CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761201Orig1s000

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:	July 23, 2021
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Qiong Fu, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 2
Application:	BLA 761201
Applicant:	Mylan Pharmaceuticals Inc.
Submission Date:	July 29, 2020
Product:	Semglee (insulin glargine-yfgn xxxx)
Dosage form(s):	injection
Strength and Container-Closure:	100 units/mL in: 10 mL multiple-dose vial 3 mL single-patient-use prefilled pen
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information (submitted on July 1, 2021), patient labeling and instructions for use (submitted on July 22, 2021), and container labels and carton labeling (submitted on June 16, 2021) are acceptable from an OBP labeling perspective.

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

n/a = not applicable for this assessment

DISCUSSION

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

CONCLUSION

The prescribing information (submitted on July 1, 2021), patient labeling and instructions for use (submitted on July 22, 2021), and container labels and carton labeling (submitted on June 16, 2021) are acceptable from an OBP labeling perspective. (see Appendix C)

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted on December 1, 2020 \\CDSESUB1\evsprod\bla761201\0011\m1\us\114-labeling\draft\labeling\draft-labeling-text-tracked-changes-word.docx)

Patient Information Labeling (submitted on July 29, 2020 \\CDSESUB1\evsprod\bla761201\0001\m1\us\114-labeling\draft\labeling\draft-patient-information-text-vial-tracked-changes-word-ma.docx and \\CDSESUB1\evsprod\bla761201\0001\m1\us\114-labeling\draft\labeling\draft-patient-information-text-pen-tracked-changes-word-mal.docx and \\CDSESUB1\evsprod\bla761201\0001\m1\us\114-labeling\draft\labeling\draft-patient-information-text-pen-tracked-changes-word-ind.docx

Instructions for Use (submitted on July 29, 2020 \\CDSESUB1\evsprod\bla761201\0001\m1\us\114-labeling\draft\labeling\draft-instructions-for-use-text-vial-tracked-changes-word-m.docx and \\CDSESUB1\evsprod\bla761201\0001\m1\us\114-labeling\draft\labeling\draft-instructions-for-use-text-pen-tracked-changes-word-in.docx and \\CDSESUB1\evsprod\bla761201\0001\m1\us\114-labeling\draft\labeling\draft-patient-information-text-pen-tracked-changes-word-mal.docx)

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

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
Recommended labeling practices (placement of dosage form outside of parenthesis and/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

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

[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.
[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."

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

Comment/Recommendation: *vial and prefilled pen labeled "Use within 28 days after initial use"*

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

Comment/Recommendation: partial label see 21 CFR 610.60(c) and dosage statement below

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

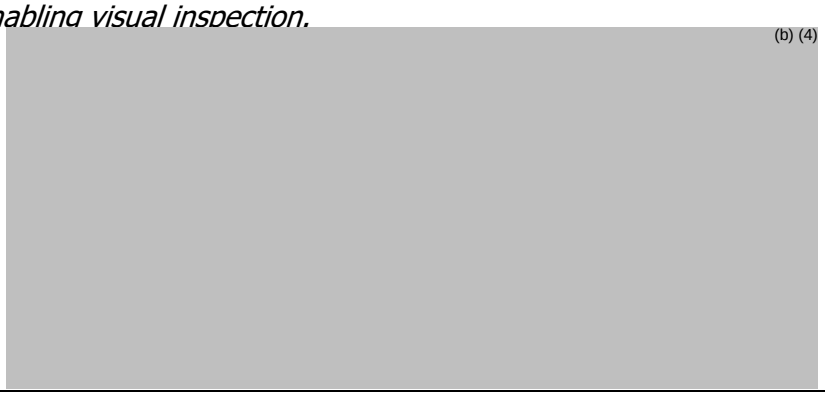
Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials.
The Applicant confirmed

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: For the vials, the label does not cover the full length or circumference and there is a 0.5 cm gap in the container label to enable visual inspection. For the cartridges, once the cap of the pen is removed, there is no label covering the visible part of cartridge enabling visual inspection.

(b) (4)



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

Comment/Recommendation: Consider revising from "For subcutaneous injection only" to "For subcutaneous use only"
The Applicant revised as requested

***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

Comment/Recommendation: *partial label space considerations for vial and prefilled pen*

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: *the package type term "multiple-dose vial" is on the vial label; partial label space considerations for prefilled pen*

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	✓ Yes

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	☐ 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

Comment/Recommendation: Per 21 CFR 610.60(c), partial label for multiple dose containers (single-patient-use containers contain multiple doses), the recommended individual dose is required. Add "Dosage: See Prescribing Information" to the vial container labels (see also 21 CFR 201.55). *The Applicant revised as requested*

Space consideration for the pen container label

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

Comment/Recommendation: *Partial label limited space considerations for vial and prefilled pen*

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
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ 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

[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.

Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

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: *product contains metacresol*

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

Comment/Recommendation: Revise from "unopened" and "opened" storage statements for the vial presentation to: "**Storage:** Refrigerate at 2° to 8°C (36° to 46°F) until first use. Avoid freezing. Discard if frozen. After first use, store at room temperature (up to 30°C [86°F]) and discard after 28 days. Protect from direct heat and light."

for the pen presentation to: "**Storage:** Refrigerate at 2° to 8°C (36° to 46°F) until first use. Avoid freezing. Discard if frozen. After first use of a Semglee pen, store the pen at room temperature (up to 30°C [86°F]) and discard after 28 days. Protect from direct heat and light."
The Applicant revised to "below 30°C [86°F])" instead of using the recommended language "up to 30°C [86°F])". For clarity for the end user, we recommend that the storage statement indicate the maximum room temperature using "up to" since "below" includes temperatures into the refrigerated and freezing ranges.
The Applicant revised as requested

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

Comment/Recommendation: *see dosage statement recommendation*

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

Comment/Recommendation:
For the one count and three count prefilled pen carton labeling: revise the route of administration to "For subcutaneous use only" and delete the statement (b) (4) " which provides the incorrect dosage form (b) (4) . *The Applicant revised as requested*

For the five-count prefilled pen carton labeling: revise the route of administration to "For subcutaneous use only". *The Applicant revised*

For the multiple-dose vial carton labeling: revise the route of administration to "For subcutaneous use only" and relocate the route of administration to appear after the strength statement on the principal display panel. *The Applicant revised*

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: Consider revising the inactive ingredient names to appear in alphabetical order, to include the pH adjusters, and to match the prescribing information as follows:

For the vial presentation: "Each mL contains 100 units of insulin glargine-yfgn, and inactive ingredients: glycerol (20 mg), metacresol (2.7 mg), polysorbate-20 (20 mcg), zinc chloride (content adjusted to provide 30 mcg zinc ion), and Water for Injection, USP. The pH is approximately 4. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and sodium hydroxide." *The Applicant revised as requested*

For the pen presentation: "Each mL contains 100 units of insulin glargine-yfgn, and inactive ingredients: glycerol (20 mg), metacresol (2.7 mg), zinc chloride (content adjusted to provide 30 mcg zinc ion), and Water for Injection, USP. The pH is approximately 4. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and sodium hydroxide." *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: see prescribing information

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 Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ 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) and 21 CFR 610.61(i)	✓ 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	✓ Yes ☐ No ☐ N/A

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*	

Comment/Recommendation: At this time, we acknowledge that in general, FDA's guidance documents do not establish legally enforceable responsibilities and we note that the required safety statement, "For single patient use only", is prominently displayed on the PDP. Although it is not associated with the container closure, requesting the applicant to include the package type term, "single-patient-use", may result in labeling that is cluttered and redundant.

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: For all carton labeling, we note that the revised the dosage statement in your June 11, 2021 carton labeling submission uses outdated language that does not align with language used for PLR formatted labeling. Your carton labeling submission dated July 29, 2020 had the current language "Recommended dosage: see Prescribing Information". This language is preferred and is consistent with more recently FDA approved labeling."

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)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	☐ 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

Comment/Recommendation: Added identifying characteristics of the dosage form *The Applicant revised as requested*

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: Deleted the proprietary name from the first paragraph since this paragraph discusses the drug substance. *The Applicant revised as requested* We added the minimum potency: "*In vivo* assay confirms the minimum potency of insulin glargine is NLT 15 units/mg". *The Applicant revised as requested* We provide the units for the molecular weight, 6063 Da. *The Applicant revised as requested* Added "sterile" see 21 CFR 201.57(c)(12) *The Applicant revised as requested* Revised inactive ingredients to appear in alphabetical order and added subsections for vial and pen *The Applicant revised as requested* *Internal Note non required information retained in section 11 (e.g., mechanism of action) will first be revised in the reference product's (Lantus) labeling.*

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	☐ 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

Comment/Recommendation: Added identifying characteristics of the dosage form *The Applicant revised as requested*

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: added the manufacturer information *The Applicant revised as requested*

Medication Guide Evaluation (N/A)

Patient Information Labeling Evaluation

PATIENT INFORMATION LABELING	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A

PATIENT INFORMATION LABELING	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for Patient Labeling: 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

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

Comment/Recommendation: revised inactive ingredients to appear in alphabetical order
The Applicant revised as requested

PATIENT INFORMATION LABELING	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ 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

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: We note that for the prefilled pen, the route of administration that should appear in lower case letters on line 3 is missing. However, per the FDA Guidance for Industry Labeling for Biosimilar Products, "If the FDA-approved patient labeling for the reference product includes Instructions for Use (IFU), the IFU for the proposed biosimilar product should incorporate relevant information from the IFU for the reference product and present the information in a similar manner." Accordingly, the reference product will need to be updated first.

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	✓ Yes ☐ No ☐ N/A

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)	

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). *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

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information (submitted on July 1, 2021 \\CDSESUB1\evsprod\bla761201\0034\m1\us\114-labeling\draft\labeling\draft-labeling-text-clean-pdf.pdf)

Instructions for Use (submitted on July 22, 2021 \\CDSESUB1\evsprod\bla761201\0035\m1\us\114-labeling\draft\labeling\draft-instructions-for-use-text-vial-clean-pdf-malaysia.pdf and \\CDSESUB1\evsprod\bla761201\0035\m1\us\114-labeling\draft\labeling\draft-instructions-for-use-text-pen-clean-pdf-malaysia.pdf)

Patient Information (submitted on July 22, 2021 \\CDSESUB1\evsprod\bla761201\0035\m1\us\114-labeling\draft\labeling\draft-patient-information-text-vial-clean-pdf-malaysia.pdf and \\CDSESUB1\evsprod\bla761201\0035\m1\us\114-labeling\draft\labeling\draft-patient-information-text-pen-clean-pdf-malaysia.pdf)

5 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: 7/23/2021 03:03:52PM
GUID: 50814c7000007a3d59329f660d8ddf02

Qiong Fu

Digitally signed by Qiong Fu
Date: 7/23/2021 04:05:53PM
GUID: 5c5af23f004dca70cf7a20351e44cac2

If approved, Semglee (insulin glargine-yfgn; MYL-1501D) will be an interchangeable biosimilar with U.S.-licensed Lantus.[1]

Recommendation: **Approval**

BLA Number: 761201
Office of Pharmaceutical Quality
Application Team Lead Assessment Number: 3
Assessment Date: June 23, 2021

Addendum: The OPQ Executive Summary memorandum uploaded to Panorama on March 29, 2021 and the Addendum uploaded on April 15, 2021 still apply and are valid. This addendum is to provide an assessment of the revised comparative analytical assessment reports submitted by the Applicant on April 23, 2021.

Drug Name/Dosage Form	Semglee (insulin glargine-yfgn; MYL-1501D) /injection
Strength/Potency	100 Units/mL in a 3 mL pre-filled pen and in a 10 mL vial
Route of Administration	subcutaneous
Rx/OTC dispensed	Rx
Indication	To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Applicant/Sponsor	Mylan Pharmaceuticals Inc
US agent, if applicable	N/A

Product Overview:

SEMGLEE (insulin glargine-yfgn) is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. Semglee is homologous with human insulin with the exception of a substitution of the amino acid glycine by asparagine at position A21, and two arginine residues added to the C-terminus of the B-chain. Semglee is produced by recombinant DNA technology utilizing *Pichia pastoris*. Semglee is supplied as a pre-filled pen and a vial for subcutaneous injection. Semglee is a proposed interchangeable biosimilar to U.S.-licensed Lantus.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Qiong Fu	DBRRII/OBP/OPQ
Drug Product		
Immunogenicity		
Labeling	Vicky Borders-Hemphill	DBRRII/OBP/OPQ
Facility	Michael Shanks, Virginia Carroll	DBM/OPMA/OPQ
Microbiology DS	Michael Shanks	DBM/OPMA/OPQ
Microbiology DP	Virginia Carroll	DBM/OPMA/OPQ
Facility secondary Assessor	Candace Gomez-Broughton	DBM/OPMA/OPQ
Microbiology Branch Chief	Candace Gomez-Broughton	DBM/OPMA/OPQ
Regulatory Business Process Manager	Anika Lalmansingh	OPRO/OPQ
Application Team Lead	Anjali Shukla	DBRRII/OBP/OPQ

[1]Header has been corrected for clarity.

Submissions Assessed:

Additional Submission Assessed	Document Date
761201/0027	4/23/2021
761201/0029 (responses to OBP IR*)	5/18/2021

*IR: Information Request sent to the Applicant

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: **Approval**

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761201 for SEMGLEE manufactured by Mylan Pharmaceuticals, Inc. The data submitted in this application are adequate to support the conclusion that:

- The manufacture of Semglee is well-controlled and leads to a product that is pure and potent.
- Semglee is highly similar to U.S.-licensed Lantus, 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.

On April 23, 2021 (SDN 0027), the Applicant submitted revised comparative analytical assessment reports for IR-B Phosphorylation assay, IR-Phosphorylation Assay and Rabbit Bioassay. The amended reports were submitted to report corrected data after errors were discovered in the analyses performed originally. At the Late Cycle Meeting with the Applicant held on April 29, 2021, Mylan confirmed that there was no change in the raw data. The differences between the updated values in the revised reports and those previously submitted to the BLA are minor and do not impact any of the comparative analytical assessment conclusions for any attribute. Refer to the Applicant's summary chart below for details. For additional details, see the Addendum to the OBP technical review. The updated analyses continue to support that Semglee is highly similar to U.S.-licensed Lantus, notwithstanding minor differences in clinically inactive components. Therefore, the Office of Pharmaceutical Quality, CDER recommends approval of STN 761201 for SEMGLEE manufactured by Mylan Pharmaceuticals, Inc.

Table 1: Detailed Summary of Changes to Module 3 Analytical Similarity for Cartridge and Vial

Module 3	Report Name	Report Sub-section No.	Affected Tables/Figures and Page no.	Revised Data Specifics	Impact of Change
3.2.R.1 Analytical Similarity Assessment (Cartridges)	CDL/TR/LR.19.0091/20/001 AS Report (Cartridges)	Section 3.2.R.1 - CDL/TR/LR.19.0091/20/001- Subsection 4.4.2.1.2 **IRB assay**	Section 3.2.R.1 - CDL/TR/LR.19.0091/20/001 Table 16 to Table 19; Section 3.2.R.1 - CDL/TR/LR.19.0091/20/001 Figure 10 to Figure 14	Change in 2nd decimal observed for all values. Relative potency of all samples is determined using PLA (Parallel line analysis). As per the current STP, Best Range is used in PLA for calculation of relative potency however, analysts chose the Maximum Range. The data has been reanalysed using Best Range as per the STP and revised values have been presented. The difference in potency values analysed by Best Range vs. Maximum Range was only in second decimals and these minor differences in the Potency values did NOT change the conclusion.	No impact observed on previously reported conclusion.
		Section 3.2.R.1 - CDL/TR/LR.19.0091/20/001 – Subsection 4.4.2.1.4 **HepG2 assay**	Section 3.2.R.1 - CDL/TR/LR.19.0091/20/001- Table 25; Section 3.2.R.1- CDL/TR/LR.19.0091/20/001 Figure 22	Change in one MYL-1501D cartridge batch value (Batch BS15005866). Average of 2 assays (n=2) reported instead of average of 3 (n=3) assays values as per current STP.	
		Section 3.2.R.1 - CDL/TR/LR.19.0091/20/001 – Subsection 4.4.2.2.5 **Rabbit Bioassay**	Section 3.2.R.1 - CDL/TR/LR.19.0091/20/001- Table 47	Change in all estimated potency values – total 21 batches. Potency values of insulin and glargine pharmacopeial reference standards used were swapped inadvertently during calculation of estimated potency values for MYL-1501D and reference product batches. Values were re-estimated using the potency values listed in the CoA of the reference standards.	
3.2.R.1 Analytical Similarity Assessment (Vial)	CDL/TR/LR.19.0091/20/002 AS Report (Vial)	Section 3.2.R.1 - CDL/TR/LR.19.0091/20/002 – Subsection 4.3.4.1.2- **IRB Assay**	Section 3.2.R.1 - CDL/TR/LR.19.0091/20/002 Table 12 and Table 13 Section 3.2.R.1- CDL/TR/LR.19.0091/20/002 Figure 8 and Figure 9	Change in 2nd decimal observed for all values. Relative potency of all samples is determined using PLA (Parallel line analysis). However, previously reported values utilized maximum range of linear point allocation for fit rather than best range of linear point allocation. The best range of linear point allocation has now been applied to all samples and revised values have been presented.	No impact observed on previously reported conclusion.
		Section 3.2.R.1 - CDL/TR/LR.19.0091/20/002 – Subsection 4.5.1.3.2 **IRB Assay**	Section 3.2.R.1- CDL/TR/LR.19.0091/20/002- Table 73 to Table 76 Section 3.2.R.1 - CDL/TR/LR.19.0091/20/002 Figure 66 to Figure 70		

Source: BLA 761201 SDN 0027 Section 1.11.4 Table 1.

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

None

Anjali Shukla

Digitally signed by Anjali Shukla
Date: 6/23/2021 04:51:07PM
GUID: 57f29f4500712615c8f3d6ddc11716a9

Patrick Lynch

Digitally signed by Patrick Lynch
Date: 6/24/2021 02:44:50PM
GUID: 54bfb193000693c35f4278034f85d77a

First Biosimilar: If approved, Semglee (insulin glargine-yfgn) will be the first interchangeable biosimilar to U.S.-licensed Lantus.

Recommendation: **Approval**

BLA Number: 761201
Office of Pharmaceutical Quality
Application Team Lead Assessment Number: 2
Assessment Date: April 15, 2021

Addendum: The Executive Summary memorandum uploaded to Panorama on March 29, 2021 still applies and is valid. This addendum is to update the OPQ recommendation from Pending to Approval following finalization of the microbiology assessment.

Drug Name/Dosage Form	Semglee (insulin glargine-yfgn) /injection
Strength/Potency	100 Units/mL in a 3 mL pre-filled pen and in a 10 mL vial
Route of Administration	subcutaneous
Rx/OTC dispensed	Rx
Indication	To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Applicant/Sponsor	Mylan Pharmaceuticals Inc
US agent, if applicable	N/A

Product Overview:

SEMGLEE (insulin glargine-yfgn) is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. Semglee is homologous with human insulin with the exception of a substitution of the amino acid glycine by asparagine at position A21, and two arginine residues added to the C-terminus of the B-chain. Semglee is produced by recombinant DNA technology utilizing *Pichia pastoris*. Semglee is supplied as a pre-filled pen and a vial for subcutaneous injection. Semglee is a proposed interchangeable biosimilar to U.S.-licensed Lantus.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Qiong Fu	DBRRII/OBP/OPQ
Drug Product		
Immunogenicity		
Labeling	Vicky Borders-Hemphill	DBRRII/OBP/OPQ
Facility	Michael Shanks, Virginia Carroll	DBM/OPMA/OPQ
Microbiology DS	Michael Shanks	DBM/OPMA/OPQ
Microbiology DP	Virginia Carroll	DBM/OPMA/OPQ
Facility secondary Assessor	Candace Gomez-Broughton	DBM/OPMA/OPQ
Microbiology Branch Chief	Candace Gomez-Broughton	DBM/OPMA/OPQ
Regulatory Business Process Manager	Anika Lalmansingh	OPRO/OPQ
Application Team Lead	Anjali Shukla	DBRRII/OBP/OPQ

Submissions Assessed:

Additional Submission Assessed	Document Date
761201/0026 (responses to OPMA IR)	4/8/2021

*IR: Information Request sent to the Applicant

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: **Approval**

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761201 for SEMGLEE manufactured by Mylan Pharmaceuticals, Inc. The data submitted in this application are adequate to support the conclusion that:

- The manufacture of Semglee is well-controlled and leads to a product that is pure and potent.
- Semglee is highly similar to U.S.-licensed Lantus, 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.

The OPQ Executive Summary memorandum uploaded to Panorama on March 29, 2021 noted that the Office of Pharmaceutical Quality, CDER recommendation on approvability of STN 761201 was pending final microbiology recommendation. The pending drug product microbiology technical assessment was finalized on April 15, 2021, and recommends approval. Therefore, this addendum is submitted to provide the final OPQ recommendation of approval of BLA 761201 for SEMGLEE manufactured by Mylan Pharmaceuticals, Inc.

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

None

Anjali Shukla

Digitally signed by Anjali Shukla
Date: 4/15/2021 10:25:14PM
GUID: 57f29f4500712615c8f3d6ddc11716a9

Patrick Lynch

Digitally signed by Patrick Lynch
Date: 4/16/2021 08:28:16AM
GUID: 54bfb193000693c35f4278034f85d77a

First Biosimilar: If approved, Semglee (insulin glargine-yfgn) will be the first interchangeable biosimilar to U.S.-licensed Lantus.

Recommendation: Approval pending final Microbiology recommendation (See Section IA)

BLA Number: 761201
Office of Pharmaceutical Quality
Application Team Lead Assessment Number: 1
Assessment Date: March 29, 2021

Drug Name/Dosage Form	Semglee (insulin glargine-yfgn) /injection
Strength/Potency	100 Units/mL in a 3 mL pre-filled pen and in a 10 mL vial
Route of Administration	subcutaneous
Rx/OTC dispensed	Rx
Indication	To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Applicant/Sponsor	Mylan Pharmaceuticals Inc
US agent, if applicable	N/A

Product Overview:

SEMGLEE (insulin glargine-yfgn) is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. Semglee is homologous with human insulin with the exception of a substitution of the amino acid glycine by asparagine at position A21, and two arginine residues added to the C-terminus of the B-chain. Semglee is produced by recombinant DNA technology utilizing *Pichia pastoris*. Semglee is supplied as a pre-filled pen and a vial for subcutaneous injection. Semglee is a proposed interchangeable biosimilar to U.S.-licensed Lantus.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Qiong Fu	DBRRII/OBP/OPQ
Drug Product		
Immunogenicity		
Labeling	Vicky Borders-Hemphill	DBRRII/OBP/OPQ
Facility	Michael Shanks, Virginia Carroll	DBM/OPMA/OPQ
Microbiology DS	Michael Shanks	DBM/OPMA/OPQ
Microbiology DP	Virginia Carroll	DBM/OPMA/OPQ
Facility secondary Assessor	Candace Gomez-Broughton	DBM/OPMA/OPQ
Microbiology Branch Chief	Candace Gomez-Broughton	DBM/OPMA/OPQ
Regulatory Business Process Manager	Anika Lalmansingh	OPRO/OPQ
Application Team Lead	Anjali Shukla	DBRRII/OBP/OPQ

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Julie Van der Waag	DROCHEN/ORO/OND
Cross-disciplinary Team Lead	Patrick Archdeacon	DDLO/OCHEN/OND
Medical Officer	Ann Miller	DDLO/OCHEN/OND
Pharmacology/Toxicology	Patricia Brundage, Federica Basso	DPTCHEN/OCHEN/OND
Clinical Pharmacology	Lin Zhou, Manoj Khurana	DCEP/OCP/OTS

Statistics	Roberto Crackel,Yun Wang	DBII/OB/OTS
CDRH	David Wolloscheck,Rumi Young	DHT3C /OHT3/OPEQ /CDRH
DMEPA	Ariane Conrad, Millie Shah	DMEPA/OMEPRM/OSE
OTBB	Stacey Ricci, Sarah Schrieber, Nina Brahme, Ruby (Chin-Ann) Wu, Eva Temkin, Andrew Zacher, Christine Corser, Leila Hann, Sarah Brown, Tyree Newman	OTBB/OND

1. Names:

a. Proprietary Name: Semglee
b. Trade Name: Semglee
c. Non-Proprietary Name/USAN: insulin glargine-yfgn
d. CAS Name: 160337-95-1
e. Company Code: MYL-1501D
f. INN Name: insulin glargine-yfgn
h. OBP systematic name: RPROT P01308 (INS_HUMAN) INSULIN [MYL1501D]

Submissions Assessed:

Submission(s) Assessed	Document Date
761201/0001	7/29/2020
761201/0004 (responses to OBP IR* #1)	9/9/2020
761201/0005 (responses to OPMA IR)	9/18/2020
761201/0012 (responses to OPMA IR)	12/16/2020
761201/0013 (response to OPMA IR)	1/8/2021
761201/0017 (responses to OBP IR #2)	2/16/2021
761201/0018 (responses to OBP IR #2)	2/19/2021
761201/0020 (responses to OBP IR #3)	2/26/2021
761201/0021 (responses to OBP IR #4)	3/1/2021
761201/0023 (responses to OBP IR #5)	3/16/2021

*IR: Information Request sent to the Applicant

Quality Assessment 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 Assessment Completed	Comments
(b) (4)	III		(b) (4)	3	N/A	N/A	No review required at this time as relevant information related to compatibility with the product was provided in the BLA.
	III			3	N/A	N/A	No review required at this time as relevant information related to compatibility with the product was provided in the BLA.
	V			2	Adequate	04/02/2020	The washing process was assessed previously.
	III			3	N/A	N/A	No review required at this time as relevant information related to compatibility with the product was provided in the BLA.
	III			3 and 2	N/A and Adequate	N/A and 06/15/2020	No review required at this time as relevant

		(b) (4)				information related to compatibility with the product was provided in the BLA (b) (4) washing process was assessed previously.
(b) (4)	V	(b) (4)	2	Adequate	05/14/2019	The washing process was assessed previously.
	III		3	N/A	N/A	No review required at this time as relevant information related to compatibility with the product was provided in the BLA.
	II		3	N/A	N/A	No review required at this time as relevant information related to compatibility with the product was provided in the BLA.
	MAF		3, and 6	N/A	N/A	No OPQ review required at this time as relevant information related to compatibility with the product was provided in the BLA. Assessment of MAF is

							deferred to CDRH.

