicity Executive Summary and Recommendation

The applicant Mylan GmbH is seeking licensure under Section 351(K) of the PHS act for a proposed biosimilar HULIO to US-licensed HUMIRA (40 mg/0.8 mL single-dose pen, 40 mg/0.8 mL single-dose prefilled plastic syringe and 20 mg/0.4 mL single-dose prefilled plastic syringe). The applicant is seeking approval of HULIO for the following indications, for which HUMIRA has been previously licensed: Rheumatoid arthritis,Juvenile Idiopathic Arthritis, Psoriatic arthritis, Ankylosing spondylitis, Adult Crohn's disease, Ulcerative colitis, Plaque psoriasis.

The immunogenicity assays were developed by the applicant to support their clinical studies:

- FKB327-001: PK similarity study using single-dose, comparing FKB327 with US-licensed Humira and EU-approved Humira in healthy volunteers
- FKB327-002: Comparative clinical study in moderate-to-severe RA patients administered multiple doses of FKB327 (vial presentation) or US-licensed Humira pre-filled syringe (PFS).
- Transition of comparative clinical Study FKB327-002 to FKB327-003: Extension study with FKB327 PFS or auto-injector (AI)
- FKB327-004: Single-dose PK similarity study in Japanese healthy volunteers comparing FKB327 PFS presentation versus US-licensed Humira PFS
- FKB327-005: Single-dose PK study in Japanese healthy volunteers comparing FKB327 vial, PFS, and AI presentations
- FKB327-006: Single-dose PK similarity study in Japanese healthy volunteers comparing FKB327 PFS and US-licensed Humira PFS

The immunogenicity assays are all based on bridging ECL format, and the assays used for Studies FKB327-002 through -006 utilized an optimized process, which employed a solid-phase extraction with acid dissociation method. By clearing extraneous antibodies and residual drug, the interference can be reduced, and assay selectivity can be improved.
Assessment of validation reports for the anti-drug antibody (ADA) and neutralizing antibody (NAb) immunogenicity assays used during the clinical studies found that the ADA and NAb assays are suitable for their intended purposes. It is noted that the NAb assays generally failed to meet the Agency recommendation of sensitivity at or below 100 ng/ml, however it is acknowledged within the Agency guidance that such levels of sensitivity may be difficult to achieve for NAb assays.

1.2 Deficiencies and Other Recommended Comments to Applicant

None

2. Assessment

Documents Reviewed	Submission Date
BLA 761154 SN 0001(01) – Section 5.3.1.4: 327-I12-003 / CCR#13-009 [**ADA**: FKB327]	07/12/19
BLA 761154 SN 0001(01) – Section 5.3.1.4: (KKC) 327-I13-010 [**ADA**: US-licensed Humira]	07/12/19
BLA 761154 SN 0001(01) – Section 5.3.1.4: (KKC) 327-I13-012 [**ADA**: EU-approved Humira]	07/12/19
BLA 761154 SN 0001(01) – Section 5.3.1.4: (KKC) 327-I13-005 [**NAb**: FKB327]	07/12/19
BLA 761154 SN 0001(01) – Section 5.3.1.4: (KKC) 327-I13-011 [**NAb**: US-licensed Humira]	07/12/19
BLA 761154 SN 0001(01) – Section 5.3.1.4: (KKC) 327-I13-006 [**NAb**: EU-approved Humira]	07/12/19
BLA 761154 SN 0001(01) – Section 5.3.1.4: (Syneos-iHC) 11487.101417.1 [**ADA**: Humira]	07/12/19
BLA 761154 SN 0001(01) – Section 5.3.1.4: (Syneos-iHC) 8913.120715.1 [**NAb**: Humira]	07/12/19

2.1 Background Immunogenicity Information

HULIO (FKB327) is a human IgG1κ antibody that specifically binds to TNF-α with high affinity, and subsequently prevents TNF-α from interaction with TNF-α receptor in a dose-dependent manner.

The immunogenicity risk associated with administration of FKB327 is substantiated by the observation of HUMIRA-induced ADA in patients, which has been associated with negative impact on efficacy. An inverse relationship has been previously described between the magnitude of ADA response and sustainability of HUMIRA efficacy, though the relationship between ADA and immune-mediated adverse events is not entirely clear. Loss-of-efficacy for HUMIRA appears to be related to immune recognition by ADA of overlapping B- and T-cell epitopes in one CDR of HUMIRA. Binding of ADA to this CDR epitope of HUMIRA, with subsequent immune complex formation, is thought to be the mechanism for blockade of drug-binding TNF-α, with consequent neutralization of drug activity.

FKB327 contains identical primary amino acid sequence to HUMIRA, with similar modifications of amino acid residues; thus FKB327 is predicted to be intrinsically comparable in immunogenicity as HUMIRA. FKB327 is manufactured (b) (4), and DP formulation contains excipients widely used for biologics. The primary container materials have minimal tungsten or leachables risk.

2.2 Validation of Anti-Drug Antibody Assays (ADA)

2.2.1 ADA Assay Method Principle

The ADA assay format that was employed consists of an electrochemiluminescent bridging assay (Meso Scale Diagnostics). Generally, on a streptavidin-coated MSD plate, biotinylated drug (FKB327) is attached, which captures ADA in the medium. The captured ADA is then detected by addition of ruthenylated drug detection reagent, which is bound by the biotin-FKB327:ADA complex, and emits luminescence upon electrification of the MSD plate. The strength of the luminescent signal is proportional to the amount of bound ruthenylated drug, which is in turn proportional to the amount of ADA present in the medium.

The SPEAD sample pre-treatment method (used for samples obtained in Studies FKB327-002 to -006) utilizes acid treatment of samples to dissociate ADA from potentially binding to drug in the matrix, then extracts ADA from the samples by binding them to an excess of biotin-bound FKB327. The biotin-FKB327:ADA complexes are then attached onto streptavidin beads and isolated from the media, allowing the ADA to be separated from the complex by further acid treatment. The extracted ADA are then attached to the MSD plate for

detection by binding to ruthenylated-FKB327 and subsequent emission of luminescent signal by the ECL assay upon electrification of the plate.

2.2.2 Validation Exercises

Table 2.1: Validation Results and Assessor Assessment for ADA assays used in PK similarity (validation reports 327-I12-003 / CCR#13-009, 327-I13-010, 327-I13-012) and comparative clinical studies (Validation Reports 11487.101417.1)

Validation Parameter	FKB327-001 Validation Reports: • 327-I12-003 • CCR#13-009 (FKB327)	FKB327-001 Validation Report: • 327-I13-010 (US-licensed Humira)	FKB327-001 Validation Report: • 327-I13-012 (EU-approved Humira)	FKB327-002, -003, -004, -005, -006 Validation Report: • 11487.101417.1	*Assessor Comment*
Contract Research Org	(b) (4)				*None*
Assay principle	Bridging ECL format for both screening and specificity confirmation	Bridging ECL format for both screening and specificity confirmation	Bridging ECL format for both screening and specificity confirmation	Bridging ECL format with SPEAD sample pre-treatment, for both screening and specificity confirmation	*All assays use the same general principle of ECL ligand-binding assay; ECL bridging immunoassay is appropriate for the studies. comparative clinical study used optimized assay with sample pre-treatment.*
Sample Pretreatment (Acid dissociation)	n/a	n/a	n/a	SPEAD (solid phase extraction with acidic dissociation)	*The SPEAD procedure of antibody extraction from serum samples with acid dissociation used for the ADA assay is an improvement and may reduce interference*
Positive control (PC)	Cynomolgus monkey anti-FKB327 purified polyclonal antibody (b) (4) lot 303073-2); 5.0 mg/ml (-80ºC storage; 2-8ºC after thaw)				*The same PC antibody is used for all ADA assays*
Detection reagent	Ruthenylated-FKB327 (b) (4) lot 1563-33); 1.28 mg/ml (-20ºC)	Ruthenylated-US-licensed-Humira (b) (4) lot 1563-34); 1.23	Ruthenylated-EU-approved-Humira (b) (4) lot 1563-32);	Ruthenylated-FKB327 (b) (4) lot SS 680081) 0.5 mg/ml	*The detection reagents are appropriately specific for the drug*