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

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be assessed.

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

Document	Application Number	Description
BLA	210605	Semglee is currently licensed under deemed 351(a) BLA 210605

3. Consults: No consults requested by OPQ

4. Environmental Assessment of Claim of Categorical Exclusion:

Pursuant to 21 CFR §25.15(d), Mylan Pharmaceuticals Inc. requested a categorical exclusion from the preparation of an environmental assessment report for Semglee (insulin glargine-yfgn). The reasons supporting this request for categorical exclusion are as follows:
1) In accordance with 21 CFR §25.31(a), this is a biologic license application, for marketing approval of a proposed biosimilar, which is not expected to increase the use of the active moiety.
2) There is no anticipated change in the level of the substance in the environment as a result of Mylan's manufacture of the drug product and consequently, no increase in environmental effects associated with the use and disposal from use of this product. The methods employed in the manufacture of the biological product are in compliance with all applicable local, state and federal environmental regulations.

The Applicant's claim of a categorical exclusion is accepted.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Approval pending final Microbiology recommendation.

The Office of Pharmaceutical Quality, CDER, recommendation on approvability of STN 761201 for SEMGLEE manufactured by Mylan Pharmaceuticals, Inc is pending final Microbiology recommendation.

The Office of Pharmaceutical Quality, CDER does not note any product quality deficiencies that would preclude approval of BLA 761201 for SEMGLEE manufactured by Mylan Pharmaceuticals, Inc. at this time. The data submitted in this application are adequate to support that Semglee is highly similar to U.S.-licensed Lantus, notwithstanding minor differences in clinically inactive components.
However, the drug product microbiology assessment is ongoing at the time of finalizing this memorandum. Final OPQ recommendation will be provided in a future addendum to this OPQ Executive Summary memorandum upon completion of the OPMA microbiology assessment.

B. Approval Action Letter Language:

- Manufacturing location:
    - Drug Substance:
      Biocon Sdn. Bhd. (930330-U),
      No.1, Jalan Bioteknologi 1,
      Kawasan Perindustrian SiLC,
      79200 Iskandar puteri
      Johor, Malaysia.
      FEI: 3011248248
    - Drug Product:
      Biocon Sdn. Bhd. (930330-U),
      No.1, Jalan Bioteknologi 1,
      Kawasan Perindustrian SiLC,
      79200 Iskandar puteri
      Johor, Malaysia.
      FEI: 3011248248
- Fill size and dosage form
  100 Units/mL in 3 mL pre-filled pen
  100 Units/mL in 10 mL multiple dose vial
- Dating period:
    - Drug Product: 24 months: 5°C±3°C

- Drug Substance: (b) (4) months: (b) (4) C
- For packaged products: N/A
- Stability Option:

  We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

- Exempt from lot release:

  - Yes
  - Rationale, if exempted: specified product
    Note: Semglee is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

Semglee (insulin glargine-yfgn), referred to as MYL-1501D, is a proposed interchangeable biosimilar to U.S.-licensed Lantus (insulin glargine). Insulin glargine is a long-acting analog of human insulin. Semglee is indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus as is approved for U.S.-licensed Lantus. Semglee has the same strength, dosage form, and route of administration as U.S.-licensed Lantus.

The data provided in the BLA support a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus, notwithstanding minor differences in clinically inactive components (refer to Section II of this memo). The proposed presentations of MYL-1501D 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 U.S.-licensed Lantus. The strength of MYL-1501D vials and pre-filled pen is the same as that of U.S.-licensed Lantus.

The MYL-1501D manufacturing process and overall control strategy are sufficient to ensure consistent manufacture of a drug product that is safe and effective. The immunogenicity assays are suitable and sensitive to detect anti-drug antibodies to MYL-1501D and U.S.-licensed Lantus. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage (see Sections III G Establishment Information and III H Facilities).

The approval of MYL-1501D as an interchangeable biosimilar to U.S.-licensed Lantus will increase treatment options for patients currently undergoing therapy for diabetes.

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

None

II. Comparative Analytical Assessment

A. Analytical Assessment Overview and Conclusions

The Applicant performed two studies as part of the comparative analytical assessment between MYL-1501D and U.S.-licensed Lantus as described below:

i. A study that compared a total of 10 MYL-1501D cartridge lots and 24 U.S.-licensed Lantus pre-filled pen (PFP) lots where cartridges are integrated into the PFP. The 10 MYL-1501D cartridge lots included lots used in the clinical PK/PD similarity studies, comparative clinical studies, and lots representative of the clinical and the proposed commercial drug product. These 10 MYL-1501D cartridge lots included 6 lots manufactured using Process VI (proposed commercial manufacturing process) drug substance (DS) and 4 lots manufactured using Process V DS. Comparability between lots manufactured using DS Process V and VI has been established (Refer to BLA 210605 CDTL Review and Division Summary Memo for Regulatory Action, June 11, 2020; BLA 210605 OPQ Executive Summary, May 22, 2020; BLA 210605 OPQ Executive Summary, April 5, 2018).
The proposed presentations of MYL-1501D include a 10 ml vial and a pre-filled pen integrated with a 3 ml cartridge. The cartridge is the primary container closure system of the pre-filled pen DP and the assembly process of the cartridge into the pen was demonstrated to have no impact on the quality attributes of MYL-1501D. Therefore, it is acceptable to include MYL-1501D cartridge lots in the comparative analytical assessment of MYL-1501D and U.S.-licensed Lantus.

ii. A study that compared a total of 5 MYL-1501D vial lots, and 34 U.S.-licensed Lantus lots (24 PFP lots + 10 vial lots). The MYL-1501D vial lots included the vial lot used in the clinical PK/PD similarity study MYL-1501D-1004, process validation lots, and lots representative of the proposed commercial drug product. For statistical evaluation, the U.S.-licensed Lantus quality ranges were established by combining data obtained from U.S.-licensed Lantus PFP lots and U.S.-licensed Lantus vial lots. Mylan chose to justify this approach by demonstrating analytical comparability between U.S.-licensed Lantus vial and PFP lots, and FDA found this acceptable.

Expiration dates for the U.S.-licensed Lantus PFP lots range from June 2014 to October 2017 and U.S.-licensed Lantus vial lots range from March 2017 to June 2018, which spans the shelf life of U.S.-licensed Lantus. These lots were adequate to capture potential lot-to-lot variability in the reference product over time.

The comparative analytical assessment was comprised of extensive comparative physicochemical and functional assessment of the quality attributes of MYL-1501D and U.S.-licensed Lantus. Mylan used an acceptable risk-based approach for statistical evaluation of analytical results. The highest ranked attributes tested using quantitative assays were evaluated using both equivalence testing and quality ranges on the same sets of data. The OBP Assessor's evaluation was based on the quality ranges approach for these attributes. Low to high risk attributes tested using quantitative assays were evaluated using quality ranges calculated to account for reference product manufacturing variability and assay variability. Attributes tested using qualitative assays were evaluated using graphical representation and data tables. Additionally, for attributes measured by multiple orthogonal methods amenable to statistical assessment of quality ranges, at least one method was evaluated statistically and the rest were evaluated using graphical and/or data table comparisons. Results from method validation or qualification studies support the suitability of the methods used in the comparative analytical assessment. The applicant also provided a comparison of stability under forced degradation conditions of thermal stress (60℃), pH (pH 2 and pH 10), oxidative stress, photo exposure and mechanical stress. The comparative forced degradation studies support that MYL-1501D and U.S.-licensed Lantus have a similar degradation profile.

Based on our assessment, the MYL-1501D and U.S.-licensed Lantus data supports a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus, notwithstanding minor differences in clinically inactive components. MYL-1501D has the same strength, dosage form, and routes of administration as U.S.-licensed Lantus. The applicant used a comprehensive array of analytical methods that were suitable to evaluate critical quality attributes of MYL-1501D and U.S.-licensed Lantus to support the demonstration that the products are highly similar. Numbers of lots tested and data analyses were appropriate to allow for a meaningful evaluation of the results of the comparative analytical studies. While differences were observed in a limited number of attributes, these do not preclude a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus.

B. Results of Comparative Analytical Assessment

The results of these analytical comparisons support a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus and the results are summarized in Table A below:

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

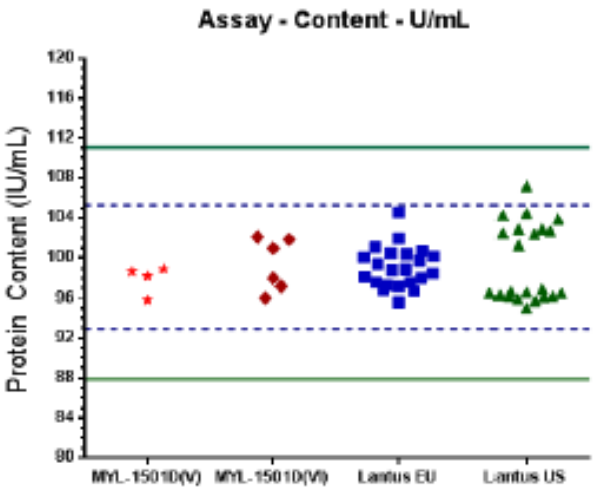
Physico-chemical/Functional characteristics	Quality Attribute Assessed	MYL-1501D cartridge vs U.S.-Lantus PFP Supports a demonstration of highly similar	MYL-1501D vial vs U.S.-Lantus PFP+vial Supports a demonstration of highly similar
Amino acid sequence	Peptide Mass Fingerprint (PMF)	Yes	Yes
	Intact mass	Yes	Yes
	Reduced mass (reduced ESI-MS)	Yes	Yes
Conformation (secondary and higher order structure)	FTIR	Yes	Yes
	Far UV CD	Yes	Yes
	Extrinsic fluorescence	Yes	Yes
	Intrinsic fluorescence	Yes	Yes
	Near UV CD	Yes	Yes
	DSC (for Tm °C)	Yes	Yes
	PMF (Non-reduced)	Yes	Yes
	DLS (for hydrodynamic radius)	Yes	Yes
	X-Ray	Yes	Yes
	NMR	Yes	Yes
Protein content	RP-HPLC Assay	Yes	Yes

Zinc Content		**AAS**	**Yes**	**Yes**
Size variants: Aggregates/HMWP		**SEC-HPLC**	**Yes**	**Yes**
		SEC-MALLS	**Yes**	**Yes**
		AUC	**Yes**	**Yes**
Product variants	**Des TRR**	**RP-HPLC**	**Yes**	**Yes**
	Des R and B3 Deamidation		**Yes**	**Yes**
	A15 deamidation		**Yes**	**Yes**
	Insulin glargine		**Yes**	**Yes**
	Glycerol ester		**Yes**	**Yes**
	Citric acid conjugate		**Yes**	**Yes**
	Acetylation		**Yes**	**Yes**
Isoelectric point (pI)			**Yes**	**Yes**
Mitogenic activity		**IR-A cell-based phosphorylation assay**	**Yes**	**Yes**
		Mitogenic assay using Saos2 cells	**Yes**	**Yes**
		IR short form (IR-A) binding kinetic assay	**Yes**	**Yes**
		IGF1R receptor binding kinetics	**Yes**	**Yes**
Metabolic activity		**IR-B cell-based phosphorylation assay**	**Yes**	**Yes**
		Glucose uptake assay using 3T3-L1 cells	**Yes**	**Yes**
		IR long form (IR-B) receptor binding kinetics	**Yes**	**Yes**
		IR autophosphorylation	**Yes**	**Yes**
		Adipogenesis assay using 3T3-L1 cells	**Yes**	**Not Performed***
		Inhibition of Stimulated Lipolysis assay using 3T3-L1 cells	**Yes**	**Not performed***

* The absence of data with MYL-1501D 100 Units/mL in a 10 mL vial from these assays is acceptable because data from an orthogonal method (i.e., glucose uptake) are available and support a demonstration of highly similar. Further, data from the Adipogenesis assay using 3T3-L1 cells and the Inhibition of Stimulated Lipolysis assay using 3T3-L1 cells are available for MYL-1501D 100 Units/mL in a 3 mL cartridge and also support a demonstration of highly similar.

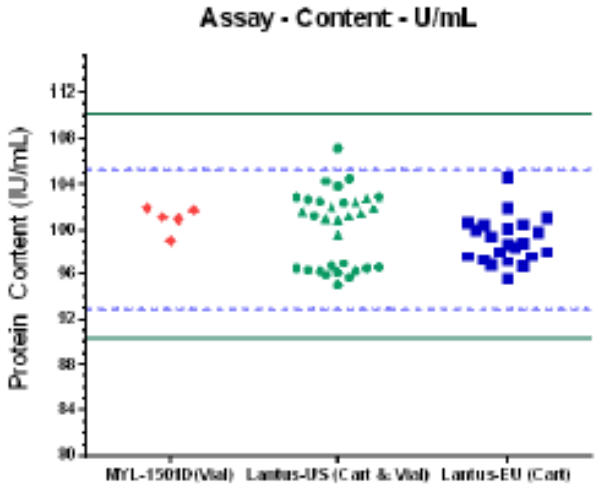
Scatter plots for protein content (Assay) of U.S.-licensed Lantus and MYL-1501D cartridge and vial lots are presented below. Solid green lines depict the quality range established for U.S.-licensed Lantus. Dotted blue lines and blue squares depict data from E.U.-approved Lantus (refer to section C).

Comparison of MYL-1501D cartridge lots with U.S.-Lantus PFP lots



Orange: MYL-1501D cartridge lots from DS Process V
Red: MYL-1501D cartridge lots from DS Process VI
Green: U.S.-Lantus PFP lots

Comparison of MYL-1501D vial lots with U.S.-Lantus PFP + vial lots



Orange: MYL-1501D vial lots
Green: U.S.-Lantus cartridge + vial lots
U.S.-Lantus PFP lots are denoted by green circles and U.S.-Lantus vials by green triangles.

C. Analytical Studies to Support the use of a Non-U.S.-licensed Comparator Product

Not applicable. Data generated from studies using EU-approved Lantus were not used to support a demonstration of biosimilarity. Therefore, the analytical testing results from the EU-approved Lantus submitted in the BLA were not assessed, as there was no need to establish an adequate scientific bridge.

D. Assessment of Comparative Analytical Study Results

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

Zinc content

While the zinc levels of MYL-1501D vial lots were within the quality range of U.S.-licensed Lantus lots, two out of ten MYL 1501-D cartridge lots have levels of zinc that are marginally higher (31.8 ug/100U and 33.0 ug/100U) than the quality range of U.S.-licensed Lantus PFP lots

(27.3-31.2 ug/100U). Zinc is known to impact the stability, higher order structure and pharmacokinetic profile of insulin[1]. Comparative analytical assessment of secondary structure, higher order structure, functional and biological activity and stability profiles support a conclusion that MYL-1501D lots are highly similar to U.S.-licensed Lantus lots. Additionally, the levels of zinc are controlled (b) (4). Therefore, the observed differences in zinc content do not preclude a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus.

Des R and B3 deamidation

Des R is a clipped insulin glargine variant that lacks the B32 arginine, while B3 desamido insulin glargine results from deamidation at the B3 asparagine. While the Des R and B3 desamido levels in MYL-1501D cartridge lots were within the quality range of U.S.-licensed Lantus PFP lots, the Des R and B3 desamido levels of two out of five MYL-1501D vial lots (0.06% and 0.07%) are marginally lower than the quality range of U.S.-licensed Lantus (0.08% - 0.55%). No impact of this difference is seen on the biological activity of MYL-1501D in comparison to U.S.-licensed Lantus. Due to the low levels of the DesR and B3 deasmido variants in both MYL-1501D and U.S.-licensed Lantus, the marginal observed difference in levels, and comparable biological activity of MYL-1501D and U.S.-licensed Lantus, the observed difference in DesR and B3 deamidation levels does not preclude a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus.

E. Same strength

MYL-1501D has the same dosage form and route of administration as U.S.-licensed Lantus. Mylan is seeking approval of 100 Units/mL MYL-1501D in a 10 mL vial and 100 Units/mL in a 3 mL pre-filled pen. U.S.-licensed Lantus is available at 100 Units/mL in a 10 mL vial and in a 3 mL pre-filled pen[2]. Comparative concentration (Units/mL) was assessed as part of the comparative analytical assessment. The extractable volume and fill weight data were also assessed in the context of manufacturing control. Based on the comparative concentration data and manufacturing data, the 100 Units/mL MYL-1501D in 3mL pre-filled pen and 10 mL vial 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 U.S.-licensed Lantus. The strength of MYL-1501D vial and pre-filled pen is the same as that of U.S.-licensed Lantus.

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 OPQ primary technical reviews.

[1] Dunn, M.F. Zinc–Ligand Interactions Modulate Assembly and Stability of the Insulin Hexamer – A Review. *Biometals* **18,** 295–303 (2005). https://doi.org/10.1007/s10534-005-3685-y

[2] U.S. Prescribing Information, U.S.-licensed Lantus, Accessed 3/12/2021 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021081s073s074lbl.pdf

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

CQA (type)	Risk	Origin	Control Strategy	Other
Aggregates	Safety and Efficacy	Manufacturing process, Stability	(b) (4)	N/A
Glycosylated variants	Safety and Efficacy	Manufacturing process		N/A
Deamidated variants	Efficacy	Manufacturing process		N/A
Clipped variants	Efficacy	Manufacturing process		N/A
Content	Efficacy	Intrinsic to the molecule, Manufacturing process		N/A
Identity	Safety and Efficacy	Intrinsic to the molecule		N/A

			(b) (4)	

B. Drug Substance 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 OPQ primary technical reviews.

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

CQA (type)	Risk	Origin	Control Strategy	Other
Residual solvents- (b) (4)	Safety	Manufacturing process	(b) (4)	N/A
(b) (4) content	Safety	Manufacturing process		N/A
(b) (4)	Stability and Efficacy	Added during manufacturing process		N/A
Host cell protein	Safety	Fermentation		N/A
Host cell DNA	Safety	Fermentation		N/A
(b) (4)	Safety	Added during manufacturing process		N/A
(b) (4)	Efficacy	(b) (4)		N/A

Assay (content)	Efficacy	Manufacturing process	(b) (4)	N/A
High molecular weight proteins	Safety and Efficacy	Manufacturing process, Stability		N/A
Related Compounds	Safety and Efficacy	Manufacturing process, Stability		N/A
Bacterial endotoxin	Safety and Purity	Raw material and manufacturing process		N/A
Total aerobic count (bioburden)	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw material and manufacturing process		N/A

- Description: MYL-1501D (insulin glargine-yfgn) is a long-acting analog of human insulin with 53 amino acids in 2 chains. The A chain is composed of 21 amino acids and the B chain is composed of 32 amino acids. The A and B chains are connected by 2 disulfide linkages. In addition, the A chain has a single intra-chain disulfide linkage. The primary sequence of insulin glargine-yfgn differs from that of human insulin by 3 amino acids: asparagine at position A21 instead of glycine and 2 arginines added to the C terminus of the B chain.

- Mechanism of Action (MoA): MYL-1501D (insulin glargine-yfgn) is a long-acting analog of human insulin. The primary activity of insulin glargine-yfgn is regulation of glucose metabolism. Insulin glargine-yfgn lowers blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin glargine-yfgn inhibits lipolysis in adipocytes, inhibits proteolysis and enhances protein synthesis.

- Potency Assay: Potency of MYL-1501D (insulin glargine-yfgn) DS is determined by RP-HPLC where the area of the main peak is used to calculate the content as % w/w. Potency is reported in Units/mg (b) (4)

- Reference Materials: Mylan uses a 'working standard' (WS) (b) (4) Upon

(b) (4)

A protocol is provided for the qualification of a WS. The protocol contains adequate testing and acceptance criteria. The Applicant has committed to establish a two-tier reference standard system.

- Critical starting materials or intermediates: (b) (4) A two-tiered cell banking system comprising of the Master Cell Bank (MCB) and a Working Cell Bank (WCB), with appropriate characterization, stability testing program, and storage conditions, has been implemented to ensure consistent manufacture of the product.

- Manufacturing process summary: (b) (4) In-process controls are implemented throughout the manufacturing process to ensure consistent quality at each stage.

  From a microbiological perspective, overall, the process is under adequate microbial control. (b) (4) . Adequate controls are in place to maintain microbiological product quality during maximum hold periods and throughout the manufacturing process.

- Container closure: (b) (4)

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

C. Drug Product 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	Other
Content (assay)	Efficacy	Intrinsic to the molecule, manufacturing process	(b) (4)	N/A
Related compounds	Safety and Efficacy	Manufacturing process, Stability		N/A
High molecular weight proteins	Safety and Efficacy	Manufacturing process, Stability		N/A
m-cresol content	Safety, stability	Formulation		N/A
pH	Stability	Formulation		N/A
Osmolality	Safety, Stability	Formulation		N/A
Zinc content	Efficacy	Formulation		N/A
Sterility	Safety, Purity and Efficacy	Manufacturing process, container closure integrity failure		N/A

(b) (4)

Appearance	Stability	Formulation		N/A
Endotoxin	Safety, Purity	Raw materials, manufacturing process		N/A
Container Closure Integrity	Safety, Stability	Breach during manufacture or storage		N/A
Particulate matter	Safety and Efficacy	Formulation, filling, stability		N/A
Dose Accuracy (pen)	Efficacy	Pre-filled pen		N/A
Polysorbate (vial)	Safety, Efficacy and Stability	Formulation		N/A

- Potency and Strength: Potency of the DP is determined using a RP-HPLC assay. The strength of the DP is 100 Units/mL in a 3 mL pre-filled pen and in a 10 mL vial.

- Summary of Product Design: MYL-1501D is supplied as a 10 mL vial and a 3 mL pre-filled pen. The primary container closure of the pre-filled pen is a cartridge.

- List of Excipients:
  Vial: m-cresol (2.7 mg/mL), glycerol (b) (4) (20 mg/mL), zinc (30 ug/mL), polysorbate-20 (20 ug/mL), hydrochloric acid, sodium hydroxide, water for injection.
  Pre-filled pen: m-cresol (2.7 mg/mL), glycerol (b) (4) (20 mg/mL), zinc (30 ug/mL), hydrochloric acid, sodium hydroxide, water for injection.

- 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: (b) (4) The components of the pre-filled pen do not come into contact with the drug product.

- Dating period and storage conditions: The DP shelf life is 24 months stored at 5°C±3°C. Unopened vial or pre-filled syringe DP may be stored for up to 28 days at room temperature (up to 30°C). In-use (opened) vial may be stored up to 28 days refrigerated (2-8°C) or at room temperature (up to 30°C). In-use (opened) pre-filled pen may be stored for up to 28 days at room temperature (up to 30°C, not to be refrigerated).

- List of co-package components, if applicable: none

D. Biopharmaceutics Considerations: none

E. Novel Approaches/Precedents: If approved, MYL-1501D will be the first interchangeable biosimilar to U.S.-licensed Lantus.

F. Any Special Product Quality Labeling Recommendations: none

G. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug substance manufacturing, quality control testing [chemical/physical, microbiological (non-sterility)], release, primary packaging, secondary packaging, storage and/or distribution of drug substance and storage of working cell bank	Biocon Sdn. Bhd. (930330-U), No.1, Jalan Bioteknologi 1, Kawasan Perindustrian SiLC, 79200 Iskandar Puteri, Johor, Malaysia.	DUNS: 865785591 FEI **:** 3011248248	Acceptable. Inspection waived. See waiver memo for more information	N/A	Approve
Characterization of the master cell bank and working cell bank and stability testing of the master cell bank (quality control testing – biological)	(b) (4)		No Evaluation Required based on responsibilities	N/A	No Evaluation Required
Master cell bank and working cell bank preparation and Storage	Biocon Biologics India Limited, 20th K. M. Hosur Road,	DUNS: 675486243 FEI:	No Evaluation Required based on responsibilities	N/A	No Evaluation Required

	Electronics City, Bengaluru-560 100, India	3015283245			
Rabbit bioidentity testing of drug substance	(b) (4)		Compliance History and Status Reviewed	N/A	Approve
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacturing, filling, primary packaging, quality control testing [Chemical/Physical, Microbiological (sterility and nonsterility) testing] of the 3 mL cartridges and pre-filled pen assembly (secondary packaging), quality control testing [Chemical/Physical] of the pre-filled pens and secondary packaging in carton box.	Biocon Sdn. Bhd. (930330-U), No.1, Jalan Bioteknologi 1, Kawasan Perindustrian SiLC, 79200 Iskandar Puteri, Johor, Malaysia.	DUNS: 865785591 FEI: 3011248248	Acceptable. Inspection waived. See waiver memo for more information	N/A	Approve

H. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Biocon Sdn. Bhd. (FEI 3011248248), proposed for DS and DP manufacture. All proposed manufacturing and testing facilities are acceptable based on

their current CGMP compliance status and recent relevant inspectional coverage. OBP and OPMA concurred on the issued inspection waiver of this facility, Biocon Sdn. Bhd. (FEI 3011248248).

I. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
1. Annual stability protocol
2. Comparability protocol for establishment of new Working Cell Bank
3. Protocol for qualification of new working standard

ii. Outstanding assessment issues/residual risk: none

iii. Future inspection points to consider: none

b. Drug Product

i. Protocols approved:
1. Annual stability protocol

ii. Outstanding assessment issues/residual risk: Drug Product microbiology assessment is ongoing at the time of finalizing this memorandum. OPQ recommendation on approvability of STN 761201 is pending final microbiology recommendation. Final OPQ recommendation will be provided in a future addendum to this OPQ Executive summary memorandum upon completion of the OPMA microbiology assessment.

iii. Future inspection points to consider: none

Anjali Shukla

Digitally signed by Anjali Shukla
Date: 3/29/2021 03:41:57PM
GUID: 57f29f4500712615c8f3d6ddc11716a9

Patrick Lynch

Digitally signed by Patrick Lynch
Date: 3/29/2021 04:05:00PM
GUID: 54bfb193000693c35f4278034f85d77a

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

/s/

ANIKA A LALMANSINGH
07/02/2021 11:22:52 AM

ANJALI A SHUKLA
07/02/2021 11:25:00 AM

If approved, Semglee (insulin glargine-yfgn; MYL-1501D) will be an interchangeable biosimilar with U.S.-licensed Lantus.[1]

Recommendation: **Approval**

BLA Number: 761201
Office of Pharmaceutical Quality
Application Team Lead Assessment Number: 3
Assessment Date: June 23, 2021

Addendum: The OPQ Executive Summary memorandum uploaded to Panorama on March 29, 2021 and the Addendum uploaded on April 15, 2021 still apply and are valid. This addendum is to provide an assessment of the revised comparative analytical assessment reports submitted by the Applicant on April 23, 2021.

Drug Name/Dosage Form	Semglee (insulin glargine-yfgn; MYL-1501D) /injection
Strength/Potency	100 Units/mL in a 3 mL pre-filled pen and in a 10 mL vial
Route of Administration	subcutaneous
Rx/OTC dispensed	Rx
Indication	To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Applicant/Sponsor	Mylan Pharmaceuticals Inc
US agent, if applicable	N/A

Product Overview:

SEMGLEE (insulin glargine-yfgn) is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. Semglee is homologous with human insulin with the exception of a substitution of the amino acid glycine by asparagine at position A21, and two arginine residues added to the C-terminus of the B-chain. Semglee is produced by recombinant DNA technology utilizing *Pichia pastoris*. Semglee is supplied as a pre-filled pen and a vial for subcutaneous injection. Semglee is a proposed interchangeable biosimilar to U.S.-licensed Lantus.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Qiong Fu	DBRRII/OBP/OPQ
Drug Product		
Immunogenicity		
Labeling	Vicky Borders-Hemphill	DBRRII/OBP/OPQ
Facility	Michael Shanks, Virginia Carroll	DBM/OPMA/OPQ
Microbiology DS	Michael Shanks	DBM/OPMA/OPQ
Microbiology DP	Virginia Carroll	DBM/OPMA/OPQ
Facility secondary Assessor	Candace Gomez-Broughton	DBM/OPMA/OPQ
Microbiology Branch Chief	Candace Gomez-Broughton	DBM/OPMA/OPQ
Regulatory Business Process Manager	Anika Lalmansingh	OPRO/OPQ
Application Team Lead	Anjali Shukla	DBRRII/OBP/OPQ

[1]Header has been corrected for clarity.

Submissions Assessed:

Additional Submission Assessed	Document Date
761201/0027	4/23/2021
761201/0029 (responses to OBP IR*)	5/18/2021

*IR: Information Request sent to the Applicant

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: **Approval**

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761201 for SEMGLEE manufactured by Mylan Pharmaceuticals, Inc. The data submitted in this application are adequate to support the conclusion that:

- The manufacture of Semglee is well-controlled and leads to a product that is pure and potent.
- Semglee is highly similar to U.S.-licensed Lantus, 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.

On April 23, 2021 (SDN 0027), the Applicant submitted revised comparative analytical assessment reports for IR-B Phosphorylation assay, IR-Phosphorylation Assay and Rabbit Bioassay. The amended reports were submitted to report corrected data after errors were discovered in the analyses performed originally. At the Late Cycle Meeting with the Applicant held on April 29, 2021, Mylan confirmed that there was no change in the raw data. The differences between the updated values in the revised reports and those previously submitted to the BLA are minor and do not impact any of the comparative analytical assessment conclusions for any attribute. Refer to the Applicant's summary chart below for details. For additional details, see the Addendum to the OBP technical review. The updated analyses continue to support that Semglee is highly similar to U.S.-licensed Lantus, notwithstanding minor differences in clinically inactive components. Therefore, the Office of Pharmaceutical Quality, CDER recommends approval of STN 761201 for SEMGLEE manufactured by Mylan Pharmaceuticals, Inc.

Table 1: Detailed Summary of Changes to Module 3 Analytical Similarity for Cartridge and Vial

Module 3	Report Name	Report Sub-section No.	Affected Tables/Figures and Page no.	Revised Data Specifics	Impact of Change
3.2.R.1 Analytical Similarity Assessment (Cartridges)	CDL/TR/LR.19.0091/20/001 AS Report (Cartridges)	Section 3.2.R.1 - CDL/TR/LR.19.0091/20/001- Subsection 4.4.2.1.2 **IRB assay**	Section 3.2.R.1 - CDL/TR/LR.19.0091/20/001 Table 16 to Table 19; Section 3.2.R.1 - CDL/TR/LR.19.0091/20/001 Figure 10 to Figure 14	Change in 2nd decimal observed for all values. Relative potency of all samples is determined using PLA (Parallel line analysis). As per the current STP, Best Range is used in PLA for calculation of relative potency however, analysts chose the Maximum Range. The data has been reanalysed using Best Range as per the STP and revised values have been presented. The difference in potency values analysed by Best Range vs. Maximum Range was only in second decimals and these minor differences in the Potency values did NOT change the conclusion.	No impact observed on previously reported conclusion.
		Section 3.2.R.1 - CDL/TR/LR.19.0091/20/001 – Subsection 4.4.2.1.4 **HepG2 assay**	Section 3.2.R.1 - CDL/TR/LR.19.0091/20/001- Table 25; Section 3.2.R.1- CDL/TR/LR.19.0091/20/001 Figure 22	Change in one MYL-1501D cartridge batch value (Batch BS15005866). Average of 2 assays (n=2) reported instead of average of 3 (n=3) assays values as per current STP.	
		Section 3.2.R.1 - CDL/TR/LR.19.0091/20/001 – Subsection 4.4.2.2.5 **Rabbit Bioassay**	Section 3.2.R.1 - CDL/TR/LR.19.0091/20/001- Table 47	Change in all estimated potency values – total 21 batches. Potency values of insulin and glargine pharmacopeial reference standards used were swapped inadvertently during calculation of estimated potency values for MYL-1501D and reference product batches. Values were re-estimated using the potency values listed in the CoA of the reference standards.	
3.2.R.1 Analytical Similarity Assessment (Vial)	CDL/TR/LR.19.0091/20/002 AS Report (Vial)	Section 3.2.R.1 - CDL/TR/LR.19.0091/20/002 – Subsection 4.3.4.1.2- **IRB Assay**	Section 3.2.R.1 - CDL/TR/LR.19.0091/20/002 Table 12 and Table 13 Section 3.2.R.1- CDL/TR/LR.19.0091/20/002 Figure 8 and Figure 9	Change in 2nd decimal observed for all values. Relative potency of all samples is determined using PLA (Parallel line analysis). However, previously reported values utilized maximum range of linear point allocation for fit rather than best range of linear point allocation. The best range of linear point allocation has now been applied to all samples and revised values have been presented.	No impact observed on previously reported conclusion.
		Section 3.2.R.1 - CDL/TR/LR.19.0091/20/002 – Subsection 4.5.1.3.2 **IRB Assay**	Section 3.2.R.1- CDL/TR/LR.19.0091/20/002- Table 73 to Table 76 Section 3.2.R.1 - CDL/TR/LR.19.0091/20/002 Figure 66 to Figure 70		

Source: BLA 761201 SDN 0027 Section 1.11.4 Table 1.

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

None

Anjali Shukla

Digitally signed by Anjali Shukla
Date: 6/23/2021 04:51:07PM
GUID: 57f29f4500712615c8f3d6ddc11716a9

Patrick Lynch

Digitally signed by Patrick Lynch
Date: 6/24/2021 02:44:50PM
GUID: 54bfb193000693c35f4278034f85d77a

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

BLA STN 761201

Addendum

Semglee [Insulin glargine-yfgn]
[MYL-1501D, proposed interchangeable biosimilar to U.S.-licensed Lantus]

Mylan Pharmaceuticals Inc.

Qiong Fu, PhD, Product Quality Reviewer
Anjali Shukla, PhD, Application Technical Lead

Division of Biotechnology Research and Review II (DBRRII)
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

OBP CMC Addendum Review Data Sheet

1. BLA#: 761201

2. Review Date: 06/23/2021

3. Communications with Applicant:

Communication/Document:	Date:
Late-cycle meeting with Applicant	04/29/2021

4. Submission Reviewed in this Addendum:

Submission:	Date Received:	Review Completed (yes or no)
761201/0027	04/23/2021	Yes
761201/0029 (responses to OBP IR*)	5/18/2021	Yes

*IR: Information Request sent to the Applicant

5. Administrative:

Name and Title	Signature and Date
Anjali Shukla, Ph.D. Application Technical Lead, DBRRII/OBP/OPQ/CDER	See electronic signature and date
Qiong Fu, Ph.D. Primary Assessor, DBRRII/OBP/OPQ/CDER	See electronic signature and date

Summary of Addendum

The product quality review memorandum for BLA-761201 completed and uploaded into Panorama on March 22, 2021 still applies and is valid. This addendum is to provide an assessment of the revised comparative analytical assessment reports submitted by the Applicant on April 23, 2021.

On April 23, 2021, the Applicant submitted updated Comparative Analytical Assessment (CAA) Reports in eCTD Section 3.2.R to report corrected assay results (CDL/TR/LR.19.0091/20/001 version 03 and CDL/TR/LR.19.0091/20/002 version 03, referred to as CAA report 1 and CAA report 2 thereafter, respectively).

The revised reports include updated analysis results for IR-B Phosphorylation assay, IR Phosphorylation assay, and Rabbit Bioassay. The amended reports were submitted to report corrected data after errors were discovered in the analyses performed originally. At the Late Cycle Meeting held with the Applicant on April 29, 2021, Mylan confirmed that there was no change in the raw data used and that the changed values in the revised reports compared to those previously submitted to the BLA were only due to the re-analyses performed.

The differences between the updated values in the revised reports and those previously submitted to the BLA are minor and do not impact the comparative analytical assessment conclusions for any attribute. The updated comparative analytical assessment reports continue to support a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus, notwithstanding minor differences in clinically inactive components. From a product quality perspective, BLA-761201 is recommended for approval.

Background

The product quality review memorandum for BLA-761201 was completed and uploaded into Panorama on March 22, 2021. It can be found at this link (BLA-761201 CMC Review Memo Final). However, on April 23, 2021, the Applicant submitted updated Analytical Similarity Assessment (CAA) Reports in eCTD Section 3.2.R to correct some reported values for 3 out of 30 test methods in two CAA reports. A summary of all updates being made as a result of this review is provided below:

1) In IR-B Phosphorylation assay in both CAA report 1 and 2, the relative potency values have been recalculated using Best Range in Parallel Line Analysis (PLA) software per the current effective standard test procedure (STP), while the previous STP permitted analysts to choose Maximum Range. The relevant reports have been updated, and the difference in potency values analyzed by Best Range vs. Maximum Range was only in second decimals.

2) In the IR-Phosphorylation assay in CAA report 1, for one lot out of 54 lots, only 2 runs of that lot were averaged and reported as the average, although 3 independent runs were performed, while an average of 3 was reported as per the procedure for all others 53 lots. This report has been updated and corrected value from N=3 for that lot has presented.

3) In the Rabbit Bioassay in CAA report 1, the study was done using two USP reference standards (USP Insulin Reference Standard and USP Insulin Glargine Reference Standard). While calculating the relative potencies, the potency values of the two reference standards were misapplied. The updated data reflects calculations with the appropriate potency values.

Assessor's Comment: *During the late-cycle meeting on 04/29/2021, the Applicant confirmed that there was no change to the raw data. The purpose of this addendum is to provide assessment of the updated CAA reports submitted on April 23, 2021. No additional changes were identified in the CMC information received on April 23, 2021.*

Changes and Assessment

Assessor's Note: *As previously described in the BLA-761201 CMC Review Memo Final uploaded March 22, 2021, data generated from studies using E.U.-approved Lantus were not used in this application to support a demonstration of biosimilarity. Therefore, the analytical testing results from the E.U.-approved Lantus submitted in the BLA were not assessed, as there was no need to establish an adequate scientific bridge. Additionally, while the Applicant evaluated results of some assays using both equivalence testing and quality ranges on the same sets of data, the OBP Assessor's evaluation was based on the quality ranges approach for these attributes.*

1) IR-B Phosphorylation assay in both CAA report 1 and 2

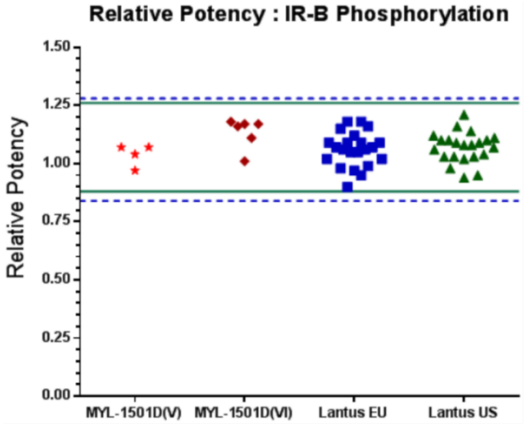
The Applicant stated that the relative potency values of IR-B phosphorylation in CHO-K1 cells in both CAA report 1 and 2 are recalculated as per the current Standard Test Protocol (STP) using the Best Range, while Maximum Range was selected for calculating relative potency before as per the previous STP. Data has been reanalyzed using the Best Range and updated in both CAA reports.

CDL/TR/LR.19.0091/20/001 (CAA report 1 for similarity comparison between MYL-1501D cartridges and U.S.-Lantus cartridges): changes in subsection 4.4.2.1.2 "Insulin Receptor-B Phosphorylation Assay" are summarized in the following table (Assessor generated):

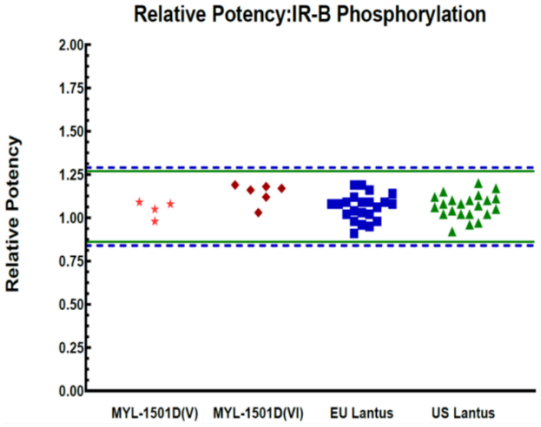
Updates in subsection 4.4.2.1.2 "Insulin Receptor-B Phosphorylation Assay" of CAA report 1		**Previous**	**Updated**	***Assessor's Comment***
Table 16: Relative Potency (Insulin Receptor-B Phosphorylation) for **US-approved Lantus**	Mean of Lantus Lots (Mean R)	1.07	1.07	*The changes reported are in the 2nd decimal values for most results, resulting in slight change in the QR (0.86~1.27). Refer to Assessor's comment below.*
	Standard Deviation of Lantus Lots (σR)	0.06	0.07	
	Minimum	0.94	0.92	
	Maximum	1.21	1.20	
	Quality Range (mean±3SD)	0.88~1.26	0.86~1.27	
Table 18: Relative Potency (Insulin Receptor-B Phosphorylation) for **MYL-1501D**	Mean of MYL-1501D Lots	1.10	1.11	*Change in 2nd decimal observed for all values, but still within the QR (0.86~1.27). Refer to Assessor's comment below.*
	Standard Deviation of MYL-1501D Lots	0.07	0.07	
	Minimum	0.97	0.98	
	Maximum	1.18	1.19	
Table 19: Equivalence testing results for IR-B Phosphorylation Assay		Updated per the current relative potency values.		*See Assessor's note above. OBP assessment is based on the quality ranges approach.*
Figure 10: Representative PLA graph for Insulin Receptor-B Phosphorylation Assay for US-approved Lantus		The updated version is per the current relative potency values.		*The relative potency values change in 2nd decimal; the new PLA graphs support similar dose response as that presented in the previous version of the report. This is acceptable.*
Figure 12: Representative PLA graph for Insulin Receptor-B Phosphorylation Assay for MYL-1501D				
Figure 13: Scatter Plot Distribution for Relative potency (IR-B phosphorylation activity) of MYL-1501D, EU-approved Lantus and US-approved Lantus		See side-by-side comparison below.		*The relative IR-B phosphorylation potency for all MYL-1501D lots are 100% within the QR (0.86~1.27).*
Figure 14: Graphical plots for Equivalence test for IR-B phosphorylation assay		Updated per the current relative potency values.		*See Assessor's note above. OBP assessment is based on the quality ranges approach.*

Figure 13: Scatter Plot Distribution for Relative potency (IR-B phosphorylation activity) of MYL-1501D, EU-approved Lantus® and US-approved Lantus®

Previous version



Updated version



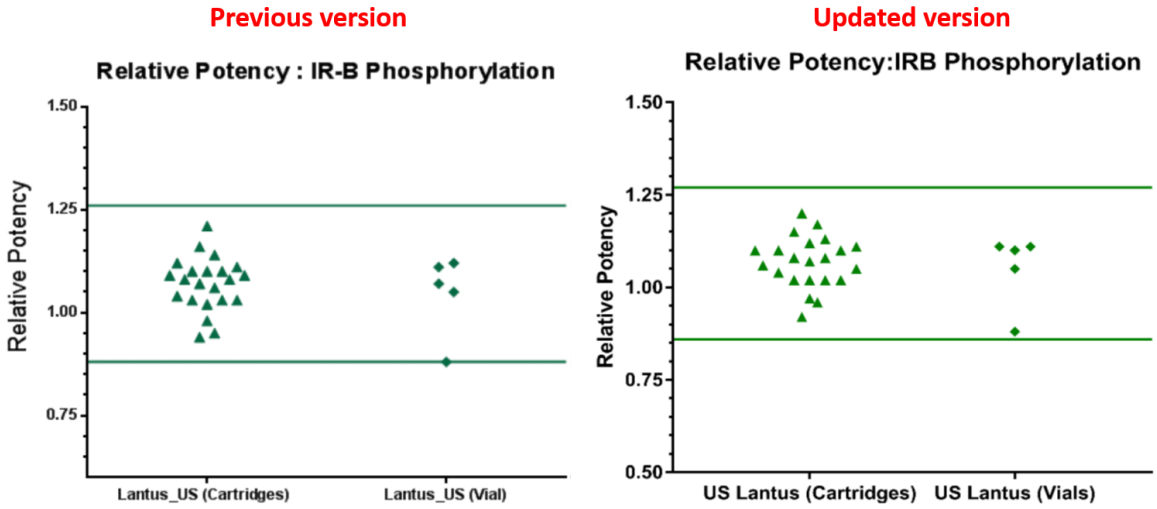
Assessor's Comment: *The revised potency values in Table 16 to Table 18 in CAA report 1 differ in second decimal values when compared to the previously reported values. Representative PLA graphs for insulin IR-B phosphorylation assay (Figure 10 to Figure 12, not shown here) have been updated per the current relative potency values. The revised graphs show similar dose response curves as that shown in the previous report. The updated relative IR-B phosphorylation potency for all MYL-1501D lots (Min-Max range: 0.98~1.19) are 100% within the updated QR of U.S.-Lantus cartridge lots (0.86~1.27), therefore still support the previous conclusion that the IR-B phosphorylation potency of MYL-1501D cartridge presentation is highly similar to that of the U.S.-licensed Lantus cartridge presentation.*

CDL/TR/LR.19.0091/20/002 (CAA report 2): changes in subsection 4.3.4.1.2 "Insulin Receptor-B Phosphorylation Assay" (for similarity comparison between U.S.-Lantus vials and cartridges) are summarized in the following table (Assessor generated):

Updates in subsection 4.3.4.1.2 "Insulin Receptor-B Phosphorylation Assay" of CAA report 2		**Previous**	**Updated**	***Assessor's Comment***
Table 12: Relative Potency (Insulin Receptor-B Phosphorylation) for **US-licensed Lantus (Cartridges)**	Mean of Lantus Lots (Mean R)	1.07	1.07	*Change in 2nd decimal observed for most values, resulting in slight change of the QR (0.86~1.27). Refer to Assessor's comment below.*
	Standard Deviation of Lantus Lots (σR)	0.06	0.07	
	Minimum	0.94	0.92	
	Maximum	1.21	1.20	
	Quality Range (mean±3SD)	0.88~1.26	0.86~1.27	
Table 13: Relative Potency (Insulin Receptor-B Phosphorylation) for **US-licensed Lantus (Vials)**	Mean of Lantus Lots (Mean R)	1.05	1.05	*Change in 2nd decimal observed for most values, but still within the cartridge QR (0.86~1.27). Refer to Assessor's comment below.*
	Standard Deviation of Lantus Lots (σR)	0.10	0.10	
	Minimum	0.88	0.88	
	Maximum	1.12	1.11	
Figure 8: Representative PLA graph for Insulin Receptor-B Phosphorylation Assay for US-approved Lantus (Cartridge)		The updated version is per the current relative potency values.		*The relative potency values only change in 2nd decimal; the new PLA graphs support similar dose response as that presented in the previous version of the report. This is acceptable.*
Figure 9: Representative PLA graph for Insulin Receptor-B Phosphorylation Assay for US-approved Lantus (Vial)				

Figure 10: Scatter Plot Distribution for Relative potency (IR-B phosphorylation activity) of US-approved Lantus (Cartridge & Vial)	See side-by-side comparison below.	*The relative IR-B phosphorylation potency for all US vial lots are 100% within the cartridge QR (0.86~1.27).*

Figure 10: Scatter Plot Distribution for Relative potency (IR-B phosphorylation activity) of US-approved Lantus® (Cartridge & Vial)



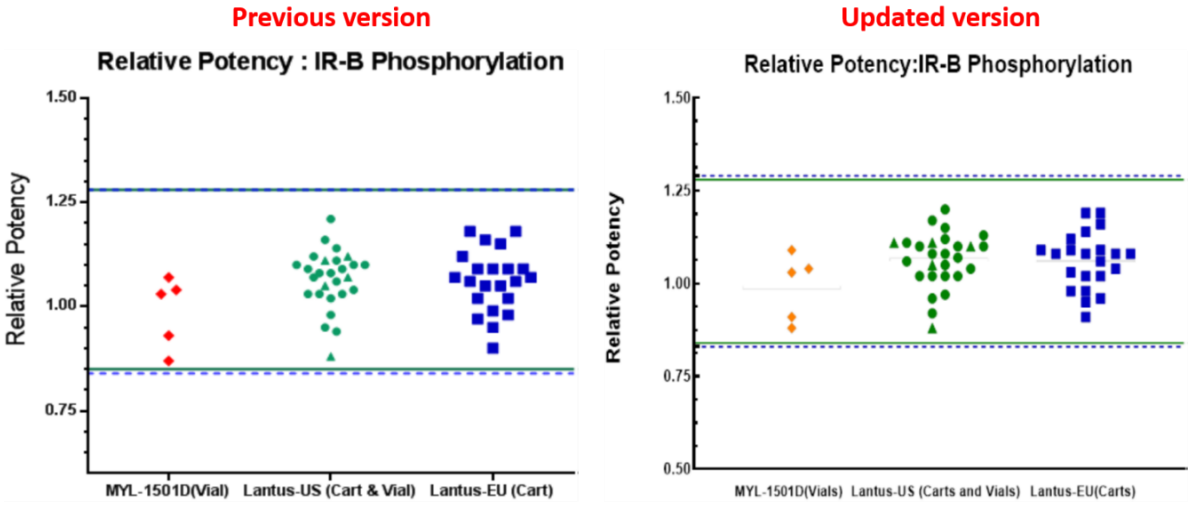
Assessor's Comment: *Of note, in the amendment submitted by the Sponsor on 04/23/2021, the two solid green lines in Figure 10 did not appear to represent the updated QR (0.86 and 1.27) as shown in Table 12. On 05/18/2021 in response to the Agency's IR, the Sponsor corrected this discrepancy and provided updated Figure 10 with the two solid green lines repositioned to 0.86 and 1.27 as shown above. Most of the updated potency values in Table 12 and Table 13 in CAA report 2 differ in second decimal when compared to the previously reported values. Representative PLA graphs for insulin IR-B phosphorylation assay (Figure 8 and Figure 9, not shown here) have been updated per the current relative potency values and they show similar dose response as that presented in the previous version. The updated relative IR-B phosphorylation potency for all U.S.-Lantus vial lots (Min-Max range: 0.88~1.11) are 100% within the updated QR of U.S.-Lantus cartridge lots (0.86~1.27), therefore support the previous conclusion that the IR-B phosphorylation potency is highly similar between U.S.-licensed Lantus vial presentation and cartridge presentation.*

CDL/TR/LR.19.0091/20/002 (CAA report 2): changes in subsection 4.5.1.3.2 "Insulin Receptor-B Phosphorylation Assay" (for similarity comparison between MYL-1501D vials and U.S.-Lantus vials and cartridges) are summarized in the following table (Assessor generated):