		mg/ml (-20ºC)	1.21 mg/ml (-20ºC)	(-20ºC)	*being tested*
Depletion reagent	FKB327 (FKB lot TVK120117); 53.92 mg/ml (2º-8ºC storage)	US-licensed Humira (Abbott lot 201292E); 48.62 ml/ml (2º-8ºC storage)	EU-approved Humira (Abbott lot 14270XD17); 50.37 mg/ml (2º-8ºC storage)	- FKB327 (FKB lot VK003); 50.0 mg/ml (2º-8ºC storage) - Humira (Abbvie lot 1046566); 49.73 mg/ml (2º-8ºC storage)	*The depletion reagents are appropriately specific for the drug being tested*
PC Dose Curve and Hook Effect	8, 16, 32, 64, 128, 256, 512, 1024 ng/ml; no hook effect observed	8, 16, 32, 64, 128, 256, 512, 1024 ng/ml; no hook effect observed	8, 16, 32, 64, 128, 256, 512, 1024 ng/ml; no hook effect observed	0.153-5000 ng/ml; no hook effect observed	*The dose ranges and absence of hook effect are acceptable*
LPC	100 ng/ml	100 ng/ml	100 ng/ml	LPC-1: 72.0 ng/ml LPC-2: 100 ng/ml	*LPC is selected to meet criteria of consistent positive result in screening and confirmatory assay, above assay sensitivity, and consistent positivity in selectivity experiments*
HPC	5000 ng/ml	5000 ng/ml	5000 ng/ml	5000 ng/ml	*HPC is chosen to cover high antibody response in patients*
Matrix and NC	Naïve human serum ((b) (4) Lot (b) (4) 703153; storage at ≤-20ºC)	Naïve human serum ((b) (4) Lot (b) (4) 703153; storage at ≤-20ºC)	Naïve human serum ((b) (4) Lot (b) (4) 703153; storage at ≤-20ºC)	Normal human serum (b) (4)	*Use of normal human serum is acceptable, all NHS came from the same supplier*
MRD	1:2	1:2	1:2	1:6	*MRD is appropriate based on assay validation results*
NC system suitability range	48.7-56.2 RLU	43.5-56.7 RLU	44.8-54.5 RLU	62.167-97.375 ECLU	*NC system suitability ranges are acceptable*
LPC system suitability range	68.7-114.0 RLU	73.5-118.8 RLU	77.8-105.2 RLU	LPC-1 (72 ng/ml): 191.5-267.0 ECLU LPC-2 (100 ng/ml): 235.5-335.0 ECLU	*The LPC system suitability ranges are acceptable; the assay responses indicate generally higher LU output for the comparative clinical*

					study assay as compared to the pK similarity assay, this may be due to the effect of the SPEAD process in the comparative clinical study assay to remove serum components which could potentially lower the signal output in assays that do not use SPEAD
HPC system suitability range	1795.8-4353.5 RLU	2196.0-4370.8 RLU	2224.5-3554.0 RLU	5236-13361 ECLU	*The HPC system suitability ranges are acceptable; the assay responses indicate generally higher LU output for the comparative clinical study assay as compared to the pK similarity assay; no hook effect was observed at high antibody concentration*
Antigenic Equivalence testing (Competitive DOE)	PC conc. (0-5000 ng/ml) competed with unlabeled FKB327 (lot# (b) (4) 120117) at 0-5000 ng/ml *Response was similar to US-licensed Humira and EU-approved Humira across the concentrations tested*	PC conc. (0-5000 ng/ml) competed with unlabeled Reference Product (US-licensed Humira) lot# 201292E) at 0-5000 ng/ml *Response was similar to FKB327 and EU-approved Humira across the concentrations tested*	PC conc. (0-5000 ng/ml) competed with unlabeled Reference Product (EU-approved Humira lot#14270XD17) at 0-5000 ng/ml *Response was similar to FKB327 and US-licensed Humira across the concentrations tested*	Spiking serum with 50.2 µg/ml of either FKB327 or Humira reduced assay signal by at least 50.0%	*Assay responses were similar between FKP327 and Humira (US-licensed and EU-approved), indicating antigenic equivalence, providing justification to support antigenic similarity between FKB327 and Humira (US-licensed and EU-approved)*
Screening cut- point (SCP)	12.3 RLU additive normalization factor: 30	12.4 RLU additive normalization factor: 30	14.2 RLU additive normalization factor: 30	1.082 SCP factor: 50 lots normal human	*SCP for the assays were determined using*

Floating CP: Mean NC response × normalization factor [1.15]	male, 30 female; six independent assays, two analysts, three unique days; Shapiro-Wilk test for normality, two outliers excluded; SCP determined from 95th percentile, 5% FP-rate	male, 30 female; six independent assays, two analysts, three unique days; Shapiro-Wilk test for normality, one outlier excluded; SCP determined from 95th percentile, 5% FP-rate	male, 30 female; six independent assays, two analysts, three unique days; Shapiro-Wilk test for normality, two outliers excluded; SCP determined from 95th percentile, 5% FP-rate	serum tested over 8 days by 2 analysts; 30 lots RA patient serum tested with no significant difference found compared to normal serum; SCP factor determined from 95th percentile, 5% FP-rate	*untreated baseline patient samples and 5% false-positive rate*
Confirmatory cut-point (CCP) Floating	30.3% inhibition (excess FKB327): 30 male, 30 female; 99th percentile of observed inhibition	35.7% inhibition (excess US-licensed Humira): 30 male, 30 female; 99th percentile of observed inhibition	28.5% inhibition (excess EU-approved Humira): 30 male, 30 female; 99th percentile of observed inhibition	% inhibition (1% FP-rate): - FKB327 normal human serum: 35.946% - FKB327 RA patient serum: 32.863% - Humira normal human serum: 40.480% - Humira RA patient serum: 46.554%	*CCP for the assays were appropriately determined using 1% false-positive rate for assay inhibition*
Titer Cut Point (TCP)	10,000 ng/ml PC – 4/4 titers 1:256 1,000 ng/ml PC – 4/4 titers 1:16	10,000 ng/ml PC – 3/4 titers 1:256, 1/4 titer 1:1024 1,000 ng/ml PC – 3/4 titers 1:16, 1/4 titer 1:64	10,000 ng/ml PC – 1/4 titers 1:64, 3/4 titer 1:256 1,000 ng/ml PC – 4/4 titers 1:16	n/a	*Titer cut point evaluations are acceptable*
Assay Drug tolerance	250 ng/ml PC detectable in 500 ng/ml free FKB327; 500 ng/ml PC detectable in 1000 ng/ml FKB327	250 ng/ml PC and 500 ng/ml PC detectable in 500 ng/ml free US-licensed Humira	250 ng/ml PC detectable in 250 ng/ml free EU-approved Humira; 500 ng/ml PC detectable in 500 ng/ml free EU-approved Humira	- 72 ng/ml PC detectable in up to 50.0 µg/ml FKB327, 5000 ng/ml PC detectable in ≥200 µg/ml FKB327 - 72 ng/ml PC detectable in up to 50.0 µg/ml Humira, 5000 ng/ml PC detectable in ≥200 µg/ml Humira	*Use of the SPEAD procedure as described effectively lowers the presence of drug in the samples, to mitigate any effect of residual drug in the assay. C_{max} is ~ 4 µg/mL. The assay drug tolerance is adequate.*
Target (TNFα) tolerance	Not tested	Not tested	Not tested	Not tested	*Target tolerance was not tested for any of the ADA assay validations. For the comparative clinical*