Updates in subsection 4.5.1.3.2 "Insulin Receptor-B Phosphorylation Assay" of CAA report 2		**Previous**	**Updated**	***Assessor's Comment***
Table 73: Relative Potency (Insulin Receptor-B Phosphorylation) for **US-approved Lantus (Cartridges & Vials)**	Mean of Lantus Lots (Mean R)	1.07	1.06	*Change in 2nd decimal observed for most values, resulting in slight change in the QR (0.84~1.28). Refer to Assessor's comment below.*
	Standard Deviation of Lantus Lots (σR)	0.07	0.07	
	Minimum	0.88	0.88	
	Maximum	1.21	1.20	
	Quality Range (mean±3SD)	0.85~1.28	0.84~1.28	
	Mean of MYL-1501D Lots	0.99	0.99	

Table 75: Relative Potency (Insulin Receptor-B Phosphorylation) for **MYL-1501D (Vials)**	Standard Deviation of MYL-1501D Lots	0.08	0.09	*The changes reported are in the 2nd decimal values for most results and are still within the QR (0.84~1.28). Refer to Assessor's comment below.*
	Minimum	0.87	0.88	
	Maximum	1.07	1.09	
Table 76: Equivalence testing results for IR-B Phosphorylation Assay		Updated per the current relative potency values.		*See Assessor's note above. OBP assessment is based on the quality ranges approach.*
Figure 66: Representative PLA graph for Insulin Receptor-B Phosphorylation Assay for US-approved Lantus (Vial)		The updated version is per the current relative potency values.		*The relative potency values only change in 2nd decimal; the new PLA graphs support similar dose response as that presented in the previous version of the report. This is acceptable.*
Figure 68: Representative PLA graph for Insulin Receptor-B Phosphorylation Assay for MYL-1501D (Vial)				
Figure 69: Scatter Plot Distribution for Relative potency (IR-B phosphorylation activity) of MYL-1501D, US-approved Lantus and EU-approved Lantus		See side-by-side comparison below.		*The relative IR-B phosphorylation potency for all MYL-1501D vial lots are 100% within the QR (0.84~1.28).*
Figure 70: Graphical plots for Equivalence test for IR-B phosphorylation assay		Updated per the current relative potency values.		*See Assessor's note above. OBP assessment is based on the quality ranges approach.*

Figure 69: Scatter Plot Distribution for Relative potency (IR-B phosphorylation activity) of MYL-1501D, US-approved Lantus® and EU-approved Lantus®



Assessor's Comment: *Most of the updated potency values in Table 73 to Table 75 in CAA report 1 differ in second decimal when compared to the previously reported values. Representative PLA graphs for insulin IR-B phosphorylation assay (Figure 66 to Figure 68, not shown here) have been updated per the current relative potency values and they support similar dose response as that presented in the previous version. The updated relative IR-B phosphorylation potency for all MYL-1501D vial lots (Min-Max range: 0.88~1.09) are 100% within the updated QR of U.S.-Lantus lots (0.84~1.28), therefore supports the previous conclusion that the IR-B phosphorylation potency is highly similar between MYL-1501D vial presentation and U.S.-licensed Lantus cartridge and vial presentation.*

2) IR-Phosphorylation assay in CAA report 1

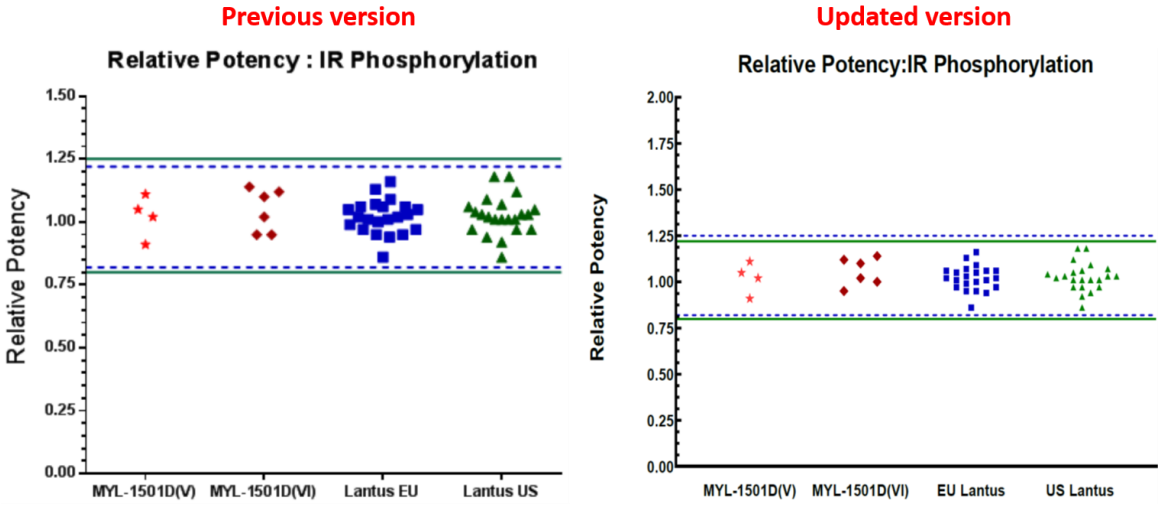
The average relative potency for insulin receptor phosphorylation in HepG2 cells for one MYL-1501D lot (BS15005866) was determined to be incorrectly reported. As per the test procedure, average of three

independent analysis is to be reported for each lot. In 53 out of 54 samples analyzed, mean of 3 was reported as per the procedure, however, for this lot (BS15005866), although 3 independent runs were performed, by error only average of 2 was reported. This has been corrected and new value from N=3 is now reported for this MYL-1501D lot BS15005866. There is no change to U.S.-Lantus results.

CDL/TR/LR.19.0091/20/001 (CAA report 1 for cartridges): change in subsection 4.4.2.1.4 "Insulin receptor phosphorylation assay using HepG2 cells" is summarized in the following table (Assessor generated):

Updates in subsection 4.4.2.1.4 "Insulin receptor phosphorylation assay using HepG2 cells" of CAA report 1		**Previous**	**Updated**	***Assessor's Comment***
Table 25: Relative potency (Insulin receptor phosphorylation) for **MYL-1501D**	Lot BS15005866 (DS Process VI)	0.95	1.00	*Change in 2nd decimal only for one MYL-1501D lot. Refer to Assessor's comment below.*
	Mean of MYL-1501D Lots	1.04	1.04	
	Standard Deviation of MYL-1501D Lots	0.08	0.08	
	Minimum	0.91	0.91	
	Maximum	1.14	1.14	
Figure 22: Scatter Plot Distribution for relative potency (IR phosphorylation) of MYL-1501D, EU-approved Lantus and US-approved Lantus		See side-by-side comparison below.		*The relative IR phosphorylation potency for all MYL-1501D lots are 100% within the QR (0.80~1.25).*

Figure 22: Scatter Plot Distribution for relative potency (IR phosphorylation) of MYL-1501D, EU-approved Lantus® and US-approved Lantus®



Assessor's Comment: *The only difference between the previous and current Table 25 is the relative potency value for MYL-1501D lot BS15005866, which was incorrectly calculated by averaging the results from 2 runs and now is corrected by averaging the results from all 3 runs. This was confirmed by the Assessor from the assay reports. However, this only changes the individual value for lot BS15005866 from 0.95 to 1.00 but does not change the mean, SD, or min/max range of MYL-1501D lots. In addition, there is no change to U.S.-Lantus results including the QR (0.80~1.25). The relative IR phosphorylation potency for MYL-1501D lots are 100% within the QR of U.S.-Lantus cartridges (0.80~1.25), therefore still supports the previous conclusion that the IR phosphorylation potency of MYL-1501D cartridge presentation is highly similar to that of the U.S.-licensed Lantus cartridge presentation.*

3) Rabbit Bioassay in CAA report 1

The relative pharmacological potency (blood glucose lowering effect) of MYL-1501D, and US-Lantus against the USP insulin glargine and/or USP human insulin was determined in the rabbit potency assay per USP <121>. In the amendment submitted on 04/23/2021, the Sponsor stated that the relative potency values for MYL-1501D, U.S.-Lantus in the previous version of Table 47 were miscalculated because the potency value of the two reference standards was misapplied (with the potency value of USP Insulin Glargine Standard used in the assays performed with the USP Insulin Reference Standard and vice versa). These potency values were recalculated using the correct USP standard potency value and updated in the new version of Table 47. Changes in potency values between the old and the new version of Table 47 are shown in the following table (Assessor generated, with the previous values crossed out). Rabbit bioassay is not presented in CAA report 2.

(b) (4)

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(b) (4)

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Overall, the recalculated in-vivo potency values of MYL-1501D, and US-Lantus, have comparable range of values as before, still supporting that the MYL-1501D and U.S.-Lantus lots are comparable and compliant with the USP <121> acceptance criterion of 'NLT 15 U/mg'. It was confirmed from the Rabbit Bioassay reports submitted that there was no change in raw data. As previously stated in the OBP CMC assessment memo uploaded on March 22, 2021, per current OBP recommendation, the rabbit bioassay is not recommended to be included in the comparative analytical assessment to support a demonstration of highly similar for insulin products. Therefore, the results of rabbit bioassay are not included in our assessment of highly similar between MYL-1501D and U.S.-Lantus. The similarity of potency is assessed by other assays including content, metabolic assays and mitogenic assays.

Updates in eCTD Sections

The details of the impacted eCTD Sections related to product quality are provided in Table 1 below.

eCTD Section	**File Name**	**Subsection No.**	**Changes or Affected Tables/Figures**	**Revised Data Specifies**	***Assessor's Comment***
1.11.4 Multiple Module Information Amendment	Multidisciplinary Amendment – Summary of Changes in Analytical Similarity	NA	NA	NA	*This file provides a summary of changes in CAA reports.*
2.3.R Regional Information	Regional Information	Subsection 2.3.R.1.1.2 Analytical Similarity Study for MYL-1501D in Cartridges	Table 2.3.R/3	In Table 2.3.R/3: Quality attributes and the corresponding tests and assessment, the assessment for Rabbit Bioassay has been changed from "Data Table" to "Quality ranges (±3SD)".	*The statistical assessment for Rabbit Bioassay should still be "Data Table", according to CAA report 1. This change does not impact the similarity assessment.*
3.2.R Regional Information	Analytical Similarity Assessment	NA	Table 3.2.R/5; Links to CAA report 1 and 2 has been updated.	In Table 3.2.R/5: Quality attributes and the corresponding tests and assessment, the assessment for Rabbit Bioassay has been changed from "Data Table" to "Quality ranges (±3SD)".	*The statistical assessment for Rabbit Bioassay should still be "Data Table", according to CAA report 1. This change does not impact the similarity assessment.*

	CDL/TR/LR.19. 0091/20/001 CAA Report 1 (Cartridges) (version 03 to replace version 01)	Subsection 4.4.2.1.2 IR-B phosphorylation assay	Table 16 to Table 19; Figure 10 to Figure 14	Change in 2nd decimal observed for most values. Relative potency of all samples is determined using PLA (Parallel line analysis). As per the current STP, Best Range is used in PLA for calculation of relative potency however, analysts chose the Maximum Range. The data has been re-analyzed using Best Range as per the STP and revised values are presented. Representative PLA graphs and scatter plot are updated per relative potency values.	*Refer to assessment in the above section "Changes and Assessment".*
		Subsection 4.4.2.1.4 IR phosphorylation assay	Table 25; Figure 22	Change in one MYL-1501D cartridge batch value (Batch BS15005866). Average of 2 assays (n=2) reported instead of average of 3 (n=3) assays values as per current STP.	*Refer to assessment in the above section "Changes and Assessment".*
		Subsection 4.4.2.2.5 Rabbit Bioassay	Table 47	Change in all estimated potency values for all 21 batches. Potency values of insulin and glargine pharmacopeial reference standards used were misapplied during calculation of estimated potency values for MYL-1501D and reference product batches. Values were re-estimated using the potency values listed in the CoA of the reference standards.	*Refer to assessment in the above section "Changes and Assessment".*
	CDL/TR/LR.19. 0091/20/002 CAA Report 2 (Vials) (version 03 to replace version 01)	Subsection 4.3.4.1.2- IR-B phosphorylation Assay	Table 12 and Table 13, Figure 8 to Figure 10	Change in 2nd decimal observed for most values. Relative potency of all samples is determined using PLA (Parallel line analysis). However, previously reported values utilized maximum range of linear point allocation for fit rather than best range of linear point allocation. The best range of linear point allocation has now been applied to all samples and revised values are presented. Representative PLA graphs and scatter plot are updated per relative potency values.	*Refer to assessment in the above section "Changes and Assessment".*
		Subsection 4.5.1.3.2 IR-B phosphorylation Assay	Table 73 to Table 76, Figure 66 to Figure 70		

Assessor's Comment: *All updates as showing above have been verified to be acceptable. In addition to the above changes, the revised reports included edits in the titles and related text for X-ray Crystallography Figures 85 (in CAAA report 1), Figure 133 and 134 (in CAA report 2) for increased clarity; and Figure 56 is replaced with a new Figure 56 (in CAA report 2) which compares the US vial batch 5F193A, US cartridge batch 4F1179A, and published glargine structure 4IYD. These changes are in accordance with response to OBP IR#2 received on 02/16/2021, and have been previously assessed to be acceptable in BLA-761201 CMC Review Memo Final.*

Overall, the updated comparative analytical similarity information submitted by Applicant on 04/23/2021 still supports a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus, notwithstanding minor differences in clinically inactive components.

Qiong Fu

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Anjali Shukla

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Date: 6/23/2021 04:37:43PM
GUID: 57f29f4500712615c8f3d6ddc11716a9

First Biosimilar: If approved, Semglee (insulin glargine-yfgn) will be the first interchangeable biosimilar to U.S.-licensed Lantus.

Recommendation: **Approval**

BLA Number: 761201
Office of Pharmaceutical Quality
Application Team Lead Assessment Number: 2
Assessment Date: April 15, 2021

Addendum: The Executive Summary memorandum uploaded to Panorama on March 29, 2021 still applies and is valid. This addendum is to update the OPQ recommendation from Pending to Approval following finalization of the microbiology assessment.

Drug Name/Dosage Form	Semglee (insulin glargine-yfgn) /injection
Strength/Potency	100 Units/mL in a 3 mL pre-filled pen and in a 10 mL vial
Route of Administration	subcutaneous
Rx/OTC dispensed	Rx
Indication	To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Applicant/Sponsor	Mylan Pharmaceuticals Inc
US agent, if applicable	N/A

Product Overview:

SEMGLEE (insulin glargine-yfgn) is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. Semglee is homologous with human insulin with the exception of a substitution of the amino acid glycine by asparagine at position A21, and two arginine residues added to the C-terminus of the B-chain. Semglee is produced by recombinant DNA technology utilizing *Pichia pastoris*. Semglee is supplied as a pre-filled pen and a vial for subcutaneous injection. Semglee is a proposed interchangeable biosimilar to U.S.-licensed Lantus.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Qiong Fu	DBRRII/OBP/OPQ
Drug Product		
Immunogenicity		
Labeling	Vicky Borders-Hemphill	DBRRII/OBP/OPQ
Facility	Michael Shanks, Virginia Carroll	DBM/OPMA/OPQ
Microbiology DS	Michael Shanks	DBM/OPMA/OPQ
Microbiology DP	Virginia Carroll	DBM/OPMA/OPQ
Facility secondary Assessor	Candace Gomez-Broughton	DBM/OPMA/OPQ
Microbiology Branch Chief	Candace Gomez-Broughton	DBM/OPMA/OPQ
Regulatory Business Process Manager	Anika Lalmansingh	OPRO/OPQ
Application Team Lead	Anjali Shukla	DBRRII/OBP/OPQ

Submissions Assessed:

Additional Submission Assessed	Document Date
761201/0026 (responses to OPMA IR)	4/8/2021

*IR: Information Request sent to the Applicant

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: **Approval**

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761201 for SEMGLEE manufactured by Mylan Pharmaceuticals, Inc. The data submitted in this application are adequate to support the conclusion that:

- The manufacture of Semglee is well-controlled and leads to a product that is pure and potent.
- Semglee is highly similar to U.S.-licensed Lantus, 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.

The OPQ Executive Summary memorandum uploaded to Panorama on March 29, 2021 noted that the Office of Pharmaceutical Quality, CDER recommendation on approvability of STN 761201 was pending final microbiology recommendation. The pending drug product microbiology technical assessment was finalized on April 15, 2021, and recommends approval. Therefore, this addendum is submitted to provide the final OPQ recommendation of approval of BLA 761201 for SEMGLEE manufactured by Mylan Pharmaceuticals, Inc.

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

None

Anjali Shukla

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Date: 4/15/2021 10:25:14PM
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Patrick Lynch

Digitally signed by Patrick Lynch
Date: 4/16/2021 08:28:16AM
GUID: 54bfb193000693c35f4278034f85d77a

First Biosimilar: If approved, Semglee (insulin glargine-yfgn) will be the first interchangeable biosimilar to U.S.-licensed Lantus.

Recommendation: **Approval**

BLA Number: 761201
Office of Pharmaceutical Quality
Application Team Lead Assessment Number: 2
Assessment Date: April 15, 2021

Addendum: The Executive Summary memorandum uploaded to Panorama on March 29, 2021 still applies and is valid. This addendum is to update the OPQ recommendation from Pending to Approval following finalization of the microbiology assessment.

Drug Name/Dosage Form	Semglee (insulin glargine-yfgn) /injection
Strength/Potency	100 Units/mL in a 3 mL pre-filled pen and in a 10 mL vial
Route of Administration	subcutaneous
Rx/OTC dispensed	Rx
Indication	To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Applicant/Sponsor	Mylan Pharmaceuticals Inc
US agent, if applicable	N/A

Product Overview:

SEMGLEE (insulin glargine-yfgn) is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. Semglee is homologous with human insulin with the exception of a substitution of the amino acid glycine by asparagine at position A21, and two arginine residues added to the C-terminus of the B-chain. Semglee is produced by recombinant DNA technology utilizing *Pichia pastoris*. Semglee is supplied as a pre-filled pen and a vial for subcutaneous injection. Semglee is a proposed interchangeable biosimilar to U.S.-licensed Lantus.

Quality Assessment Team:

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Drug Product		
Immunogenicity		
Labeling	Vicky Borders-Hemphill	DBRRII/OBP/OPQ
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Microbiology DS	Michael Shanks	DBM/OPMA/OPQ
Microbiology DP	Virginia Carroll	DBM/OPMA/OPQ
Facility secondary Assessor	Candace Gomez-Broughton	DBM/OPMA/OPQ
Microbiology Branch Chief	Candace Gomez-Broughton	DBM/OPMA/OPQ
Regulatory Business Process Manager	Anika Lalmansingh	OPRO/OPQ
Application Team Lead	Anjali Shukla	DBRRII/OBP/OPQ

Submissions Assessed:

Additional Submission Assessed	Document Date
761201/0026 (responses to OPMA IR)	4/8/2021

*IR: Information Request sent to the Applicant

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: **Approval**

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761201 for SEMGLEE manufactured by Mylan Pharmaceuticals, Inc. The data submitted in this application are adequate to support the conclusion that:

- The manufacture of Semglee is well-controlled and leads to a product that is pure and potent.
- Semglee is highly similar to U.S.-licensed Lantus, 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.

The OPQ Executive Summary memorandum uploaded to Panorama on March 29, 2021 noted that the Office of Pharmaceutical Quality, CDER recommendation on approvability of STN 761201 was pending final microbiology recommendation. The pending drug product microbiology technical assessment was finalized on April 15, 2021, and recommends approval. Therefore, this addendum is submitted to provide the final OPQ recommendation of approval of BLA 761201 for SEMGLEE manufactured by Mylan Pharmaceuticals, Inc.

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

None

Anjali Shukla

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Date: 4/15/2021 10:25:14PM
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Patrick Lynch

Digitally signed by Patrick Lynch
Date: 4/16/2021 08:28:16AM
GUID: 54bfb193000693c35f4278034f85d77a

First Biosimilar: If approved, Semglee (insulin glargine-yfgn) will be the first interchangeable biosimilar to U.S.-licensed Lantus.

Recommendation: Approval pending final Microbiology recommendation (See Section IA)

BLA Number: 761201
Office of Pharmaceutical Quality
Application Team Lead Assessment Number: 1
Assessment Date: March 29, 2021

Drug Name/Dosage Form	Semglee (insulin glargine-yfgn) /injection
Strength/Potency	100 Units/mL in a 3 mL pre-filled pen and in a 10 mL vial
Route of Administration	subcutaneous
Rx/OTC dispensed	Rx
Indication	To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Applicant/Sponsor	Mylan Pharmaceuticals Inc
US agent, if applicable	N/A

Product Overview:

SEMGLEE (insulin glargine-yfgn) is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. Semglee is homologous with human insulin with the exception of a substitution of the amino acid glycine by asparagine at position A21, and two arginine residues added to the C-terminus of the B-chain. Semglee is produced by recombinant DNA technology utilizing *Pichia pastoris*. Semglee is supplied as a pre-filled pen and a vial for subcutaneous injection. Semglee is a proposed interchangeable biosimilar to U.S.-licensed Lantus.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Qiong Fu	DBRRII/OBP/OPQ
Drug Product		
Immunogenicity		
Labeling	Vicky Borders-Hemphill	DBRRII/OBP/OPQ
Facility	Michael Shanks, Virginia Carroll	DBM/OPMA/OPQ
Microbiology DS	Michael Shanks	DBM/OPMA/OPQ
Microbiology DP	Virginia Carroll	DBM/OPMA/OPQ
Facility secondary Assessor	Candace Gomez-Broughton	DBM/OPMA/OPQ
Microbiology Branch Chief	Candace Gomez-Broughton	DBM/OPMA/OPQ
Regulatory Business Process Manager	Anika Lalmansingh	OPRO/OPQ
Application Team Lead	Anjali Shukla	DBRRII/OBP/OPQ

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Julie Van der Waag	DROCHEN/ORO/OND
Cross-disciplinary Team Lead	Patrick Archdeacon	DDLO/OCHEN/OND
Medical Officer	Ann Miller	DDLO/OCHEN/OND
Pharmacology/Toxicology	Patricia Brundage, Federica Basso	DPTCHEN/OCHEN/OND
Clinical Pharmacology	Lin Zhou, Manoj Khurana	DCEP/OCP/OTS

Statistics	Roberto Crackel,Yun Wang	DBII/OB/OTS
CDRH	David Wolloscheck,Rumi Young	DHT3C /OHT3/OPEQ /CDRH
DMEPA	Ariane Conrad, Millie Shah	DMEPA/OMEPRM/OSE
OTBB	Stacey Ricci, Sarah Schrieber, Nina Brahme, Ruby (Chin-Ann) Wu, Eva Temkin, Andrew Zacher, Christine Corser, Leila Hann, Sarah Brown, Tyree Newman	OTBB/OND

1. Names:

a. Proprietary Name: Semglee
b. Trade Name: Semglee
c. Non-Proprietary Name/USAN: insulin glargine-yfgn
d. CAS Name: 160337-95-1
e. Company Code: MYL-1501D
f. INN Name: insulin glargine-yfgn
h. OBP systematic name: RPROT P01308 (INS_HUMAN) INSULIN [MYL1501D]

Submissions Assessed:

Submission(s) Assessed	Document Date
761201/0001	7/29/2020
761201/0004 (responses to OBP IR* #1)	9/9/2020
761201/0005 (responses to OPMA IR)	9/18/2020
761201/0012 (responses to OPMA IR)	12/16/2020
761201/0013 (response to OPMA IR)	1/8/2021
761201/0017 (responses to OBP IR #2)	2/16/2021
761201/0018 (responses to OBP IR #2)	2/19/2021
761201/0020 (responses to OBP IR #3)	2/26/2021
761201/0021 (responses to OBP IR #4)	3/1/2021
761201/0023 (responses to OBP IR #5)	3/16/2021

*IR: Information Request sent to the Applicant

Quality Assessment 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 Assessment Completed	Comments
(b) (4)	III		(b) (4)	3	N/A	N/A	No review required at this time as relevant information related to compatibility with the product was provided in the BLA.
	III			3	N/A	N/A	No review required at this time as relevant information related to compatibility with the product was provided in the BLA.
	V			2	Adequate	04/02/2020	The washing process was assessed previously.
	III			3	N/A	N/A	No review required at this time as relevant information related to compatibility with the product was provided in the BLA.
	III			3 and 2	N/A and Adequate	N/A and 06/15/2020	No review required at this time as relevant

		(b) (4)				information related to compatibility with the product was provided in the BLA (b) (4) washing process was assessed previously.
(b) (4)	V	(b) (4)	2	Adequate	05/14/2019	The washing process was assessed previously.
	III		3	N/A	N/A	No review required at this time as relevant information related to compatibility with the product was provided in the BLA.
	II		3	N/A	N/A	No review required at this time as relevant information related to compatibility with the product was provided in the BLA.
	MAF		3, and 6	N/A	N/A	No OPQ review required at this time as relevant information related to compatibility with the product was provided in the BLA. Assessment of MAF is

							deferred to CDRH.

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

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be assessed.

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

Document	Application Number	Description
BLA	210605	Semglee is currently licensed under deemed 351(a) BLA 210605

3. Consults: No consults requested by OPQ

4. Environmental Assessment of Claim of Categorical Exclusion:

Pursuant to 21 CFR §25.15(d), Mylan Pharmaceuticals Inc. requested a categorical exclusion from the preparation of an environmental assessment report for Semglee (insulin glargine-yfgn). The reasons supporting this request for categorical exclusion are as follows:
1) In accordance with 21 CFR §25.31(a), this is a biologic license application, for marketing approval of a proposed biosimilar, which is not expected to increase the use of the active moiety.
2) There is no anticipated change in the level of the substance in the environment as a result of Mylan's manufacture of the drug product and consequently, no increase in environmental effects associated with the use and disposal from use of this product. The methods employed in the manufacture of the biological product are in compliance with all applicable local, state and federal environmental regulations.