					studies, any TNFα present in the patient samples would be eliminated from the assay by means of the SPEAD step.
Sensitivity	26.5 ng/ml PC in pooled NHS	18.9 ng/ml PC in pooled NHS	28.2 ng/ml PC in pooled NHS	22.23 ng/ml	*The validated sensitivities meet the 100 ng/ml Agency recommendation, and are acceptable*
Repeatability/Intra-assay variability	NC %CV=8.5 LPC %CV=2.8 HPC %CV=11.7	NC %CV=8.5 LPC %CV=4.3 HPC %CV=7.2	NC %CV=7.7 LPC %CV=6.2 HPC %CV=5.6	- Screening: LPC1 %CV= ≤11.0% LPC2 %CV= ≤10.7% HPC %CV= ≤10.0% - Confirmatory (FKB327): LPC1 %CV= ≤2.93% LPC2 %CV= ≤2.38% HPC %CV= ≤2.94% - Confirmatory (Humira): LPC1 %CV= ≤2.83% LPC2 %CV= ≤1.99% HPC %CV= ≤2.16%	*The intra-assay variability of the assays was found to be acceptable*
Intermediate Precision (IP)/inter-assay variability	NC %CV=8.9 LPC %CV=16.6 HPC %CV=27.7	NC %CV=11.6 LPC %CV=17.5 HPC %CV=26.2	NC %CV=9.7 LPC %CV=12.7 HPC %C=19.9	- Screening: LPC1 %CV= 10.3% LPC2 %CV= 11.3% HPC %CV=13.4% - Confirmatory (FKB327): LPC1 %CV= 2.62% LPC2 %CV= 3.12% HPC %CV= 2.57% - Confirmatory (Humira): LPC1 %CV= 3.79% LPC2 %CV= 2.19% HPC %CV= 2.65%	*The intermediate precision of the assays was found to be acceptable*

Selectivity	10 µg/ml FKB327 resulted in decreased assay readout of 500 ng/ml PC to unspiked level; serum interference not evaluated	10 µg/ml US-licensed Humira resulted in decreased assay readout of 500 ng/ml PC to unspiked level; serum interference not evaluated	10 µg/ml EU-approved Humira resulted in decreased assay readout of 500 ng/ml PC to unspiked level; serum interference not evaluated	Analyses of sera from both normal and RA patients returned results that were not significantly different; spike of either FKB327 or Humira resulted in signal inhibition exceeding the CCP for all PC concentrations, in both normal and RA patient serum	*The comparative clinical study immunogenicity assay was found adequate in lack of non-specific serum lot-to-lot interferences*
Stability	Not tested	Not tested	Not tested	- Freeze/thaw stability (-80ºC to ambient): 5 cycles - Bench stability (ambient): 24 hours	*The assay stability was demonstrated in the immunogenicity assay*
Lipemia	Not tested	Not tested	Not tested	No matrix effects observed	*Lipid presence was not shown to significantly affect the performance of the assay (SPEAD process would eliminate residual lipid contamination from samples)*
Hemolysis	Not tested	Not tested	Not tested	No matrix effects observed	*Hemolyzed serum was not shown to significantly affect the performance of the assay (SPEAD process would eliminate residual hemolytic contamination from samples)*
ADA Assay Assessment	*The ADA assay described in the 327-I12-003 / CCR#13-009 validation report is suitable for the intended purpose of*	*The ADA assay described in the 327-I13-010 validation report is suitable for the intended purpose of preliminary*	*The ADA assay described in the 327-I13-012 validation report is suitable for the intended purpose of preliminary*	*The ADA assay described in the 11487.101417.1 validation report is suitable for the intended purpose of*	

	preliminary immunogenicity analysis for pK study of FKB327	*immunogenicity analysis for pK study of FKB327*	*immunogenicity analysis for pK study of FKB327*	*immunogenicity analysis for comparative clinical study of FKB327*	

Additional Assessor Comments: *The ADA assay method principles are generally similar between the ADA assays associated with the pK similarity, and comparative clinical studies, with the exception of the SPEAD procedure for antibody extraction that was utilized for the comparative clinical studies. The ADA assay validations are acceptable, with sensitivity well within the expectation of the Agency. The ADA assay for pK study was missing several important aspects of the validation, such as evaluation of stability, and resistance to the effects of lipemia and hemolysis, however these were demonstrated adequately for the assay testing patients, which was enhanced by the inclusion of a sample pre-treatment regimen consisting of acid treatment and extraction of ADA. Antigenic equivalence testing demonstrated that assay responses were similar between FKP327, and US-licensed Humira, which support that the putative biosimilar FKP327 possesses similar immunogenic characteristics as the US-licensed HUMIRA.*

2.3 Validation of Neutralizing Antibody (NAb) Assays

2.3.1 Method Principle

The NAb assay methodology is based on a competitive inhibition of ruthenylated-drug from binding to MSD plate-bound TNF-α by a subset of ADA in the media which specifically interfere with the drug:TNF-α binding (thus "neutralizing", NAb). Without the presence of NAb in the media, the ruthenylated-drug is free to bind the plate-bound TNF-α, and be detected by the ECL mechanism upon electrification of the plate. However, in the presence of NAb, the ruthenylated-drug is sterically prevented from binding to the plate-bound TNF-α, and the ECL signal is proportionally reduced. The magnitude of reduction to luminescent signal, as compared to the signal without the presence of any NAb, indirectly gives the indication of NAb quantity in the media.

In a similar manner to the ADA assay, the Applicant utilized the SPEAD process for samples obtained in Studies FKB327-002 to -006. Acid dissociation of ADA from drug in the serum is followed by neutralization and extraction of ADA by binding to biotinylated FKB327, and attachment to streptavidin beads. ADA is recovered from the biotinylated FKB327-streptavidin bead complex by a further acid treatment, and the recovered ADA is then assayed for neutralizing capacity by binding to ruthenylated-FKB327, and measuring any diminishment in subsequent binding of the ruthenylated-FKB327 to TNF-α bound on the MSD plate. As discussed above, any interference by the SPEAD-treated ADA to the capacity of the ruthenylated-FKB327 for binding the TNF-α on the MSD plate is detected by reduction of luminescent signal upon plate electrification, as compared to ruthenylated-FKB327 binding to the TNF-α-coated MSD plate in the absence of NAb.

2.3.2 Validation Exercises

Table 2.2: Validation Results and Assessor Assessment for NAb assays used in PK similarity (validation reports 327-I12-005, 327-I12-011, 327-I12-006) and Comparative clinical studies (Validation Reports 8913.120715.1)

Validation Parameter	FKB327-001 Validation Reports: • 327-I13-005 (FKB327)	FKB327-001 Validation Reports: • 327-I13-011 (US-licensed Humira)	FKB327-001 Validation Reports: • 327-I13-006 (EU-approved Humira)	FKB327-002, -003, -004, -005, -006 Validation Report: • 8913.120715.1	*Assessor Comment*
Contract Research Org	(b) (4)				*None*
Assay principle	Competitive ligand-binding ECL assay, MSD Sector Imager 2400 device	Competitive ligand-binding ECL assay, MSD Sector Imager 2400 device	Competitive ligand-binding ECL assay, MSD Sector Imager 2400 device	Competitive ligand-binding ECL assay with sample pre-treatment, MSD Sector Imager 6000 device	*All assays use the same general principle of ECL ligand-binding assay; ECL bridging immunoassay is appropriate for the studies. Assay was optimized with pre-treatment of samples from patients.*
Sample Pretreatment (Acid dissociation)	n/a	n/a	n/a	SPEAD (solid phase extraction with acidic dissociation)	*The SPEAD procedure of antibody extraction from serum samples with acid dissociation used for the NAb assay is an improvement as it may reduce interference of matrix.*
Positive control (PC)	Cynomolgus monkey anti-FKB327 purified polyclonal antibody ((b) (4) lot 303073-2); 5.0 mg/ml (-80º storage; 2-8ºC after thaw)				*The same PC antibody is used for all NAb assays*
PC Dose Curve	125, 250, 500, 1000,	125, 250, 500, 1000,	125, 250, 500, 1000,	31.25-5000.0 ng/ml;	*The dose ranges and*