The Applicant's claim of a categorical exclusion is accepted.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Approval pending final Microbiology recommendation.

The Office of Pharmaceutical Quality, CDER, recommendation on approvability of STN 761201 for SEMGLEE manufactured by Mylan Pharmaceuticals, Inc is pending final Microbiology recommendation.

The Office of Pharmaceutical Quality, CDER does not note any product quality deficiencies that would preclude approval of BLA 761201 for SEMGLEE manufactured by Mylan Pharmaceuticals, Inc. at this time. The data submitted in this application are adequate to support that Semglee is highly similar to U.S.-licensed Lantus, notwithstanding minor differences in clinically inactive components.
However, the drug product microbiology assessment is ongoing at the time of finalizing this memorandum. Final OPQ recommendation will be provided in a future addendum to this OPQ Executive Summary memorandum upon completion of the OPMA microbiology assessment.

B. Approval Action Letter Language:

- Manufacturing location:
    - Drug Substance:
      Biocon Sdn. Bhd. (930330-U),
      No.1, Jalan Bioteknologi 1,
      Kawasan Perindustrian SiLC,
      79200 Iskandar puteri
      Johor, Malaysia.
      FEI: 3011248248
    - Drug Product:
      Biocon Sdn. Bhd. (930330-U),
      No.1, Jalan Bioteknologi 1,
      Kawasan Perindustrian SiLC,
      79200 Iskandar puteri
      Johor, Malaysia.
      FEI: 3011248248
- Fill size and dosage form
  100 Units/mL in 3 mL pre-filled pen
  100 Units/mL in 10 mL multiple dose vial
- Dating period:
    - Drug Product: 24 months: 5°C±3°C

- Drug Substance: (b) (4) months: (b) (4) °C
- For packaged products: N/A
- Stability Option:

  We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

- Exempt from lot release:

  - Yes
  - Rationale, if exempted: specified product
    Note: Semglee is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

Semglee (insulin glargine-yfgn), referred to as MYL-1501D, is a proposed interchangeable biosimilar to U.S.-licensed Lantus (insulin glargine). Insulin glargine is a long-acting analog of human insulin. Semglee is indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus as is approved for U.S.-licensed Lantus. Semglee has the same strength, dosage form, and route of administration as U.S.-licensed Lantus.

The data provided in the BLA support a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus, notwithstanding minor differences in clinically inactive components (refer to Section II of this memo). The proposed presentations of MYL-1501D 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 U.S.-licensed Lantus. The strength of MYL-1501D vials and pre-filled pen is the same as that of U.S.-licensed Lantus.

The MYL-1501D manufacturing process and overall control strategy are sufficient to ensure consistent manufacture of a drug product that is safe and effective. The immunogenicity assays are suitable and sensitive to detect anti-drug antibodies to MYL-1501D and U.S.-licensed Lantus. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage (see Sections III G Establishment Information and III H Facilities).

The approval of MYL-1501D as an interchangeable biosimilar to U.S.-licensed Lantus will increase treatment options for patients currently undergoing therapy for diabetes.

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

None

II. Comparative Analytical Assessment

A. Analytical Assessment Overview and Conclusions

The Applicant performed two studies as part of the comparative analytical assessment between MYL-1501D and U.S.-licensed Lantus as described below:

i. A study that compared a total of 10 MYL-1501D cartridge lots and 24 U.S.-licensed Lantus pre-filled pen (PFP) lots where cartridges are integrated into the PFP. The 10 MYL-1501D cartridge lots included lots used in the clinical PK/PD similarity studies, comparative clinical studies, and lots representative of the clinical and the proposed commercial drug product. These 10 MYL-1501D cartridge lots included 6 lots manufactured using Process VI (proposed commercial manufacturing process) drug substance (DS) and 4 lots manufactured using Process V DS. Comparability between lots manufactured using DS Process V and VI has been established (Refer to BLA 210605 CDTL Review and Division Summary Memo for Regulatory Action, June 11, 2020; BLA 210605 OPQ Executive Summary, May 22, 2020; BLA 210605 OPQ Executive Summary, April 5, 2018).
The proposed presentations of MYL-1501D include a 10 ml vial and a pre-filled pen integrated with a 3 ml cartridge. The cartridge is the primary container closure system of the pre-filled pen DP and the assembly process of the cartridge into the pen was demonstrated to have no impact on the quality attributes of MYL-1501D. Therefore, it is acceptable to include MYL-1501D cartridge lots in the comparative analytical assessment of MYL-1501D and U.S.-licensed Lantus.

ii. A study that compared a total of 5 MYL-1501D vial lots, and 34 U.S.-licensed Lantus lots (24 PFP lots + 10 vial lots). The MYL-1501D vial lots included the vial lot used in the clinical PK/PD similarity study MYL-1501D-1004, process validation lots, and lots representative of the proposed commercial drug product. For statistical evaluation, the U.S.-licensed Lantus quality ranges were established by combining data obtained from U.S.-licensed Lantus PFP lots and U.S.-licensed Lantus vial lots. Mylan chose to justify this approach by demonstrating analytical comparability between U.S.-licensed Lantus vial and PFP lots, and FDA found this acceptable.

Expiration dates for the U.S.-licensed Lantus PFP lots range from June 2014 to October 2017 and U.S.-licensed Lantus vial lots range from March 2017 to June 2018, which spans the shelf life of U.S.-licensed Lantus. These lots were adequate to capture potential lot-to-lot variability in the reference product over time.

The comparative analytical assessment was comprised of extensive comparative physicochemical and functional assessment of the quality attributes of MYL-1501D and U.S.-licensed Lantus. Mylan used an acceptable risk-based approach for statistical evaluation of analytical results. The highest ranked attributes tested using quantitative assays were evaluated using both equivalence testing and quality ranges on the same sets of data. The OBP Assessor's evaluation was based on the quality ranges approach for these attributes. Low to high risk attributes tested using quantitative assays were evaluated using quality ranges calculated to account for reference product manufacturing variability and assay variability. Attributes tested using qualitative assays were evaluated using graphical representation and data tables. Additionally, for attributes measured by multiple orthogonal methods amenable to statistical assessment of quality ranges, at least one method was evaluated statistically and the rest were evaluated using graphical and/or data table comparisons. Results from method validation or qualification studies support the suitability of the methods used in the comparative analytical assessment. The applicant also provided a comparison of stability under forced degradation conditions of thermal stress (60℃), pH (pH 2 and pH 10), oxidative stress, photo exposure and mechanical stress. The comparative forced degradation studies support that MYL-1501D and U.S.-licensed Lantus have a similar degradation profile.

Based on our assessment, the MYL-1501D and U.S.-licensed Lantus data supports a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus, notwithstanding minor differences in clinically inactive components. MYL-1501D has the same strength, dosage form, and routes of administration as U.S.-licensed Lantus. The applicant used a comprehensive array of analytical methods that were suitable to evaluate critical quality attributes of MYL-1501D and U.S.-licensed Lantus to support the demonstration that the products are highly similar. Numbers of lots tested and data analyses were appropriate to allow for a meaningful evaluation of the results of the comparative analytical studies. While differences were observed in a limited number of attributes, these do not preclude a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus.

B. Results of Comparative Analytical Assessment

The results of these analytical comparisons support a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus and the results are summarized in Table A below:

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

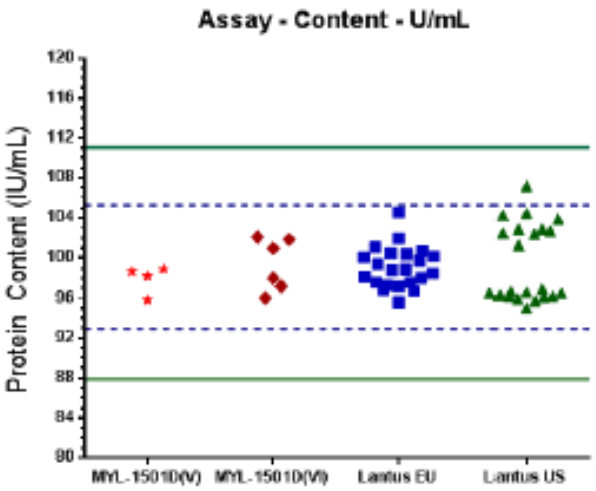
Physico-chemical/Functional characteristics	Quality Attribute Assessed	MYL-1501D cartridge vs U.S.-Lantus PFP Supports a demonstration of highly similar	MYL-1501D vial vs U.S.-Lantus PFP+vial Supports a demonstration of highly similar
Amino acid sequence	Peptide Mass Fingerprint (PMF)	Yes	Yes
	Intact mass	Yes	Yes
	Reduced mass (reduced ESI-MS)	Yes	Yes
Conformation (secondary and higher order structure)	FTIR	Yes	Yes
	Far UV CD	Yes	Yes
	Extrinsic fluorescence	Yes	Yes
	Intrinsic fluorescence	Yes	Yes
	Near UV CD	Yes	Yes
	DSC (for Tm °C)	Yes	Yes
	PMF (Non-reduced)	Yes	Yes
	DLS (for hydrodynamic radius)	Yes	Yes
	X-Ray	Yes	Yes
	NMR	Yes	Yes
Protein content	RP-HPLC Assay	Yes	Yes

Zinc Content		**AAS**	**Yes**	**Yes**
Size variants: Aggregates/HMWP		**SEC-HPLC**	**Yes**	**Yes**
		SEC-MALLS	**Yes**	**Yes**
		AUC	**Yes**	**Yes**
Product variants	**Des TRR**	**RP-HPLC**	**Yes**	**Yes**
	Des R and B3 Deamidation		**Yes**	**Yes**
	A15 deamidation		**Yes**	**Yes**
	Insulin glargine		**Yes**	**Yes**
	Glycerol ester		**Yes**	**Yes**
	Citric acid conjugate		**Yes**	**Yes**
	Acetylation		**Yes**	**Yes**
Isoelectric point (pI)			**Yes**	**Yes**
Mitogenic activity		**IR-A cell-based phosphorylation assay**	**Yes**	**Yes**
		Mitogenic assay using Saos2 cells	**Yes**	**Yes**
		IR short form (IR-A) binding kinetic assay	**Yes**	**Yes**
		IGF1R receptor binding kinetics	**Yes**	**Yes**
Metabolic activity		**IR-B cell-based phosphorylation assay**	**Yes**	**Yes**
		Glucose uptake assay using 3T3-L1 cells	**Yes**	**Yes**
		IR long form (IR-B) receptor binding kinetics	**Yes**	**Yes**
		IR autophosphorylation	**Yes**	**Yes**
		Adipogenesis assay using 3T3-L1 cells	**Yes**	**Not Performed***
		Inhibition of Stimulated Lipolysis assay using 3T3-L1 cells	**Yes**	**Not performed***

* The absence of data with MYL-1501D 100 Units/mL in a 10 mL vial from these assays is acceptable because data from an orthogonal method (i.e., glucose uptake) are available and support a demonstration of highly similar. Further, data from the Adipogenesis assay using 3T3-L1 cells and the Inhibition of Stimulated Lipolysis assay using 3T3-L1 cells are available for MYL-1501D 100 Units/mL in a 3 mL cartridge and also support a demonstration of highly similar.

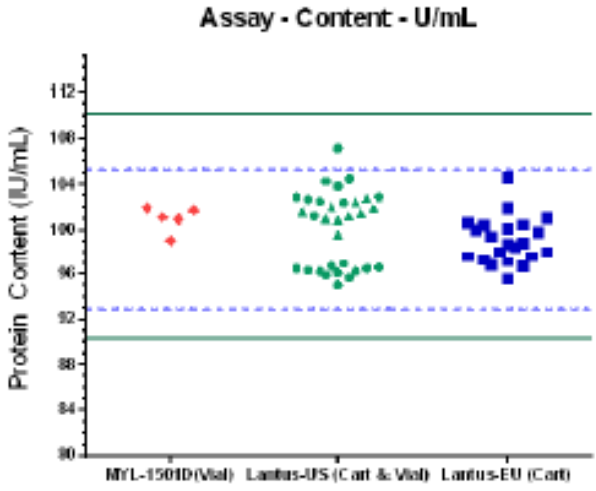
Scatter plots for protein content (Assay) of U.S.-licensed Lantus and MYL-1501D cartridge and vial lots are presented below. Solid green lines depict the quality range established for U.S.-licensed Lantus. Dotted blue lines and blue squares depict data from E.U.-approved Lantus (refer to section C).

Comparison of MYL-1501D cartridge lots with U.S.-Lantus PFP lots



Orange: MYL-1501D cartridge lots from DS Process V
Red: MYL-1501D cartridge lots from DS Process VI
Green: U.S.-Lantus PFP lots

Comparison of MYL-1501D vial lots with U.S.-Lantus PFP + vial lots



Orange: MYL-1501D vial lots
Green: U.S.-Lantus cartridge + vial lots
U.S.-Lantus PFP lots are denoted by green circles and U.S.-Lantus vials by green triangles.

C. Analytical Studies to Support the use of a Non-U.S.-licensed Comparator Product

Not applicable. Data generated from studies using EU-approved Lantus were not used to support a demonstration of biosimilarity. Therefore, the analytical testing results from the EU-approved Lantus submitted in the BLA were not assessed, as there was no need to establish an adequate scientific bridge.

D. Assessment of Comparative Analytical Study Results

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

Zinc content

While the zinc levels of MYL-1501D vial lots were within the quality range of U.S.-licensed Lantus lots, two out of ten MYL 1501-D cartridge lots have levels of zinc that are marginally higher (31.8 ug/100U and 33.0 ug/100U) than the quality range of U.S.-licensed Lantus PFP lots

(27.3-31.2 ug/100U). Zinc is known to impact the stability, higher order structure and pharmacokinetic profile of insulin[1]. Comparative analytical assessment of secondary structure, higher order structure, functional and biological activity and stability profiles support a conclusion that MYL-1501D lots are highly similar to U.S.-licensed Lantus lots. Additionally, the levels of zinc are controlled at drug substance and drug product release and stability. Therefore, the observed differences in zinc content do not preclude a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus.

Des R and B3 deamidation

Des R is a clipped insulin glargine variant that lacks the B32 arginine, while B3 desamido insulin glargine results from deamidation at the B3 asparagine. While the Des R and B3 desamido levels in MYL-1501D cartridge lots were within the quality range of U.S.-licensed Lantus PFP lots, the Des R and B3 desamido levels of two out of five MYL-1501D vial lots (0.06% and 0.07%) are marginally lower than the quality range of U.S.-licensed Lantus (0.08% - 0.55%). No impact of this difference is seen on the biological activity of MYL-1501D in comparison to U.S.-licensed Lantus. Due to the low levels of the DesR and B3 deasmido variants in both MYL-1501D and U.S.-licensed Lantus, the marginal observed difference in levels, and comparable biological activity of MYL-1501D and U.S.-licensed Lantus, the observed difference in DesR and B3 deamidation levels does not preclude a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus.

E. Same strength

MYL-1501D has the same dosage form and route of administration as U.S.-licensed Lantus. Mylan is seeking approval of 100 Units/mL MYL-1501D in a 10 mL vial and 100 Units/mL in a 3 mL pre-filled pen. U.S.-licensed Lantus is available at 100 Units/mL in a 10 mL vial and in a 3 mL pre-filled pen[2]. Comparative concentration (Units/mL) was assessed as part of the comparative analytical assessment. The extractable volume and fill weight data were also assessed in the context of manufacturing control. Based on the comparative concentration data and manufacturing data, the 100 Units/mL MYL-1501D in 3mL pre-filled pen and 10 mL vial 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 U.S.-licensed Lantus. The strength of MYL-1501D vial and pre-filled pen is the same as that of U.S.-licensed Lantus.

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 OPQ primary technical reviews.

[1] Dunn, M.F. Zinc–Ligand Interactions Modulate Assembly and Stability of the Insulin Hexamer – A Review. *Biometals* **18,** 295–303 (2005). https://doi.org/10.1007/s10534-005-3685-y

[2] U.S. Prescribing Information, U.S.-licensed Lantus, Accessed 3/12/2021 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021081s073s074lbl.pdf

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

CQA (type)	Risk	Origin	Control Strategy	Other
Aggregates	Safety and Efficacy	Manufacturing process, Stability	(b) (4)	N/A
Glycosylated variants	Safety and Efficacy	Manufacturing process		N/A
Deamidated variants	Efficacy	Manufacturing process		N/A
Clipped variants	Efficacy	Manufacturing process		N/A
Content	Efficacy	Intrinsic to the molecule, Manufacturing process		N/A
Identity	Safety and Efficacy	Intrinsic to the molecule		N/A

			(b) (4)	

B. Drug Substance 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 OPQ primary technical reviews.

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

CQA (type)	Risk	Origin	Control Strategy	Other
Residual solvents- (b) (4)	Safety	Manufacturing process	(b) (4)	N/A
content	Safety	Manufacturing process		N/A
(b) (4)	Stability and Efficacy	Added during manufacturing process		N/A
Host cell protein	Safety	Fermentation		N/A
Host cell DNA	Safety	Fermentation		N/A
(b) (4)	Safety	Added during manufacturing process		N/A
	Efficacy	(b) (4)		N/A

Assay (content)	Efficacy	Manufacturing process	(b) (4)	N/A
High molecular weight proteins	Safety and Efficacy	Manufacturing process, Stability		N/A
Related Compounds	Safety and Efficacy	Manufacturing process, Stability		N/A
Bacterial endotoxin	Safety and Purity	Raw material and manufacturing process		N/A
Total aerobic count (bioburden)	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw material and manufacturing process		N/A

- Description: MYL-1501D (insulin glargine-yfgn) is a long-acting analog of human insulin with 53 amino acids in 2 chains. The A chain is composed of 21 amino acids and the B chain is composed of 32 amino acids. The A and B chains are connected by 2 disulfide linkages. In addition, the A chain has a single intra-chain disulfide linkage. The primary sequence of insulin glargine-yfgn differs from that of human insulin by 3 amino acids: asparagine at position A21 instead of glycine and 2 arginines added to the C terminus of the B chain.

- Mechanism of Action (MoA): MYL-1501D (insulin glargine-yfgn) is a long-acting analog of human insulin. The primary activity of insulin glargine-yfgn is regulation of glucose metabolism. Insulin glargine-yfgn lowers blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin glargine-yfgn inhibits lipolysis in adipocytes, inhibits proteolysis and enhances protein synthesis.

- Potency Assay: Potency of MYL-1501D (insulin glargine-yfgn) DS is determined by RP-HPLC where the area of the main peak is used to calculate the content as % w/w. Potency is reported in Units/mg (b) (4)

- Reference Materials: Mylan uses a 'working standard' (WS) (b) (4)

(b) (4)

A protocol is provided for the qualification of a WS. The protocol contains adequate testing and acceptance criteria. The Applicant has committed to establish a two-tier reference standard system.

- Critical starting materials or intermediates: (b) (4) A two-tiered cell banking system comprising of the Master Cell Bank (MCB) and a Working Cell Bank (WCB), with appropriate characterization, stability testing program, and storage conditions, has been implemented to ensure consistent manufacture of the product.

- Manufacturing process summary: (b) (4) In-process controls are implemented throughout the manufacturing process to ensure consistent quality at each stage.

  From a microbiological perspective, overall, the process is under adequate microbial control. (b) (4) Adequate controls are in place to maintain microbiological product quality during maximum hold periods and throughout the manufacturing process.

- Container closure: (b) (4)

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

C. Drug Product 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	Other
Content (assay)	Efficacy	Intrinsic to the molecule, manufacturing process	(b) (4)	N/A
Related compounds	Safety and Efficacy	Manufacturing process, Stability		N/A
High molecular weight proteins	Safety and Efficacy	Manufacturing process, Stability		N/A
m-cresol content	Safety, stability	Formulation		N/A
pH	Stability	Formulation		N/A
Osmolality	Safety, Stability	Formulation		N/A
Zinc content	Efficacy	Formulation		N/A
Sterility	Safety, Purity and Efficacy	Manufacturing process, container closure integrity failure		N/A

			(b) (4)	
Appearance	Stability	Formulation		N/A
Endotoxin	Safety, Purity	Raw materials, manufacturing process		N/A
Container Closure Integrity	Safety, Stability	Breach during manufacture or storage		N/A
Particulate matter	Safety and Efficacy	Formulation, filling, stability		N/A
Dose Accuracy (pen)	Efficacy	Pre-filled pen		N/A
Polysorbate (vial)	Safety, Efficacy and Stability	Formulation		N/A

- Potency and Strength: Potency of the DP is determined using a RP-HPLC assay. The strength of the DP is 100 Units/mL in a 3 mL pre-filled pen and in a 10 mL vial.

- Summary of Product Design: MYL-1501D is supplied as a 10 mL vial and a 3 mL pre-filled pen. The primary container closure of the pre-filled pen is a cartridge.

- List of Excipients:
  Vial: m-cresol (2.7 mg/mL), glycerol (b) (4) (20 mg/mL), zinc (30 ug/mL), polysorbate-20 (20 ug/mL), hydrochloric acid, sodium hydroxide, water for injection.
  Pre-filled pen: m-cresol (2.7 mg/mL), glycerol (b) (4) (20 mg/mL), zinc (30 ug/mL), hydrochloric acid, sodium hydroxide, water for injection.

- 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) .The composition of the vial formulation is identical to the cartridge except the presence of additional excipient, polysorbate 20 in the vial presentation.

  (b) (4)

- Container closure: (b) (4) . The components of the pre-filled pen do not come into contact with the drug product.

- Dating period and storage conditions: The DP shelf life is 24 months stored at 5°C±3°C. Unopened vial or pre-filled syringe DP may be stored for up to 28 days at room temperature (up to 30°C). In-use (opened) vial may be stored up to 28 days refrigerated (2-8°C) or at room temperature (up to 30°C). In-use (opened) pre-filled pen may be stored for up to 28 days at room temperature (up to 30°C, not to be refrigerated).

- List of co-package components, if applicable: none

D. Biopharmaceutics Considerations: none

E. Novel Approaches/Precedents: If approved, MYL-1501D will be the first interchangeable biosimilar to U.S.-licensed Lantus.

F. Any Special Product Quality Labeling Recommendations: none

G. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug substance manufacturing, quality control testing [chemical/physical, microbiological (non-sterility)], release, primary packaging, secondary packaging, storage and/or distribution of drug substance and storage of working cell bank	Biocon Sdn. Bhd. (930330-U), No.1, Jalan Bioteknologi 1, Kawasan Perindustrian SiLC, 79200 Iskandar Puteri, Johor, Malaysia.	DUNS: 865785591 FEI **:** 3011248248	Acceptable. Inspection waived. See waiver memo for more information	N/A	Approve
Characterization of the master cell bank and working cell bank and stability testing of the master cell bank (quality control testing – biological)	(b) (4)		No Evaluation Required based on responsibilities	N/A	No Evaluation Required
Master cell bank and working cell bank preparation and Storage	Biocon Biologics India Limited, 20th K. M. Hosur Road,	DUNS: 675486243 FEI:	No Evaluation Required based on responsibilities	N/A	No Evaluation Required

	Electronics City, Bengaluru-560 100, India	3015283245			
Rabbit bioidentity testing of drug substance	(b) (4)		Compliance History and Status Reviewed	N/A	Approve
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacturing, filling, primary packaging, quality control testing [Chemical/Physical, Microbiological (sterility and nonsterility) testing] of the 3 mL cartridges and pre-filled pen assembly (secondary packaging), quality control testing [Chemical/Physical] of the pre-filled pens and secondary packaging in carton box.	Biocon Sdn. Bhd. (930330-U), No.1, Jalan Bioteknologi 1, Kawasan Perindustrian SiLC, 79200 Iskandar Puteri, Johor, Malaysia.	DUNS: 865785591 FEI: 3011248248	Acceptable. Inspection waived. See waiver memo for more information	N/A	Approve

H. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Biocon Sdn. Bhd. (FEI 3011248248), proposed for DS and DP manufacture. All proposed manufacturing and testing facilities are acceptable based on

their current CGMP compliance status and recent relevant inspectional coverage. OBP and OPMA concurred on the issued inspection waiver of this facility, Biocon Sdn. Bhd. (FEI 3011248248).

I. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
1. Annual stability protocol
2. Comparability protocol for establishment of new Working Cell Bank
3. Protocol for qualification of new working standard

ii. Outstanding assessment issues/residual risk: none

iii. Future inspection points to consider: none

b. Drug Product

i. Protocols approved:
1. Annual stability protocol

ii. Outstanding assessment issues/residual risk: Drug Product microbiology assessment is ongoing at the time of finalizing this memorandum. OPQ recommendation on approvability of STN 761201 is pending final microbiology recommendation. Final OPQ recommendation will be provided in a future addendum to this OPQ Executive summary memorandum upon completion of the OPMA microbiology assessment.

iii. Future inspection points to consider: none

Anjali Shukla

Digitally signed by Anjali Shukla
Date: 3/29/2021 03:41:57PM
GUID: 57f29f4500712615c8f3d6ddc11716a9

Patrick Lynch

Digitally signed by Patrick Lynch
Date: 3/29/2021 04:05:00PM
GUID: 54bfb193000693c35f4278034f85d77a

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

/s/

ANIKA A LALMANSINGH
04/16/2021 03:24:29 PM

ANJALI A SHUKLA
04/16/2021 05:03:55 PM

BLA STN 761201

Semglee [Insulin glargine-yfgn]
[MYL-1501D, proposed interchangeable biosimilar to U.S.-licensed Lantus]

Mylan Pharmaceuticals Inc.