and Hook Effect	2000, 4000 ng/ml; no hook effect observed	2000, 4000 ng/ml; no hook effect observed	2000, 4000 ng/ml; no hook effect observed	no hook effect observed	*absence of hook effect are acceptable*
LPC	1429 ng/ml	1429 ng/ml	1429 ng/ml	3500 ng/ml	*3500 ng/ml was chosen for assay LPC due to results of precision and selectivity experiments*
HPC	5000 ng/ml	5000 ng/ml	5000 ng/ml	5000 ng/ml	*HPC concentration is acceptable.*
Matrix and NC	Naïve human serum ((b) (4) Lot (b) (4)618116; storage at ≤-20ºC)	Naïve human serum ((b) (4) Lot (b) (4)618116; storage at ≤-20ºC)	Naïve human serum ((b) (4) Lot (b) (4)618116; storage at ≤-20ºC)	Normal human serum (b) (4)	*The NHS is obtained from the same vendor for all the assays, and is most likely not a source of major difference*
MRD	1:2	1:2	1:2	1:3	*The MRD for the comparative clinical NAb assay is slightly greater than the pK assay due to the SPEAD procedure*
LPC system suitability range	0.56-0.64 signal ratio	0.44-0.63 signal ratio	0.51-0.67 signal ratio	0.608-0.898 signal ratio	*Acceptable for the ECL assays*
HPC system suitability range	0.18-0.24 signal ratio	0.13-0.23 signal ratio	0.15-0.24 signal ratio	0.494-0.778 signal ratio	*Acceptable for the ECL assays*
Antigenic Equivalence testing (Competitive DOE)	PC conc. (0 to 5000 ng/ml) competed with unlabeled FKB327 (lot# (b) (4)120117) at 0 to 1000 ng/ml *Response was similar to US-licensed Humira and EU-approved Humira across the concentrations tested*	PC conc. (0 to 5000 ng/ml) competed with unlabeled Reference Product (US-licensed Humira lot# 201292E) at 0-1000 ng/ml *Response was similar to FKB327 and EU-approved Humira across the concentrations tested*	PC conc. (0-5000 ng/ml) competed with unlabeled Reference Product (EU-approved Humira lot#14270XD17) at 0-1000 ng/ml *Response was similar to FKB327 and US-licensed Humira across the*	≥50 µg/ml FKB327 and ≥100 µg/ml US-Humira can inhibit the neutralization read-out	*Both FKB327 and US- licensed Humira have similar effect on the assay; it appears the FKB327 may have slightly greater effect than US-licensed Humira, which could be a reflection of the fact that the PC antibody was raised against*

			concentrations tested		*FKB327, not US-licensed Humira, and thus may be more affected by the presence of unlabeled FKB327 than unlabeled US-licensed Humira*
NAb assay cut- point (NACP) Normalized CP: mean S/N-3.09*SD	0.79 (99th percentile, 1% FP)	0.75 (99th percentile, 1% FP)	0.76 (99th percentile, 1% FP)	Normal matrix: 0.892 CPF RA patient matrix: 0.901 CPF (99th percentile, 1% FP)	*The NACP are appropriately determined, allowing 1% false-positive rate*
Assay Drug tolerance	5000 ng/ml PC detectable in up to 100 ng/ml free FKB327	5000 ng/ml PC detectable in up to 100 ng/ml free US-*licensed* Humira	2000 ng/ml PC detectable in up to 100 ng/ml free EU-approved Humira; 5000 ng/ml PC detectable in up to 100 ng/ml free EU-approved Humira	3500 ng/ml PC detectable in up to 20µg/ml FKB327, 50µg/ml US-licensed Humira	*Tolerance to free FKB327 is slightly less than tolerance to free US- licensed Humira; this may be a result of greater specificity of the PC antibody for FKB327, which it was raised against, rather than US- licensed Humira. Given the Cmax, the drug tolerance is acceptable.*
Target (TNFα) tolerance	Not tested	Not tested	Not tested	Not tested	*The SPEAD procedure of antibody extraction from serum samples with acid dissociation make it unlikely that TNFα would remain in matrix*
Sensitivity	640 ng/ml PC in pooled NHS	664 ng/ml PC in pooled NHS	836 ng/ml PC in pooled NHS	1027 ng/ml	*The assay sensitivities are not within the Agency recommendation for*