Qiong Fu, PhD, Product Quality Reviewer
Anjali Shukla, PhD, Application Technical Lead

Division of Biotechnology Research and Review II (DBRRII)
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

OBP CMC Review Data Sheet

1. BLA#: 761201

2. Review Date: 03/22/2021

3. Primary Review Team:

a. Medical Officer	Ann Miller and Patrick Archdeacon (TL)
b. Clinical Pharmacology	Lin Zhou and Manoj Khurana (TL)
c. Pharm/Tox	Patricia Brundage and Federica Basso (TL)
d. Product Quality Team	
OPQ/OBP:	Qiong Fu and Anjali Shukla (ATL)
OPQ/OBP Biosimilar Policy:	Joel Welch and Marlene Schultz-DePalo
OPQ/OPMA Micro and Facility:	Michael Shanks (DS), Virginia Carroll (DP), and Candance Gomez-Broughton (TL)
OPQ/OBP (labeling):	Vicky Borders-Hemphill
e. Statistics:	Roberto Crackel and Yun Wang (TL)
f. OSI:	Cynthia Kleppinger and Min Lu (TL)
g. DMEPA:	Ariane Conrad and Millie Shah (TL)
h. CDRH:	David Wolloscheck and Rumi Young (TL)
i. Safety:	Marisa Petruccelli and Mitra Rauschecker (TL)
j. OPDP:	Ankur Kalola
k. Patient Labeling:	Nyedra Booker and Marcia Williams (TL)
l. DPV:	Christine Chamberlain/ Ali Niak and Christian Cao (TL)
m. DEPI:	Christian Hampp and Yandong Qiang (TL)
n. RPM:	Julie Van der Waag and Pam Lucarelli (TL) Anika Lalmansingh (CMC)

4. Major GRMP Deadlines:

a. Filing meeting:	09/11/2020
b. Mid-cycle internal meeting:	12/15/2020
c. Mid-cycle applicant meeting:	01/12/2021
d. Primary review due:	03/29/2021
e. Secondary review due:	04/05/2021
f. Internal Late-cycle meeting:	03/29/2021
g. Late-cycle applicant meeting:	04/29/2021
h. Wrap-up meeting:	05/25/2021
i. BsUFA action date:	07/27/2021

5. Communications with Applicant and OND:

Communication/Document:	Date:
Filing meeting with OND	09/11/2020
T-conference with Applicant about proposed proprietary name	09/22/2020
Mid-cycle meeting with OND	12/15/2020
Mid-cycle meeting with Applicant	01/12/2021
Labeling meeting #1	03/15/2021

Information request (OBP IR #1)	08/28/2020
CAA Information request (OBP IR #2)	02/09/2021
Information request (OBP IR #3)	02/19/2021
Information request (OBP IR #4)	02/24/2021
Information request (OBP IR #5)	03/11/2021

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
761201/0001	07/29/2020	Yes
761201/0004 (responses to OBP IR #1)	09/09/2020	Yes
761201/0017 (responses to OBP IR #2)	02/16/2021	Yes
761201/0018 (responses to OBP IR #2)	02/19/2021	Yes
761201/0020 (responses to OBP IR #3)	02/26/2021	Yes
761201/0021 (responses to OBP IR #4)	03/01/2021	Yes
761201/0023 (responses to OBP IR #5)	03/16/2021	Yes

7. Drug Product Name/Code/Type:

a. Proprietary name: Semglee
b. Non-Proprietary name/USAN: Insulin glargine-yfgn
c. CAS name: CAS registry number 160337-95-1
d. INN name: Insulin glargine-yfgn
e. Chemical name: 21^{A}-Glycine-30^{B}a-L-arginine 30^{B}b-L-arginine-insulin (human)

g. OBP systematic name: RPROT P01308 (INS_HUMAN) INSULIN [MYL1501D]
h. Other name(s): MYL-1501D (company code)

8. Pharmacological Category: long-acting human insulin analog indicated for treatment of diabetes

9. Dosage Form: injection

10. Strength/Potency:

(i): Concentration/strength of DP: 100 Units/mL
(ii): Type of potency assay(s): Assay by RP-HPLC

11. Route of Administration: subcutaneous injection

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comment (status)
		(b) (4)	Yes	No review required at this time as relevant information
			Yes	
			Yes	

(b) (4)	Yes	related to compatibility with the product was in the BLA.
	Yes	
	Yes	
	Yes	
	Yes	
	Yes	Assessment deferred to CDRH

13. Inspectional Activities: OPQ determined that the pre-license inspection of Biocon Sdn. Bhd. (FEI 3011248248) in support of BLA 761201 for Semglee (MYL-1501D, insulin glargine-yfgn) drug substance and drug product manufacture be waived.

14. Consults Requested by OBP: none

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:
If BLA-761201 is approved, Semglee will be the first interchangeable biosimilar to U.S.-licensed Lantus.

17. Administrative:

Name and Title	**Signature and Date**
Anjali Shukla, Ph.D. Application Technical Lead, DBRRII/OBP/OPQ/CDER	See electronic signature and date
Qiong Fu, Ph.D. Primary Assessor, DBRRII/OBP/OPQ/CDER	See electronic signature and date

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation

The data submitted in BLA-761201 supports the conclusion that the manufacturing process of Semglee (insulin glargine-yfgn) is well controlled and leads to a product that is pure and potent. It is recommended that Semglee be approved for human use under conditions specified in the package insert. The comparative analytical assessment performed supports a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus, notwithstanding minor differences in clinically inactive components.

II. List of Deficiencies to be Communicated: None

III. List of Post-Marketing Commitments/Requirements: None

IV. Review of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion

A claim of categorical exclusion is being made under 21 CFR 25.15 (d). In accordance with 21 CFR 25.31 (a), this is a biologic license application, for marketing approval of a proposed interchangeable biosimilar, which is not expected to increase the use of the active moiety. To the Applicant's knowledge, there is no anticipated change in the level of the substance in the environment as a result of Mylan's manufacture of the drug product and consequently, no increase in environmental effects associated with the use and disposal from use of this product. The methods employed in the manufacture of the biological product follow all applicable local, state and federal environmental regulations.

The Applicant's environmental analysis and claim of categorical exclusion are acceptable.

V. Primary Container Labeling Review

OBP assessment of the carton and container labels is performed by Vicky Borders-Hemphill and Qiong Fu. The OBP assessment for carton and container labeling will be uploaded to Panorama as a separate document.

VI. Review of Common Technical Document- Quality Module 3.2

Refer to the drug substance and drug product assessment in this review memo.

VII. Review of Immunogenicity Assays- Module 5.3.1.4

Refer to immunogenicity assay assessment in section 5.3.1.4 Immunogenicity Assays of this review memo.

Table of Contents

Description of Drug Substance and Drug Product

Assessor's Preamble: *Semglee (MYL-1501D) was approved on 06/11/2020 as 505(b)2) NDA-210605 and deemed 351(a) BLA-210605 upon approval (referred to as NDA-/deemed BLA-210605 hereafter). For the current 351(k) BLA submission BLA-761201, the majority of the data package submitted is identical to that in the NDA-/deemed BLA-210605. Per BPD Type 2 Pre-IND 140431 written responses (7/3/2020), the FDA advised the Sponsor that the 351(k) application may be submitted using relevant data and information from the approved NDA-/deemed BLA-210605. Therefore, Mylan has 'electronically cloned' information from NDA-/deemed BLA-210605 where information remains unchanged, as presented in Table 1 below from eCTD Section 1.2 Reviewer's guide and Section 2.2 Introduction of BLA-761201.*

Table 1: eCTD Structure of the 351(k) Application and cross referencing to the 351(a) BLA-210605

Module	eCTD Section	Document Name	New in the 351(k) Application	Cross-referencing to the 351(a) BLA-210605 (electronically cloned)
1	Administrative Information		Yes	
2	2.2	Introduction to Summary	Yes	
	2.3	Quality Overall Summary	Yes	
	2.4	Nonclinical Overview	Yes	
	2.5	Clinical Overview	Yes	
	2.6	Nonclinical Summary	Yes	
	2.7	Clinical Summary	Yes	
3	3.2.S	Drug Substance		Yes – same documents as 351(a) BLA
	3.2.P	Drug Product (Pen)	Device Comparative Analysis of the Semglee Pre-filled Pen is included in Section 3.2.P.2.4	The remaining documents are the same as 351(a) BLA.
	3.2.P	Drug Product (Vial)		Yes – same documents as 351(a) BLA
	3.2.A	Appendices		Yes – same documents as 351(a) BLA
	3.2.R	Regional Information	Updated Similarity Assessment Report and annexures for the vial and cartridge	The remaining documents are the same as 351(a) BLA.
4	Nonclinical Study Reports		Adipogenesis and lipolysis study reports RPT-MBN-007 and RPT-MBN-010	The remaining documents are the same as 351(a) BLA.
5	Clinical Study Reports		5.2 Tabular Listing, 5.3.1.4 Addendum to Validation Report, additional literature references.	The remaining documents are the same as 351(a) BLA.

The CMC information that is 'cloned' from NDA-/deemed BLA-210605 has previously been assessed by OPQ. The integrated OPQ quality assessment for the original NDA-210605 submission (received complete response on 5/17/2018), resubmission 1 (received complete response on 8/28/2019), and resubmission 2 (received final approval on 6/11/2020) can be found here as NDA-201605 Review 1 (dated 4/5/2018), NDA-201605 Review 2 (dated 8/22/2019), and NDA-201605 Review 3 (dated 5/22/2020), respectively. For information stated by the Applicant and confirmed by the Assessor as cloned from NDA-/deemed BLA-210605, the Assessor of the current BLA-761201 has provided assessment and brief description , and wherever applicable, the previous OPQ quality assessments linked above are referred to for detailed assessment.

Unless otherwise noted, figures and tables in this document are either adapted or copied from the application. Some figures and tables were updated during the review cycle, but this document contains only the updated final version. The Assessor's comments are distinguished by the use of italic font.

S. Drug Substance (DS)

3.2.S.1 General Information

MYL-1501D is a human insulin analogue consists of 2 chains, an "A" chain (21 amino acids) and a "B" chain (32 amino acids), connected by two inter-chain disulfide linkages. In addition, the A chain has a single intra-chain disulfide linkage.

There are two differences in the amino acid sequence between MYL-1501D and human insulin:

a) The C-terminal of the B chain is elongated by two Arginine residues in MYL-1501D.
b) The C-terminal Asparagine of the A chain is replaced by Glycine in MYL-1501D.

These differences in amino acid sequence cause a shift in the isoelectric point toward a neutral pH.

3.2.S.1.1 Nomenclature

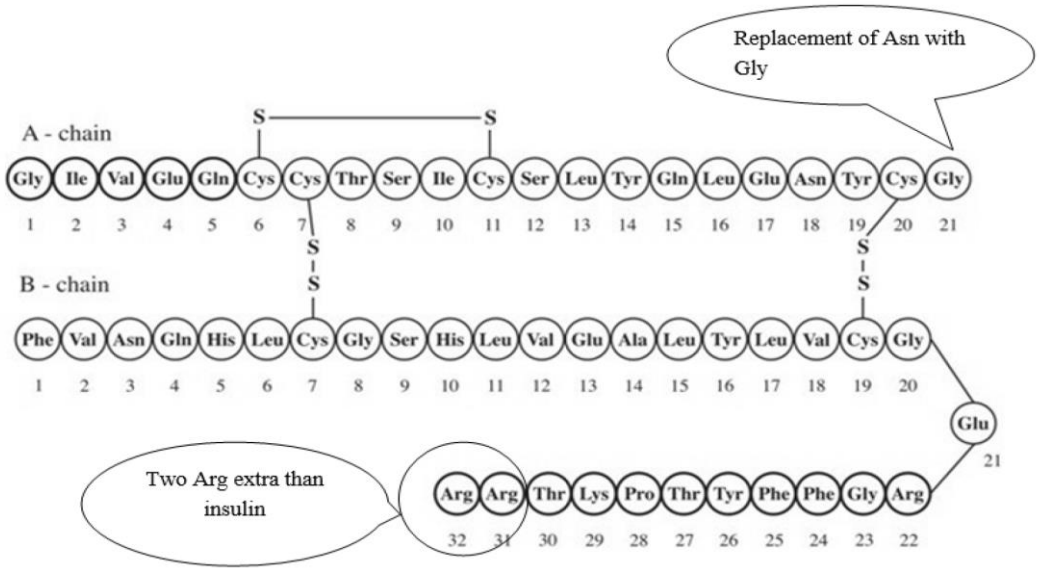
INN: Insulin glargine-yfgn
Chemical name(s): 21A-Glycine-30Ba-L-arginine-30Bb-L-arginine-insulin (human)
CAS Registry number: 160337-95-1
Company code: MYL-1501D
ATC classification: A10AE04

3.2.S.1.2 Structure

Molecular formula: $C_{267}H_{404}N_{72}O_{78}S_6$
Molecular weight: 6063 Daltons.

The amino acid sequence of the A and B chains with indicated disulfide linkages is provided in Figure 3.2.S.1.2/1 below.

Figure 3.2.S.1.2/1: Amino acid sequence of A and B chain in three-letter-code with indicated disulphide bond



The changes relative to the human insulin sequence are highlighted within the balloons

3.2.S.1.3 General Properties

The details pertaining to general properties of MYL-1501D DS are provided below in Table 2.3.S/3.

Table 2.3.S/1: General properties of MYL-1501D drug substance

Physical form	White or almost white powder
Solubility	Practically insoluble in water and in anhydrous ethanol. It is soluble in solutions of dilute mineral acids (such as hydrochloric acid).
Isoelectric point	Approximately 7.0
Biological activity	MYL-1501D and its reference product Lantus (approved insulin glargine product) were equipotent in *in vitro* metabolic and mitogenic assays; had the same *in vitro* binding characteristics and affinity for insulin receptor and IGF-1 receptors. The details of the assays and their results are described in Section 3.2.R.4 Comparative Analytical Assessment.

Assessor's Comment: *The description of the general properties, structure and functional activity of MYL-1501D is acceptable. It has been previously assessed in NDA-/deemed BLA-210605.*

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The addresses of the manufacturing and testing facility as well as contract testing organizations along with their responsibilities are provided in the table below.

Site	DUNS and FEI Number	Responsibilities
Biocon Sdn. Bhd. (930330-U), No.1, Jalan Bioteknologi 1, Kawasan Perindustrian SiLC, 79200 Iskandar Puteri, Johor, Malaysia. (referred as site **L2**)	DUNS Number: 865785591 FEI Number: 3011248248	Drug substance manufacturing, quality control testing [chemical/physical, microbiological (non-sterility)], release, primary packaging, secondary packaging, storage and/or distribution of drug substance and storage of working cell bank
Biocon Biologics India Limited, 20th K. M. Hosur Road, Electronics City, Bangalore, 560100, India (referred as **site II**)	DUNS Number: 675486243 FEI Number: 3015283245	Master cell bank and working cell bank preparation and storage
(b) (4)		Characterization of the master cell bank and working cell bank and stability testing of the master cell bank (quality control testing – biological)
		Rabbit bioidentity testing of drug substance

Assessor's Comment: *The DS manufacturing and testing sites are the same as previously described in NDA-/deemed BLA-210605. Assessment of facilities is deferred to OPMA.*

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

(b) (4)

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(b) (4)

3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment

The ongoing stability studies for the MYL-1501D DS will be continued as per the stability program and the acceptance criteria provided in eCTD Section 3.2.S.7.1.

After commercialization, annually 1 batch of DS will be placed on long-term stability studies (b) (4)

The annual stability protocol is summarized in Table 3.2.S.7.2/1. The acceptance criteria for stability studies will remain the same as provided in eCTD Section 3.2.S.4.1.

On completion of the study and based on the data generated, a shelf life of the DS will be revisited and assigned, in accordance with recommendations from ICH.

Table 3.2.S.7.2/1: Annual stability protocol post-commercialization – long-term condition (b) (4)

Test	Time in months					
	0	12	24	36	48	60
Appearance	√	√	√	√	√	√
Identification by RT comparison	√	√	√	√	√	√
% High molecular weight impurities by SEC	√	√	√	√	√	√
Related compounds- % any individual impurity (by HPLC Method A)	√	√	√	√	√	√
Related compounds- % total impurities (by HPLC Method A)	√	√	√	√	√	√
Assay (by HPLC)	√	√	√	√	√	√
Loss on drying	√	√	√	√	√	√

Assessor's Comment: *The Applicant's post-approval stability protocol for MYL-1501D DS is acceptable. Although the testing frequency does not include the 3,6,9,18 month time points as recommended per ICHQ5C, this BLA provided sufficient stability data at long-term condition for at least 48 months and under accelerated condition for 6 months that demonstrate adequate stability of the DS.* (b) (4) *he overall risk from lack of additional testing time points is low. Therefore, the post-approval long term DS stability protocol is acceptable. The*

accelerated stability studies up to 6 months provided in this BLA showed that under accelerated storage condition, the DS was compliant with long-term stability acceptance criteria for at least 6 months and no stability concerns are identified. Therefore, inclusion of accelerated stability in the DS post-approval stability protocol is not needed.

P: Drug Product (DP)

Assessor's Preamble: *The Applicant proposed two presentations of MYL-1501D drug product: 3 mL cartridge in pre-filled pen (PFP), and 10 mL in vial (vial). The DP compositions are the same for these presentations except that the vial presentation contains polysorbate 20 at a concentration of 20 µg/mL. The drug product manufacturing process for the two presentations are similar, with some differences in formulation step, filling step, and the PFP assembly step. The review below covers the common information shared among the two presentations with specific sections for each individual presentation as well. There is no change in the drug product composition, manufacturing development, formulation development, manufacturing process and process controls, container closure system, compared to that in the NDA-/deemed BLA-210605. Therefore, for detailed assessment of these unchanged sections, refer to the aforementioned NDA-210605 Review 1 (dated 4/5/2018).*

3.2.P.1 Description and Composition of the Drug Product

MYL-1501D drug product (DP) is a clear, colorless liquid, free from turbidity and foreign matter. It contains 100 U/mL of insulin glargine-yfgn, presented in either a pre-filled pen integrated with a 3-mL colorless tubular Type I glass cartridge that is sealed (b) (4) plunger stopper, or in a 10 mL clear tubular Type I glass vial closed with a (b) (4) rubber stopper and sealed using a flip-off seal. Both presentations are intended for subcutaneously injection of MYL-1501D DP, to improve glycemic control in adults and pediatric patients with Type 1 diabetes mellitus and in adults with Type-2 diabetes mellitus.
The unit quantitative composition of the MYL-1501D DP is provided in Table 3.2.P.1/1 below.

Table 3.2.P.1/1: Unit Quantitative Composition of MYL-1501D Drug Product (cartridge and vial)

Component	Quantity/mL	Quantity/ 3 mL cartridge	Quantity/ 10 mL vial	Quality standard	Function
Insulin glargine	100 units[1]	300 units	1000 units	In-house	Active ingredient
m-Cresol[2]	2.7 mg	8.1 mg	27 mg	Ph. Eur. and USP	(b) (4)
Glycerol (b) (4)	20 mg	60 mg	200 mg	Ph. Eur.	
Zinc[3] (as Zinc chloride)	30 µg	90 µg	300 µg	Ph. Eur. and USP	
Polysorbate-20 (vial only)	20 µg	-	200 µg	Ph. Eur. and USP	
Hydrochloric acid	q.s.	q.s.	q.s.	Ph. Eur. and USP	
Sodium hydroxide	q.s.	q.s.	q.s.	Ph. Eur. and USP	
Water for injection	q.s. to 1 mL	q.s. to 3 mL	q.s. to 10 mL	Ph. Eur. and USP	

(b) (4)

Assessor's Comment: *All individual components of the drug product are controlled according to compendial standards.* (b) (4) *3.2.P.4 Control of Excipients of this review memo for more information.*

3.2.P.2 Pharmaceutical Development

(b) (4)

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(b) (4)

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

A stability program was conducted for MYL-1501D DP to assess the effects of DP storage on the quality parameters of the DP (such as description, identification, pH, impurities (related compounds and HMWP), Assay, *m*-Cresol content, visible and subvisible particulate matter, seal integrity, bacterial endotoxins, and sterility). Additionally, friction force test was only performed for DP cartridges, while clarity test and polysorbate 20 content test were only conducted for DP vials. The analytical procedures employed for stability studies are the same as those used for testing and releasing the MYL-1501D DP, and the acceptance criteria are per the specifications for MYL-1501D DP (end of shelf life).

- **Stability Summary for MYL-1501D Cartridge/PFP**

The stability studies for MYL-1501D cartridges/PFPs are being conducted with the primary container closure system (a 3 mL colorless tubular Type I glass cartridge (b) (4) with a plunger stopper). The studies conducted with the drug product in cartridges include formal stability (long-term and accelerated storage conditions), force degradation, and thermal cycling.
The cartridge is further integrated into a pen which does not come into contact with the product.
Functional stability, in-use stability, and photostability studies are conducted for the pre-filled pen to demonstrate the functional stability of the pen device and the quality stability of the DP inside during storage and in-use conditions.

a) Long-term and Accelerated Stability Studies for MYL-1501D Cartridges

Stability studies were performed on multiple batches of MYL-1501D DP which are manufactured using DS from Process IV, V and VI at long-term (5°C ± 3°C) and accelerated storage conditions (25°C ± 2°C, 60 ± 5% RH). An overview of the MYL-1501D DP cartridge batches incepted for stability studies under long-term and accelerated conditions along with available stability data is presented in Table 3.2.P.8.1/2 below (assessor modified).

Table 3.2.P.8.1/2: Stability study for MYL-1501D DP cartridges at long-term and accelerated condition

DP Cartridge Batch#	Batch Size	Corresponding DS Batch and Process	DP Manufacturing Date and Site	Usage of Cartridge Batch	Available Stability Data	
					Accelerated (25°C ± 2°C)	Long term (5°C ± 3°C)
BS15009374	(b) (4)	BS15006908 (VI)	Mar 2016, L2	Process validation batch; Representative batch for Phase 1 clinical study	6 months	36 months
BS15009375		BS15007049 (VI)	Apr 2016, L2		6 months	36 months
BS15009376		BS15006908 (VI) BS15007170 (VI)	Apr 2016, L2		6 months	36 months
BS15005866		BS15005128 (VI)	Nov 2015, L2	Representative batch with process intended for commercialization; Representative batch for Phase 1 clinical study	6 months	36 months
BS15005867		BS15005256 (VI)	Nov 2015, L2		6 months	36 months
BS15006714		BS15005423 (VI)	Dec 2015, L2		6 months	36 months
C13DBBFHH-0002		ED-B13-01-001594 (V)	Dec 2013, L1	Used in Phase 3 clinical trial; Representative batch for Phase 1 clinical study	3 months	36 months
C13DBBFHH-0004		ED-B13-01-001670 (V)	Dec 2013, L1		3 months	36 months
C13DBBFHH-0005		ED-B13-01-001454 (V)	Dec 2013, L1	Representative batch for Phase 3 clinical trial; Representative batch for Phase 1 clinical study	3 months	36 months
C12BFHH-0006		EE-B12-01-000920 (IV)	Jan 2013, L1	Representative batch for Phase 1 clinical trial	6 months	36 months
C12DBBFHH-0005		EE-B12-01-001041 (IV)	Sep 2012, L1		6 months	36 months
C12DBBFHH-0006		EE-B12-01-001088 (IV)	Sep 2012, L1		6 months	36 months
C12BFHH-0005		EE-B11-01-001857 (IV) EE-B12-01-001041 (IV)	Oct 2012, L1		6 months	36 months
C12DBBFHH-0004		EE-B12-01-000829 (IV)	Aug 2012, L1		6 months	36 months
C11DEVB-0001		EE-B11-01-000963 (IV)	Aug 2012, L1		6 months	36 months
C11DEVB-0010		EE-B11-01-000963 (IV)	Nov 2012, L1		6 months	36 months
C11DEVB-0011		EE-B11-01-000963 (IV)	Nov 2012, L1		6 months	36 months

Assessor's Comment: *The provided stability data show that DP in cartridges manufactured at either site L1 or L2 with either Process IV, V or VI DS are all stable for up to 36 months under long-term condition per current specifications. Under accelerated stability conditions, these lots are compliant with current acceptance criteria up to 2~3 months , after which total impurities and/or any individual impurity are out of specifications at 6-month or 3-month timepoint for some batches (data provided in eCTD Section 3.2.P.8.3 Stability Data of the BLA, not reproduced here). The provided data showed that test for related compounds is the stability indicating assay. The Applicant provided information that the assembly process of the cartridge into the pen does not impact the quality attributes of the MYL-1501D DP. Therefore, it is acceptable to use the cartridges for stability evaluation of the PFP DP and in the comparative analytical assessment. In-use stability study and pen functionality study were performed using the PFP. The proposed shelf life is 24 months at 5°C ± 3°C. This is acceptable based on the 36 months long-term stability data provided for the 3 process validation batches and 3 additional DP batches representative of the commercial product.*

b) In-Use Stability Study for MYL-1501D PFPs

In-use stability studies of MYL-1501D DP were executed in order to determine the stability of DP in the pre-filled pens (with 3 mL integrated cartridges) during use. The in-use stability studies were conducted for up to 31 days (at 30°C ± 2°C) since the intended in-use stability condition is 28 days (below 30°C).

The study was designed to simulate the use of MYL-1501D DP in actual practice taking into consideration 2 doses per day by patients for 31 days (as a worst-case scenario). The lined seal was pierced using a BD (Becton Dickinson) 32G × 5/32" (0.23 × 4 mm) needle twice a day while ensuring the needle is in contact with the DP. The pre-filled pens were placed in horizontal position in a clean stability chamber during the course of the study. All samples were tested under 3 in-use conditions, including 30ºC ± 2ºC / 65% ± 5% RH with or without Piercing and 5ºC ± 3ºC (without Piercing) for attributes such as Assay, pH, related compounds, HMWP, *m*-Cresol content, sterility, endotoxins, preservative efficacy, and particulate matter (visible and subvisible), as well as functional tests for the PFP device.
An overview of the MYL-1501D DP PFP batches incepted for in-use stability studies along with available stability data is presented in Table 3.2.P.8.1/5 below (assessor modified).

Table 3.2.P.8.1/ 5: DP PFP Batches Subjected to In-use Stability Studies

PFP Batch#/ Cartridge Batch#	Pen Assembly Site	Cartridge Manufacturing Date and Site	Corresponding DS Batch and Process	Use of PFP Batch	Available Stability Data	
					Age when in-use studies conducted	In-use data
BS15006679/ BS15005866	Bangalore, India (L1)	Nov 2015, L2	BS15005128 (VI)	• Representative batch with process intended for commercialization • Stability study and comparability study	~2 months	31 days
BS15006930/ BS15005867		Nov 2015, L2	BS15005256 (VI)	• Analytical similarity assessment • Representative batch for Phase 1 clinical study	~2 months	31 days
BS15005937/ C13DBBFHH-0005		Dec 2013, L1	ED-B13-01-001454 (V)	• Representative batch for Phase 1/3 clinical studies • Used in stability study and comparability study	~24 months	31 days
BS16000784/ BS15009374		Mar 2016, L2	BS15006908 (VI)	• Pre-filled pen assembly PV batches for site L1	~24 months	31 days
					~36 months	31 days
BS16000807/ BS15009375		Apr 2016, L2	BS15007049 (VI)	• Pre-filled pen assembly PV batches for site L1; • Comparative Safety/Efficacy study for DP from Process VI and V (Study MYL1501D-3004)	~24 months	31 days
					~36 months	31 days
BS16000808/ BS15009376		Apr 2016, L2	BS15006908 (VI) & BS15007170 (VI)	Pre-filled pen assembly PV batches for site L1	~24 months	31 days
					~36 months	31 days
BS18006145/	Johor, Malaysia (L2) (current site)	Mar 2018, L2	BS17007615 (VI)	Representative of intended commercial batches, in-use stability study	~7 months	31 days
BS18006146/		Mar 2018, L2	BS17007706 (VI)	Representative of intended commercial batches, in-use stability study	~7 months	31 days
BS18006147/		Mar 2018, L2	BS17007706 (VI) & BS18002552 (VI)	Representative of intended commercial batches, in-use stability study	~7 months	31 days

Assessor's Comment: *The in-use stability testing conditions represent the worst-case scenario (31 days at 30°C ± 2°C with piercing every day for 24/36-month aged PFPs) of proposed in-use storage (28 days below 30°C) of product that is at the end of shelf life (24 months) , therefore are acceptable.*
The provided stability data show that 24-month aged DP PFP batches which were assembled at site L1 with cartridges either from Process V or VI DS are stable for up to 31 days at 30°C ± 2°C as per current specifications.

The provided data also show that 7-month aged DP PFP batches which were assembled at site L2 with cartridges from Process VI DS are stable for up to 31 days at 30°C ± 2°C as per current specifications. Although in-use stability data was not provided for 24-month aged DP PFP batches assembled at the current site L2, the in-use stability data from 24-month aged DP PFP batches assembled at site L1 may be used for evaluation because long term stability data does not show significant degradation by the end of shelf life, available long term stability data for the L1 and L2 PFP lots is comparable and the pen assembly process at either site L1 or L2 does not impact product quality (refer to section 3.2.P.3.5 Process Validation and/or Evaluation of this review memo for more details). Therefore, the provided in-use stability data support the proposed in-use storage conditions of 28 days below 30°C for MYL-1501D pre-filled pens.
Assessment of microbiology data is deferred to OPMA. Assessment of PFP device related data is deferred to CDRH.

c) Forced Degradation Study for MYL-1501D Cartridges

A comparative forced-degradation (FD) study was performed for MYL-1501D DP cartridges along with its reference product U.S.-licensed Lantus. The FD study was conducted to compare the similarity of stability and degradation profiles of MYL-1501D DP with U.S.-Lantus. This study was also conducted to evaluate the comparability of MYL-1501D DP manufactured with DS from Process V and VI.
In the FD study, the DP cartridges were placed under identical degradation conditions (more severe than real-time storage conditions) in order to compare the product degradation rate, mechanisms and impurity profiles. During a comparative FD study, multiple stress conditions such as high temperature, acidic and alkaline pH, photo exposure, mechanical stress (agitation) and oxidation were implicated on the batches and DP quality attributes were evaluated.

Assessor's Comment: *Forced degradation data are assessed as part of comparative analytical assessment. Refer to section 3.2.R.4.3.6 Comparative Forced Degradation Study for MYL-1501D (cartridge) and U.S.-Lantus (cartridge) of this review memo for more details.*

d) Functional Stability Study of MYL-1501D PFPs

For the purpose of evaluating impact of storage of assembled pre-filled pens at 2ºC to 8ºC on the accuracy of dose delivery, the functionality of the 3 batches of clinical configuration pen was studied for the testing of dose accuracy, dose knob, and audible feedback. Up to 36-month functional stability data are available for pre-filled pen with clinical pen configuration. Furthermore, up to 36-month data are available for the commercial pen configuration from pen assembly PV study performed at Biocon India (site L1), and up to 18-month data are available from the pen assembly PV study performed at Biocon Malaysia (site L2, the current pen assembly site).

Assessor's Comment: *Assessment of functional stability data is deferred to CDRH.*

e) Thermal Cycling Study for MYL-1501D Cartridges

Thermal cycling stability study was conducted for the MYL-1501D DP cartridges to evaluate the effect of excursion of temperatures during the shipping and transportation of the DP.
The DP presented in cartridges was exposed up to 3 thermal cycles over a period of time (freezing to -20ºC ± 5 ºC and then thawing for 30ºC ± 2 ºC, 65 ± 5 % RH and keeping at 2ºC - 8º C for pre-defined long-term) and analyzed for physicochemical and microbiological test parameters to evaluate the impact of thermal cycling on the DP.

Assessor's Comment: *The thermal cycling stability data confirms that the DP in cartridges are stable up to 36 months from inception date (51 months from the date of manufacturing) when subjected to 3 temperatures excursions. The physicochemical and microbiological parameters between the control samples and samples exposed to thermal excursion were found to be comparable. This study demonstrates that up to 3 freeze-thaw thermal cycles do not have impact on the quality of MYL-1501D DP, which also support that temperature excursion of up to 30ºC during DP shipping and transportation would not impact MYL-1501D product quality.*

f) Photostability Study for MYL-1501D PFPs

Results of forced degradation study mentioned above indicate that MYL-1501D DP is sensitive to light, therefore a photostability study was conducted with MYL-1501D DP to assess whether the proposed commercial packaging configuration protects DP from degradation following light exposure experienced during storage and routine use. DP cartridges integrated into pre-filled pens (BS16000784, BS16000807, BS16000808) were exposed to 0.6 M and 1.2 M Lux hours of light intensity and then tested for assay, any individual impurity, total impurities and HMWP. Corresponding DP cartridges not protected within PFP under the same light exposure conditions served as control.

Assessor's Comment: *Photostability data were missing in the original application and were provided by the Applicant on 02/26/2021 upon our request (OBP IR #3) in eCTD Section 1.11.1. The tested light intensity of 0.6 M and 1.2 M Lux hours is acceptable since this is in accordance with ICH Q1B Guideline. The provided photostability data show that tested quality attributes of samples within PFP are all within specifications, compared to those not within PFP which are out of specifications for HMWP, total impurity, any individual impurity and Assay, supporting that the pre-filled pen packaging configuration protects MYL-1501D from degradation following light exposure during routine use. Based on photostability data, it is appropriate that the proposed label includes instruction to store the DP 'protected from light'.*

- **Stability Summary for MYL-1501D Vials**

The stability studies for MYL-1501D vials are being conducted with the primary container closure system (a clear tubular USP Type I glass vial closed with a rubber stopper and sealed with a flip-off seal). The studies conducted with the drug product in vials include formal stability (long-term and accelerated storage conditions), in-use stability, force degradation, thermal cycling, as well as photostability.

a) Long-term and Accelerated Stability Study for MYL-1501D Vials

Stability studies were performed on multiple batches of MYL-1501D presented in vials which are manufactured at site L2 using DS from Process VI and stored horizontally under long-term (5°C ± 3°C) and accelerated storage conditions (25°C ± 2°C, 60 ± 5% RH). An overview of the vial batches incepted for stability studies under long-term and accelerated conditions along with available stability data is presented in Table 3.2.P.8.1/2 below.

Table 3.2.P.8.1/2: Stability data for MYL-1501D vials under long-term and accelerated storage condition

Vial Batch#	DP Batch Size	Corresponding DS batch and process	DP Manufacturing Date and Site	Usage of Vial Batch	Available Stability Data	
					Accelerated (25°C ± 2°C)	Long term (5°C ± 3°C)
BS16002122	(b) (4)	BS15007170 (VI)	June 2016, L2	• Process validation batch • Stability • Comparative PK/PD study for vial and cartridge presentation (Study MYL-1501D-1004)	6 months	36 months

Vial Batch#	DP Batch Size	Corresponding DS batch and process	DP Manufacturing Date and Site	Usage of Vial Batch	Available Stability Data	
					Accelerated (25°C ± 2°C)	Long term (5°C ± 3°C)
BS16002123	(b) (4)	BS15007370 (VI)	June 2016, L2	• Process validation batch • Stability	6 months	36 months
BS16002124		BS15007370 (VI) BS15006908 (VI)	June 2016, L2	• Process validation batch • Stability	6 months	36 months

Assessor's Comment: *The vial batches used for long-term and accelerated stability study represent the proposed commercial manufacturing process and scale at the current site in Johor, Malaysia (L2). The provided stability data show that DP in vials manufactured at site L2 with Process VI DS are all stable for up to 36 months under long-term condition per current specifications and are compliant with current specifications for up to 3 months under accelerated condition, after which time total impurities and any individual impurity are out of specifications at 6-month timepoint for all three batches. The provided data showed that test for related compounds is the stability indicating assay. The proposed shelf life is 24 months at 5°C ± 3°C. This is acceptable based on the 36 months long-term stability data provided for 3 PV batches as described in the table above.*

b) <u>In-Use Stability Study of MYL-1501D Vials</u>

In use stability studies of the MYL 1501D DP in vials were executed to determine the DP stability as a multi-dose product under in-use conditions. The in-use stability studies were conducted for 31 days which includes the physiochemical analysis, microbial tests and the particulate contamination. In addition, a preservative efficacy test is performed at Day 31.

The study was designed to simulate the use of the MYL-1501D DP in actual practice taking into consideration one dose per day by patients for 31 days. The rubber stopper was pierced using (b) (4) 1 mL syringe with 30G BD Ultra-fine needle once a day (considering single dose per day as per indication) while ensuring that the needle is in contact with the DP. The vials are placed horizontally in a stability chambers during the course of the study. Samples were tested for attributes such as clarity, Assay, pH, related compounds, HMWP, *m*-Cresol content, polysorbate 20 content, sterility, endotoxins, (b) (4) and particulate matter (visible and subvisible).

An overview of the MYL-1501D DP vial batches tested under the in-use conditions along with available stability data is presented in Table 3.2.P.8.1/5 below (assessor modified).

Table 3.2.P.8.1/5: DP Vial Batches Subjected to In-use Stability Studies (Mfg: manufacturing)

DP Vial Batch#	DP Mfg Date and Site	DP Batch Size	Corresponding DS batch and process	Usage of Vial Batch	In-use Conditions Tested	Available Stability Data	
						Age when in-use studies conducted	In-use data (30°C ± 2°C)
BS16002122	June 2016, L2	(b) (4)	BS15007170 (VI)	• Process validation batch • Stability • Comparative PK/PD study for vial and cartridge presentation (Study MYL-1501D-1004)	•30°C ± 2°C, 65% ± 5% RH with piercing; •5°C ± 3°C with piercing; •5°C ±3°C without piercing (control)	6~7 months	31 days
						24 months	31 days
						36 months	31 days
BS16002123	June 2016, L2		BS15007370 (VI)	• Process validation batch • Stability	•30°C ± 2°C, 65% ± 5% RH with piercing	6~7 months	31 days
BS16002124	June 2016, L2		BS15007370 (VI) BS15006908 (VI)	• Process validation batch • Stability	•30°C ± 2°C, 65% ± 5% RH with piercing	6~7 months	31 days

Assessor's Comment: *The in-use stability testing conditions represent the worst-case scenario (31 days at 30°C ± 2°C with piercing every day for 24/36-month aged vials) which can cover both the shelf-life (24 months) and label claim (28 days below 30°C) therefore are acceptable.*
Of note, results of polysorbate 20 content for 24-month old batch BS16002122 under all three conditions were missing in the original application, and this issue was communicated to the Applicant in OBP IR#3. On 02/26/2021, Mylan explained that missing polysorbate 20 information was due to instrument breakdown, and this was formally registered in the quality management system and investigated. Subsequently, the in-use study was conducted at 36-month timepoint including polysorbate 20 content to substantiate 24 months shelf-life. Their IR response is acceptable and the polysorbate 20 content for 36-month aged batch BS16002122 was within specification for up to 31 days during in-use stability study. The provided stability data show that 6~7month, 24-month and 36-month aged DP vial batch (BS16002122) which was manufactured at site L2 with Process VI DS are all stable for up to 28 days at 30°C ± 2°C as per current specifications. The provided data also show that 6~7-month aged DP vial batches (BS16002123, BS16002124) which were manufactured at site L2 with Process VI DS are stable for up to 28 days at 30°C ± 2°C as per current specifications. The in-use stability data provided for these 2 batches (BS16002123, BS16002124) did not include maximum aged product at 24-month old, however this is acceptable due to comparable release and stability data (including the in-use stability data here for 6~7-month-old batches) between these 3 PV vial batches (BS16002122, BS16002123, BS16002124). Therefore, the provided in-use stability data here support the proposed labeled in-use storage of 28 days below 30°C for MYL-1501D vials.
Assessment of microbiology data is deferred to OPMA.

c) Forced Degradation Study for MYL-1501D Vials

A comparative forced-degradation study was performed for MYL-1501D DP presented in vial and in cartridge along with the U.S.-Lantus in vial. The FD study was conducted to compare the similarity of the stability and degradation profiles of the MYL-1501D DP in vial with U.S.-Lantus in vial. Further, this study serves to evaluate the comparability of MYL-1501D DP presented in vial and in cartridge.
The same multiple stress conditions as that for the cartridge FD study were implicated on the vial batches and the same DP quality attributes were evaluated.

Assessor's Comment: *Forced degradation data are assessed as part of comparative analytical assessment. Refer to section 3.2.R.4.5.6 Comparative Forced Degradation Study for MYL-1501D (vial) and U.S.-Lantus (vial)of this review memo for more details.*

d) Thermal Cycling Study for MYL-1501D Vials

Thermal cycling stability study was conducted for MYL-1501D DP vial batches to evaluate the effect of excursion of temperatures during the shipping and transportation of the DP.
The DP presented in vials (BS16002122, BS16002123, BS16002124) was exposed up to 2 thermal cycles over a period of time (freezing to -20ºC ± 5 ºC and then thawing for 30ºC ± 2 ºC, 65 ± 5 % RH and keeping at 2ºC - 8º C for pre-defined long-term) and analyzed for physicochemical and microbiological test parameters to evaluate the impact of thermal cycling on the DP.

Assessor's Comment: *The thermal cycling stability data confirms that the DP in vials are stable up to 36 months from inception date when subjected to 2 temperatures excursions. The physicochemical and microbiological parameters between the control samples (2ºC - 8ºC) and samples exposed to thermal excursion(s) were found to be comparable for a period of 36 month. This study demonstrates that up to 2 thermal cycling conditions do not have impact on the quality of MYL-1501D DP, which also support*

that temperature excursion of up to 30ºC during DP shipping and transportation would not impact MYL-1501D product quality.

e) Photostability Study for MYL-1501D Vials

A photostability study was conducted with MYL-1501D vials to assess whether the proposed secondary packaging protects DP from degradation following light exposure during storage and routine use. DP vials (BS16002122, BS16002123, BS16002124) placed in cartons were exposed to 0.6 M and 1.2 M Lux hours of light intensity and then tested for assay, any individual impurity, total impurities and HMWP. Corresponding DP vials not protected within cartons under the same light exposure conditions served as control.

Assessor's Comment: *Photostability data for DP were missing in the original application and were provided by the Applicant on 02/26/2021 in eCTD Section 1.11.1 upon request (OBP IR #3). The tested light intensity of 0.6 M and 1.2 M Lux hours is acceptable since this is in accordance with ICH Q1B Guideline.*
The provided photostability data show that tested quality attributes of vial samples within cartons are all within specifications, compared to those not within cartons which are out of specifications for HMWP, total impurity, any individual impurity and Assay, supporting that the vial secondary packaging protects MYL-1501D from degradation following light exposure during routine use. Based on photostability data, it is appropriate that the proposed label includes instruction to store the DP 'protected from light'.

- **Shelf-Life Proposal and Claim for MYL-1501D DP**

Based on the available long-term stability data from MYL-1501D DP in cartridges/PFPs or in vials, a shelf-life of 24 months is proposed for the DP when stored at 5°C ± 3°C.
Based on the results from the in-use and photostability study for MYL-1501D DP in cartridges/PFPs or in vials, the following storage conditions are recommended for opened/pierced (in-use) vials:
"MYL-1501D DP can be stored for a maximum of 28 days below 30°C or 5°C ± 3°C once opened (in-use), protected from light."

Assessor's Comment: *Both the cartridge/PFP and the vial batches of MYL-1501D DP used in stability studies are representative of different manufacturing sites (L1 or L2), of the quality used in clinical studies, and of the material to be made at the intended commercial scale. This complies with the recommendations of ICHQ5C and is acceptable.*
Overall, the proposed shelf-life of 24 months for MYL-1501D PFP and vial DP when stored at 5°C ± 3°C is supported by long-term stability data obtained from process validation batches and additional batches representative of commercial DP for both the cartridge/PFP presentation and the vial presentation therefore are acceptable. The proposed in-use storage condition "MYL-1501D DP can be stored for a maximum of 28 days below 30°C or 5°C ± 3°C once opened (in-use), protected from light." is supported by in-use stability data on the PFP and vial and is acceptable.

3.2.P.8.2 Post-Approval Stability Commitment

The ongoing stability studies for the MYL-1501D DP will be continued as per the stability program and the acceptance criteria provided in eCTD Section 3.2.P.8.1.
After commercialization, annually one batch of DP will be placed on long-term stability studies (5°C ± 3°C). The annual stability protocol is summarized in Table 3.2.P.8.2/1 below. The acceptance criteria for stability studies will remain the same as provided in eCTD Section 3.2.P.5.1.
On completion of the study and based on the data generated, a shelf life of the DP will be revisited and assigned, in accordance with recommendations from ICH.

Table 3.2.P.8.2/1: Annual stability protocol post-commercialization – long-term condition (5°C ± 3°C)

Tests	Testing Frequency (in months)							
	Initial	3	6	9	12	18	24	36
Description	√	√	√	√	√	√	√	√
Clarity of solution (only for vial)	√	√	√	√	√	√	√	√
Identification (by HPLC)	√	√	√	√	√	√	√	√
pH	√	√	√	√	√	√	√	√
Related compounds (Total impurity and any individual impurity)	√	√	√	√	√	√	√	√
High molecular weight impurities (HMWP) (by SEC)	√	√	√	√	√	√	√	√
m-Cresol content	√	√	√	√	√	√	√	√
Polysorbate-20 (only for vial)	√	√	√	√	√	√	√	√
Particulate contamination (visible particulate)	√	√	√	√	√	√	√	√
Assay (by HPLC)	√	√	√	√	√	√	√	√
Bacterial endotoxins	√	√	√	√	√	√	√	√
Sterility	√	√	√	√	√	√	√	√
Particulate contamination (sub-visible particles ≥10 µm and ≥25 µm)	√	√	√	√	√	√	√	√
Seal integrity	√	√	√	√	√	√	√	√
Friction force test (for information only) (only for cartridge)	√	√	√	√	√	√	√	√

Assessor's Comment: *The original testing schedule in Table 3.2.P.8.2/1 only included testing at initial, 12/24/36-month time points for DP in vial, and initial, 6/12/24/36-month time points for DP in cartridge. This testing schedule is not sufficient to assess the potential stability changes of the product. For products with proposed shelf lives of greater than one year, ICH Q5C recommends that stability studies should be conducted every 3 months during the first year of storage, every 6 months during the second year, and annually thereafter. This issue has been communicated to the Applicant in OBP IR#3 on 02/19/2021. The Applicant provided the above updated annual stability protocol according to our suggestion on 02/26/2021. The updated post-approval stability commitment for MYL-1501D DP is acceptable.*

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3.2.R.4 Comparative Analytical Assessment

Overview of comparative analytical assessment

The comparative analytical assessments provided in Section 3.2.R support the following conclusions:

1. *MYL-1501D is analytically highly similar to U.S-licensed Lantus. Specifically, MYL-1501D pen (cartridge) presentation is highly similar to the pen (cartridge) presentation of U.S.-licensed Lantus, and MYL-1501D vial presentation is highly similar to the vial and the pen (cartridge) presentation of U.S.-licensed Lantus.*
   Note: The proposed presentations of MYL-1501D are a 10 ml vial and 3 ml pre-filled pen integrated with a 3 ml cartridge. The cartridge is the primary container closure system of the pre-filled pen DP and the assembly process of the cartridge into the pen was demonstrated to have no impact on the quality attributes of MYL-1501D. Therefore, it is acceptable to include MYL-1501D cartridge lots in the comparative analytical assessment of MYL-1501D and U.S.-licensed Lantus. The Applicant refers to the US-Lantus lots as 'cartridge' lots throughout the CAA reports. US-Lantus is marketed as a vial and pre-filled pen integrated with a cartridge. The Applicant clarified in the submission that the US-Lantus pre-filled pens are referred to as cartridges in the CAA. For the sake of consistency with the BLA, this memo also refers to these U.S.-Lantus pre-filled pen lots as 'cartridge' lots.

2. *Minor differences were observed for certain attributes, such as Zinc level between MYL-1501D cartridge lots and U.S.-licensed Lantus cartridge lots, and Des R and B3 deamidation levels between MYL-1501D vial lots and US-Lantus vial + cartridge lots. The risks associated with these differences were mitigated by data from orthogonal analytical methods and appropriate manufacturing control (as discussed in respective sections of this memo). These differences do not preclude a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus.*

3. *The MYL-1501D lots included in comparative analytical studies represent commercial scale lots, development lots, clinical lots, and process validation lots, and are considered independent DP lots manufactured from different drug substance (DS) lots. From the 10 MYL-1501D cartridge lots used in the comparative analytical studies, 4 lots were manufactured using Process V DS and 6 lots were produced with DS from Process VI which is the proposed commercial DS manufacturing process. All 5 MYL-1501D vial lots used in the comparative analytical studies were manufactured with Process VI DS. Comparability between lots manufactured using DS Process V and VI has been established. Some differences between Process V and VI were identified in the comparison of glycosylated variants and the A15 deamidation variant; however, residual uncertainty was mitigated by additional information and data to support no meaningful impact on biological behavior of the molecule (Refer to NDA/deemed BLA 210605 CDTL Review and Division Summary Memo for Regulatory Action, June 11, 2020; NDA/deemed BLA 210605 OPQ Executive Summary, May 22, 2020; NDA/deemed BLA 210605 OPQ Executive Summary, April 5, 2018). Therefore, it is acceptable to use MYL-1501D DP lots manufactured using Process V and VI DS in the CAA.*

4. *A total of 24 lots of cartridges and 10 lots of vials of U.S.-Lantus were used in the comparative analytical studies. U.S.-licensed Lantus lots used for the comparative analytical studies are within and span across 36 months of its shelf life. The age of lots at analysis allows for a meaningful comparison to support the demonstration of similarity.*

5. *The comparative analytical studies were performed using appropriate orthogonal analytical methods for each quality attribute, including testing for functional and biological activities, purity and impurities, primary and higher order structure, and drug product specific attributes. The method qualification/validation information provided support the suitability of the methods used in the CAA. Mylan used an acceptable risk-based approach for statistical evaluation of analytical results. The Applicant used appropriately justified quality ranges (mean ± 3 standard deviations) as acceptance criteria for quality range attributes. Other attributes which were assessed by visual comparison of results have been appropriately justified as well.*

6. *The proposed quality ranges, which are based on mean ± 3 standard deviations derived from U.S.-licensed Lantus, are deemed appropriate to serve as similarity acceptance criteria for the applicable quality attributes evaluated using a statistical approach. The Applicant also performed equivalence testing in addition to quality range assessment on assays categorized as Tier 1, however, our assessment only relies on quality range evaluation.*

7. *The comparative forced degradation studies were performed using appropriate conditions, including pH stress, temperature stress, mechanical stress, photo exposure, and oxidative stress. Results of these studies indicate that the stability and degradation pathways of MYL-1501D are similar to U.S.-licensed Lantus and the minor differences observed do not preclude a demonstration of highly similar.*

8. *MYL-1501D is a proposed interchangeable biosimilar to U.S.-licensed Lantus. MYL-1501D has the same formulation and proposed route of administration as U.S.-licensed Lantus. The protein content was evaluated as part of the comparative analytical studies and deliverable volume and fill weight were monitored as part of manufacturing process controls. The results from deliverable volume and fill weight tests support a determination that both presentations of MYL-1501D have the same strength as the corresponding presentations of U.S.-licensed Lantus.*

Regarding the submitted data generated from E.U.-approved Lantus in this section, it has been confirmed by the nonclinical and clinical reviewers that the application does not rely on any data derived from EU-Lantus to support a demonstration of biosimilarity. Therefore, the analytical testing results from the EU-approved Lantus submitted in the BLA were not assessed, as there was no need to establish an adequate scientific bridge. Although data from E.U.-approved Lantus are included in the applicant-provided figures or tables included in this memo, the EU-Lantus is not assessed in this memo.
In the following text, U.S.-licensed Lantus may be referred as U.S.-Lantus.