					100 ng/ml, however this is acceptable for NAb assays
Repeatability/Intra-assay variability	NC %CV: 5.9% LPC %CV: 8.1% HPC %CV: 8.7%	NC %CV: 5.6% LPC %CV: 6.9% HPC %CV: 5.5%	NC %CV: 2.4% LPC %CV: 4.2% HPC %CV: 4.9%	LPC %CV: 2.33% HPC %CV: 4.73%	*The intra-assay variability of the assays is acceptable*
Intermediate Precision (IP)/inter-assay variability	NC %CV: 5.9% LPC %CV: 8.4% HPC %CV: 13.5%	NC %CV: 11.3% LPC %CV: 15.4% HPC %CV: 25.3%	NC %CV: 8.3% LPC %CV: 11.9% HPC %CV: 22.1%	LPC %CV: 18.8% HPC %CV: 18.4%	*The intermediate precision of the assays is acceptable*
Selectivity	10/10 individual NHS lots spiked with PC 2000 ng/ml returned signal ratio less than unspiked and less than the cut point	10/10 individual NHS lots spiked with PC 2000 ng/ml returned signal ratio less than unspiked and less than the cut point	10/10 individual NHS lots spiked with PC 2000 ng/ml returned signal ratio less than unspiked and less than the cut point	- Normal serum: 8/10 unspiked matrix were above NACP; 10/10 sera spiked with LPC or HPC were below NACP - RA patient serum: 10/10 unspiked matrix were above NACP; 10/10 sera spiked with LPC or HPC were below NACP	*The detection of NAb by the assays was acceptable in both normal and disease-state serum*
Stability	Not tested	Not tested	Not tested	- Freeze / thaw stability (-80ºC to ambient): 5 cycles - Bench stability (ambient): 24 hours	*The NAb assay stability is acceptable*
Lipemia	Not tested	Not tested	Not tested	Not tested	*Lipemia was shown in ADA assays to not significantly affect performance of assays, and SPEAD process used would eliminate residual lipid in matrix*
Hemolysis	Not tested	Not tested	Not tested	Not tested	*Hemolysis was shown in ADA assays to not significantly affect performance of assays, and SPEAD process used would*

					eliminate residual hemolytic materials in matrix
NAb Assay Assessment	*The NAb assay described in the 327-I13-005 validation report is suitable for the intended purpose of preliminary neutralizing antibody analysis for a Ph 1 clinical trial of FKB327*	*The NAb assay described in the 327-I13-011 validation report is suitable for the intended purpose of preliminary neutralizing antibody analysis for a Ph 1 clinical trial of FKB327*	*The NAb assay described in the 327-I13-006 validation report is suitable for the intended purpose of preliminary neutralizing antibody analysis for a Ph 1 clinical trial of FKB327*	*The NAb assay described in the 8913.120715.1 validation report is suitable for the intended purpose of neutralizing antibody analysis for a Ph 3 clinical trial of FKB327*	

Additional Assessor Comments: *The results of the FKB327 neutralizing antibody assay validations indicate that they are generally suitable for the intended purpose of detecting FKB327 NAb. The assays do not appear to be as sensitive as recommended by the Agency guidance (100 ng/ml), however for NAb assays, it is reasonable, as the guidance suggests that such an expectation may be difficult to meet for neutralizing assays. The NAb assays utilize a similar analytical platform as the ADA assays, however the method principle is different (competitive ligand-binding), where the presence of NAb inhibits drug binding to plate-bound TNF-α, and results in signal diminishment. It was found that tolerance for FKB327 was not as high as tolerance for Humira; it is possible that this could be a result of greater specificity of the PC antibody for FKB327, which it was raised against. Overall, the results of the NAb assay validation do support the adequacy of the assay for analysis of patient samples, and furthermore support the similarity of FKB327 and US-licensed HUMIRA.*

2.4 Facility Inspection Summary

Refer to OASIS report for details.

2.5 Analysis of Clinical Immunogenicity Results

Refer to Clinical Pharmacology and Clinical Division reviews for details.

2.6 Information Requests Sent During Review

None

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