3.2.R.4.1 Overall CAA Strategy

U.S.-licensed Lantus has two approved presentations (cartridges contained in pre-filled injection pens and vials). The U.S.-Lantus vial presentation has an additional excipient (polysorbate 20 at target concentration of 20 µg/mL) in comparison to cartridge/pre-filled pen formulation. The same as U.S.-Lantus vials, MYL-1501D DP vial has the additional excipient of polysorbate 20 at the same concentration of 20 µg/mL in comparison to cartridge/pre-filled pen formulation. The formulation compositions of two presentations for MYL-1501D in comparison to that of U.S.-licensed Lantus are listed in Table 3.2.P.2.2/1 below.

Table 3.2.P.2.2/ 1: Formulation Compositions of MYL-1501D DP

Sr. No.	Ingredients#	MYL-1501D presented in 3 mL pre-filled pen (Formulation D)	MYL-1501D presented in 10 mL vials (Formulation D with polysorbate 20)	Quantity/mL in Lantus presented in 3 mL cartridges/pre-filled pen	Quantity/mL in Lantus presented in 10 mL vial
1	Insulin glargine	100 Units	100 Units	100 Units	100 Units
2	*m*-Cresol	2.7 mg	2.7 mg	2.7 mg	2.7 mg
3	Polysorbate 20	-	20 µg	-	20 µg
4	Glycerol (b) (4) w/w)	20 mg	20 mg	20 mg	20 mg
5	Zinc	30 µg	30 µg	30 µg	30 µg
6	Water for injection	Quantity sufficient	Quantity sufficient	Quantity sufficient	Quantity sufficient
# Aqueous solutions of sodium hydroxide and hydrochloric acid are used to adjust pH during manufacture.					

Therefore, Mylan's overall CAA strategy includes:

- An assessment conducted to demonstrate analytical similarity between MYL-1501D DP cartridges and U.S.-licensed Lantus cartridges. Results are provided in eCTD Section 3.2.R Regional Information- "CDL/TR/LR.19.0091/20/001- Analytical Similarity Assessment of MYL-1501D with US-approved Lantus and EU-approved Lantus" (referred as CAA report 1 thereafter).
- An assessment conducted to demonstrate analytical similarity between the vial presentation and the cartridge presentation of U.S.-licensed Lantus. The results demonstrate that U.S.-licensed Lantus as DP in cartridge and in vial are highly similar in physicochemical and biological attributes. Results are provided in eCTD Section 3.2.R Regional Information- "CDL/TR/LR.19.0091/20/002- Analytical Similarity Assessment of MYL-1501D (presented in vials) with US-approved Lantus and EU-approved Lantus" (referred as CAA report 2 thereafter).
- Based on the demonstrated similarity between U.S.-licensed Lantus vial and cartridge presentations as described above, results obtained from MYL-1501D vials were compared to the quality ranges established from the combined data of U.S.-licensed Lantus cartridges and vials for the analytical similarity assessment between MYL-1501D vial presentation and U.S.-licensed Lantus. Results are provided in eCTD Section 3.2.R Regional Information- CAA report 2.
- Comparative forced degradation study for MYL-1501D cartridge presentation, under heat, light, oxidative stress, pH stress, and mechanical stress conditions, has been conducted in comparison to U.S.-licensed Lantus cartridge presentation. Results are provided in eCTD Section 3.2.P.8.3 Stability data (prefill-pen).
- Comparative forced degradation study for MYL-1501D vial presentation, under heat, light, oxidative stress, pH stress, and mechanical stress conditions, has been conducted in comparison to U.S.-licensed Lantus vial presentation. Results are provided in eCTD Section 3.2.P.8.3 Stability data (vial).

3.2.R.4.2 Quality Attributes/ Criticality Risk Ranking/ Reference Standards

The approach to determine analytical similarity begins with an assessment and ranking of quality attributes that are relevant to clinical outcomes of safety and efficacy. Mylan has ranked the quality attributes of insulin glargine based on the principles of risk assessment set forth in the ICH Quality Guidelines Q8 and Q9.

A stepwise approach has been used to demonstrate analytical similarity of MYL-1501D with U.S.-licensed Lantus as listed below:

i) Identifying quality attributes that characterize the reference product in terms of its physicochemical and functional properties:

- Product variants that are present due to micro-heterogeneity and may have an impact on safety and efficacy (as listed in Table 1 below).

Table 1:Product Variants That May Have Impact on Safety and Efficacy

Molecular Parameter	Variants
Size	Aggregates / High molecular weight impurities (HMWP)
Sequence variants	Iso-glargine
Charge heterogeneity	pI variants (Des-R and Des-TRR); deamidation and isomerization

- Product attributes: Structural and specific functional attributes that may have an impact on safety and efficacy (as listed in Table 2 below).

Table 2:Structural and Functional Attributes That May Have Impact on Safety and Efficacy

Molecular Parameter	Attributes
Protein concentration	Concentration (U/mL)
Primary structure	Primary amino acid sequence
Higher order structure	Secondary (including disulfide bridging); tertiary and quaternary structure
Biological activity	Binding to target receptor and downstream effects after binding to target receptor (Metabolic activity, Mitogenic activity)
Additional attributes	Zinc content

Assessor's Comment: *The Applicant used a risk-based approach for the comparative analytical assessment. The quality attributes of insulin glargine were ranked according to their relevance to clinical outcomes of safety and efficacy. The selection of product variants and product attributes reflects their impacts on safety and efficacy. This approach is deemed appropriate and meets the Agency's current recommendations for comparative analytical assessment for proposed biosimilar insulin products.*

ii) Ranking quality attributes according to:

(a) their risk to potentially impact activity, PK/PD, safety, efficacy, and immunogenicity;
(b) the degree of uncertainty surrounding a certain quality attribute.

These quality attributes are ranked based on the risk assessment principles set forth in the ICH Quality Guidelines Q8 and Q9. The two risk ranking tools used are: Tool 1 - Impact and Uncertainty and Tool 2 - Severity and Likelihood of Severity. Based on the criticality risk ranking, quality attributes and their corresponding analytical methods were assigned appropriate tiers.

The risk ranks and the rationale for assigning a given quality attribute into these ranks is presented in the following Table 3.

Table 3:Classification of Risk Ranks Based on Criticality

Risk Rank	Rational for Risk Ranking
Very High	Attributes that may have very high impact on the efficacy, immunogenicity, safety, and/or PK/PD
High	Attributes that may have high impact on the efficacy, immunogenicity, safety, and/or PK/PD
Moderate	Attributes that may have moderate impact on the efficacy, immunogenicity, safety, and/or PK/PD
Low	Attributes that do not impact the efficacy, immunogenicity, safety, and/or PK/PD These quality attributes are assessed for maintaining consistent product quality

PD=pharmacodynamics; PK=pharmacokinetics

Assessor's Comment: *The Applicant used Tool 1 for evaluating the product variants and Tool 2 for evaluating the structural and functional attributes. The selection of risk ranking tools is appropriate for categorizing the risk levels of critical quality attributes (CQA).*

iii) Defining the statistical approach for analyzing data for each tiered quality attribute and corresponding analytical method.

Statistical approach to establish analytical similarity is based on a tiered system in which approaches of varying statistical rigor are used. Tiers have been assigned for various tests that are associated with the quality attributes, primarily based on criticality of the quality attributes. Quality attributes with very high risk and having a direct impact on the safety and efficacy of the product and the associated cell-based assays measuring these are categorized in Tier 1. In addition to criticality, other factors have also been considered in assigning tests associated with these quality attributes to a particular tier, including the nature of data generated by an analytical test and its amenability for statistical testing. Therefore, many attributes, especially those used for the determination of higher order structure, have been ranked as high risk but categorized as Tier 3. Also, based on the testing outcomes for the same quality attribute, some orthogonal tests are placed in a lower tier even though they are amenable to statistical assessments, as compared with others that are considered in a higher tier. The tiered system employs varying degrees of statistical rigor of assessment for each tier as described below.

- **Tier 1: Equivalence Test**

Equivalence Test with the Null hypothesis H0: $\mu T - \mu R \leq$ - δ or $\mu T - \mu R \geq$ δ was tested:

- Where μT stands for mean of tested product; μR stands for mean of reference product; and δ stands for pre-determined equivalence margin (EM) based on variability of the reference product (±1.5*standard deviation [σR]).
- The confidence interval approach was used to determine whether the means for functional biological measures with Test product and Reference product are similar.
- Similarity between two products was confirmed if the 90% CI of the mean difference is within the corresponding equivalence margin (- 1.5*σR, + 1.5*σR).
- When the number of reference product lots is much larger than the number of proposed biosimilar lots (e.g., more than 50 %), the following equation is made for sample size imbalance adjustment to calculate the CI of the mean difference: ($X\bar{T}$ –$X\bar{R}$) ±t1-α, df×sqrt (SB2 /nB + SR2 / nR*)

Where nR* =min (1.5*nB, nR), nB and nR are respectively the number of the proposed of the proposed biosimilar lots and the number of the reference product lots; and $X\bar{T}$ and $X\bar{R}$ are respectively the sample mean of the proposed biosimilar lots and the sample mean of the reference product lots; SB2 and SR2 are respectively the sample variance estimated by all proposed biosimilar and the reference lots; t1-α, df

is 1-α quantile of the t-distribution with degrees of freedom df, where df can be approximated by the Satterthwaite method. If the number of the proposed biosimilar lots, nB, is 50% more than the number of reference product lots, nR, a similar approach was applied with nB* =min (1.5×nR, nB) for the confidence interval calculation. Statistical analysis was done with SAS or R software.

- **Tier 2: Quality Ranges**

The quality range (QR) limits for the assays in Tier 2 were set based on the range of the values obtained for reference product variation, expressed as 3 times Standard Deviation (SD). The limits of mean ± 3SD have been considered appropriate based on the following:

- Low variability across multiple analytical methods (<20%)
- Observed variability of the reference product lots spanning the shelf life.
- Low numerical values for multiple quality attributes (impurities and related substances).
- In multiple analytical methods, a limit less than ± 3SD was found to be non-inclusive of the true observed reference product distribution.
- Number of reference product lots analyzed per test (10–22) for primary methods monitoring key quality attributes).

Analytical similarity would be accepted for the given quality attribute if at least 90% of test lot values fall within the QR as established from the US-approved Lantus® reference product lots analyzed. The lower and upper limits of the QR are calculated as follows:

Lower limit = MeanR – 3σR

Upper limit = MeanR + 3σR

σR represents the observed standard deviation from the innovator reference product lots, and MeanR represents the observed mean value from the U.S.-licensed Lantus lots for the respective quality attributes.

- **Tier 3: Graphical Representation and Data Tables**

Quality attributes with a moderate or low risk ranking are categorized in Tier 3. In addition, attributes measured by methods with qualitative outputs despite being ranked as Very High or High are included in Tier 3. Also, attributes which are measured by multiple orthogonal methods have one method categorized in the higher Tier 2 and the rest in Tier 3. These orthogonal methods are amenable to statistical assessment of QR and are still categorized in Tier 3. Attributes such as amino acid sequence are qualitative in nature but have numerical outcomes and therefore, are assessed by the Min-Max range determined from the reference product. Where applicable the qualitative profile of the proposed biosimilar MYL-1501D should match with the profile of the U.S.-licensed Lantus. For these attributes raw data/scatter plot distributions are used for assessment of similarity.

Assessor's Comment: *Per current Agency recommendation, "Guidance for Industry: Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations" (DRAFT GUIDANCE, May 2019), the Agency no longer recommends methods such as tolerance intervals be used for establishing the similarity acceptance criteria. Therefore, the criticality risk ranking approach was adopted and a quality range approach was used by the Assessor in the assessment of analytical similarity for statistically evaluated data. Although Mylan performed equivalence testing in addition to quality range approach on assays categorized as Tier 1, our similarity determination relies on the assessment by the quality range (mean ± 3 standard deviations) approach. Overall, Mylan's statistic approach for data analyzing is acceptable.*

iv) Analytical Similarity Assessment

The analytical similarity between MYL-1501D and U.S.-licensed Lantus was assessed by combining data from side-by-side testing of the products as well as stand-alone analyses conducted at different times during product development. All the lots of U.S.-Lantus and MYL-1501D products analyzed were within their respective shelf life.

The quality attributes with corresponding tests used for similarity assessment are listed in Table 5 below. Table 5 is modified by the Assessor with information combined from CAA report 1 and CAA report 2, for the cartridge presentation and the vial presentation of MYL-1501D and U.S.-Lantus.

Table 5: Quality attributes and the corresponding tests and assessment (assessor modified)

Quality Attribute		Risk Rank	Tier	Methods/tests	Analysis location	Assessment
Protein content (assay)		Very High	1	RP-HPLC assay	BRL	Equivalence testing, quality ranges
Amino acid sequence (primary structure)		Very High	3	Peptide mapping (reduced/non-reduced)	BRL	Profile comparison/overlay, data table
			3	Intact mass	BRL	Profile comparison/overlay, data table
			3	Reduced intact mass	BRL	Profile comparison/overlay, data table
Disulfide conformation and secondary structure		Very High	3	Peptide mass fingerprint-non reduced	BRL	Profile comparison/overlay, data table
			2	Far UV CD	BRL	Quality ranges (mean±3SD)
			2	Fourier transform infrared spectroscopy	BRL	Quality ranges (mean±3SD)
Higher order structure		Very High	3	Extrinsic fluorescence	BRL	Profile comparison/overlay, data table
			3	Near UV CD	BRL	Profile comparison/overlay, data table
			3	Differential scanning calorimetry (DSC)	Mylan Labs	Profile comparison/overlay, data table
			3	Intrinsic fluorescence	BRL	Profile comparison/overlay, data table
			3	Nuclear magnetic resonance (NMR)	(b) (4)	Profile comparison/overlay, data table
			3	X-ray crystallography		Profile comparison/overlay, data table
Size variant	Aggregates/ HMWP	High	2	SEC-HPLC	BRL	Quality ranges (mean±3SD)
			3	SEC-MALS	BRL	Profile comparison/overlay, data table
			3	Analytical ultracentrifuge (AUC)	(b) (4)	Profile comparison/overlay, data table
Isoelectric Point (pI)		Moderate	2	Capillary isoelectric focusing (cIEF)	BRL/Mylan Labs[#]	Quality ranges (mean±3SD)
pI variant	Des-TRR	Moderate	2	RP-HPLC	BRL	Quality ranges (mean±3SD)
	Des-R	Moderate	2	RP-HPLC	BRL	Quality ranges (mean±3SD)
Deamidation	B3, A15	Low	2	RP-HPLC	BRL	Quality ranges (mean±3SD)
Conjugate variants	Glycerol ester	Moderate	2	RP-HPLC	BRL	Quality ranges (mean±3SD)
	Citric acid conjugate	Moderate	2	RP-HPLC	BRL	Quality ranges (mean±3SD)
	Acetylation	Moderate	2	RP-HPLC	BRL	Quality ranges (mean±3SD)
Excipient	Zn content	Moderate	2	Atomic absorption spectrometry (AAS)	BRL	Quality ranges (mean±3SD)
Metabolic activity		Very High	2	IR-B (long form) receptor binding kinetics	(b) (4)	Quality ranges (mean±3SD)
			1	IR-B receptor auto-phosphorylation	BRL	Equivalence testing, quality ranges
			1	IR auto-phosphorylation in HepG2	BRL	Equivalence testing, quality ranges
			2	Glucose uptake activity in 3T3-L1 cells	BRL	Quality ranges (mean±3SD)
			2	Adipogenesis assay*	(b) (4)	Quality ranges (mean±3SD)
			2	Lipolysis inhibition assay*		Quality ranges (mean±3SD)
Mitogenic activity		Very High	2	IR-A (short form) receptor binding kinetics		Quality ranges (mean±3SD)
			1	IR-A receptor auto-phosphorylation	BRL	Equivalence testing, quality ranges
			1	IGF-1 receptor binding kinetics	BRL	Equivalence testing, quality ranges

Quality Attribute	Risk Rank	Tier	Methods/tests	Analysis location	Assessment
		2	Cell proliferation assay in Saos-2 cells	BRL	Quality ranges (mean±3SD)
In-vivo potency	Very High	2	Rabbit bioassay USP <121>*	(b) (4)	Quality ranges (mean±3SD)

*: assays only performed for Comparative Analytical Assessment of MYL-1501D (cartridge) vs U.S.-Lantus (cartridge).
#: Mylan Labs only performed cIEF for the cartridge presentation of MYL-1501D and U.S.-Lantus.
BRL: Biocon Research Limited (India)
Mylan Labs: Mylan Pharmaceuticals Private Limited (India)

(b) (4)

The detailed information for all testing sites is listed in the table below (assessor generated).For all the testing performed at each site, refer to the column "analysis location" in the above Table 5.

Site	BRL	Mylan Labs
Full name and address	Biocon Research Limited – SEZ Unit Biocon Special Economic Zone, Plot Nos. 2&3, Phase IV-B.I.A, Bommasandra-Jigani Link Road, Bangalore, 560099, India	Mylan Pharmaceuticals Private Limited, Global Biologics R&D Centre, 2nd Floor, Building # 450 Alexandria Knowledge Park, Genome Valley, Shameerpet Mandal, R.R District, Hyderabad, 500078, India

(b) (4)

Assessor's Comment: *Information for testing sites is missing in CAA report 1 so an information request (IR) (OBP IR #2) was sent to Mylan on 02/09/2021 and Mylan provided such information on 02/16/2021 as shown in the above table. Mylan's response is acceptable.*

The Applicant used a standard approach for risk assessment which is generally acceptable according to current Agency expectation. The Applicant selected a series of state-of-the-art analytical methods to assess similarity with respect to the function, structure, and heterogeneity of MYL-1501D and U.S.-licensed Lantus. For most of the quality attributes, including for metabolic activity, mitogenic activity, primary/secondary/higher order structure, the Applicant included several orthogonal methods for analysis, which could provide better assurance for the similarity determination. The Applicant stated that all methods were validated or qualified at the time of testing and demonstrated to be suitable for the intended purpose. Methods used in the CAA that are also used for release and stability testing such as protein content/Assay by RP-HPLC, product related substances by RP-HPLC, zinc content, HMWP by SEC, have been validated and the validation reports are provided in eCTD Section 3.2.P.5.3 Validation of Analytical Procedures. Refer to section 3.2.P.5.3 Validation of Analytical Procedures of this review memo for detailed assessment about method validation. Method qualification information for IR phosphorylation assay in HepG2, IR-A or IR-B phosphorylation assay, IGF-1 receptor binding kinetics assay by SPR, glucose uptake assay in 3T3-L1 cells, and cell proliferation assay in Saos-2 cells was provided in Study

BDL/TR/BR.15.003/16/002 of eCTD Section 4.2.1.1 Primary Pharmacodynamics and is found acceptable. Brief descriptions of each method are provided in the respective sections. Overall, the information provided about the methods, and method qualification/information support the suitability of the methods used in the CAA.

A tier-based strategy was used to evaluate the assay results for the comparative analytical assessment. The Applicant assigned different statistical strategy for assessing the CAA results of methods that belong to different tiers, as discussed in statistical approach previously. Per current Agency recommendation, a tier strategy and equivalence testing are no longer recommended for similarity assessment. Therefore, the Assessor used the criticality risk ranking for evaluation of comparative analytical assessment. Although the Applicant performed assessment by both the equivalence testing and quality range approach on assays categorized as Tier 1, our similarity determination only relies on the assessment of quality range provided by the Applicant.

The applicant's risk ranking is acceptable. The Applicant ranked deamidation variants B3 and A15 as 'Low'; these attributes are expected to be ranked moderate to high risk according to current OBP expectation. However, since the applicant provided quantitative data and an assessment using quality ranges, the applicant's approach is acceptable.

Comparative forced degradation studies were performed for MYL-1501D both the cartridge and the vial presentation, to compare the rates and degradation pathways between MYL-1501D and U.S.-licensed Lantus.

Some CQAs, such as host cell proteins (HCP), host cell DNA (HCD), are not appropriate for direct comparison of MYL-1501D to U.S.-Lantus due to differences in the manufacturing processes and different production host cells. These attributes, together with some other attributes, such as visual appearance, pH, osmolarity, particulate matter (visible and subvisible particulate), were not included in the comparative analytical studies but assessed as part of the commercial control strategies of MYL-1501D. This approach is consistent with recommendations in the FDA Draft Guidance for Industry Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations (2019) and is therefore acceptable.

In summary, the Applicant's overall approach for comparative analytical assessment appears to be reasonable and adequate. The results presented in CAA report 1 and CAA report 2 are discussed in the following sections.

v) Reference standards used for the comparative analytical assessment

Assessor's Comment: *In either CAA report 1 or report 2, Mylan did not provide information about reference standard (RS) used in assays where results are reported relative to a. In response to the Agency's IR (OBP IR #2 sent on 02/09/2021), on 02/16/2021, Mylan provided information of reference standards used in each assay and results for bridging studies if different reference standards were used in an assay. The information provided by Mylan is summarized as below.*

Information on the reference standards used in the CAA report 1 and 2 for each assay that requires RS are presented in the following Table 2.

CAA Report No. and Study	Tests	Reference Standard Used	Comments
CDL/TR/LR. 19.0091/20/001 (CAA report 1) Analytical similarity assessment of MYL-1501D (cartridges) with U.S.-licensed Lantus	• Protein content/ Assay	(b) (4) (source batch: BS15005256)	The batches in this study were analyzed against one of these standards. (b) (4) were qualified against the EPCRS lot 1.0.
	• IR-A phosphorylation assay • IR-B phosphorylation assay • IR autophosphorylation in HepG2 • Glucose uptake assay • Adipogenesis assay • Inhibition of stimulated lipolysis assay • Cell proliferation assay in Saos-2 cells	(b) (4) Source batch: BS15002192	All batches in this study were assessed with the same reference standard.
	• Rabbit Bioassay	USP Human Insulin Glargine Std F009M0 and USP Human Insulin standard JOJ250	USP standards (Human Insulin and Insulin Glargine) were used as reference standards for the evaluation.
CDL/TR/LR. 19.0091/20/002 (CAA report 2) Analytical similarity assessment of MYL-1501D (vials) with U.S.-licensed Lantus	• Protein content/ Assay	(b) (4) (source batch: BS15005256)	The batches in this study were analyzed against one of these standards. (b) (4) were qualified against the EPCRS lot 1.0.
	• IR-A phosphorylation assay • IR-B phosphorylation assay • IR autophosphorylation in HepG2 • Glucose uptake assay • Cell proliferation assay in Saos-2 cells	(b) (4) Source batch: BS15005256	All batches in this study were assessed with the same reference standard. Data from U.S.-Lantus vial and cartridge batches were pooled to evaluate and conclude on this assessment. Bridging studies for the two RS ((b) (4) were provided).

For the protein content/Assay, multiple lots of reference products were used. Mylan presented details of the reference standard used for protein content/ Assay in both CAA report 1 and 2 in Table 3 to Table 7 of the IR response. The details are not shown here. Mylan also provided summary of bridging studies performed between different reference standards in the following Table 8 and 9.

Table 8: Summary of Bridging Experiments in Functional Assays where two Reference standards have been used in comparative analytical assessment

Functional assays *(which report results relative to the reference standard)*	IRS Qualified	Qualified against	No. of Replicates	Mean Observed Relative Potency	Acceptance Criteria	Report Numbers
IR-A Phosphorylation assay	(b) (4)		4	1.06	0.90 - 1.10	BDL/SAR/BR.15.0003/16/004
IR-B Phosphorylation assay			4	1.03		
IR auto-phosphorylation in HepG2			4	1.04		BDL/SAR/BR.15.0003/16/001
Glucose uptake assay			4	1.09		BDL/SAR/BR.15.0003/16/004
Cell proliferation assay in Saos-2 cells			4	1.02		

Table 9: Summary of Data for Protein content/Assay obtained during reference standard qualifications

S. No	Reference standard	Qualified Against	Acceptance criteria	%Assay
1	(b) (4)	EPCRS LOT 1.0	Between 95.0% and 105.0% w/w	99.1%
2				98.0%
3				98.0%

Note: The value obtained for the reference standard when tested against the EP CRS is assigned as the assay of the reference standard.

Assessor's Comment: *Summary of bridging studies in Table 8 above indicates two references standards* (b) (4) *used in these assays for biological activity measurements were comparable, therefore support the pooling of data from various runs of the corresponding assays in CAA report 2 during the similarity assessment between MYL-1501D (vial presentation) and U.S.-Lantus (vial and cartridge presentation).*
Summary of bridging studies in Table 9 indicates the three references standard (b) (4) *used in protein content/Assay all performed very similarly to the common reference standard EPCRS LOT 1.0, therefore support the pooling of data from various runs of protein content/Assay in CAA report 1 and report 2.*
Overall, Mylan's response about reference standards used is acceptable and the presented data support the pooling of data from various runs of each corresponding assays in CAA report 1 and report 2.

3.2.R.4.3 Comparative Analytical Assessment between MYL-1501D (cartridge) and U.S.-licensed Lantus (cartridge)

Mylan stated that data used for assessment in CAA report CDL/TR/LR.19.0091/20/001 (referred as CAA report 1 in the following context) are obtained from either side-by-side testing or stand-alone analysis conducted at different times during MYL-1501D product development. The situation is the same for CAA report CDL/TR/LR.19.0091/20/002 (referred as CAA report 2 in the following context).

A summary of the analytical similarity results for MYL-1501D (cartridge) and U.S.-licensed Lantus (cartridge) are provided in the following table (assessor generated based on results presented in CAA report 1, QR: quality range). For attributes that are evaluated using quality ranges, when at least 90% of MYL-1501D lots are within the U.S.-Lantus QR, the results support a demonstration of highly similar. In the following table, 'Yes' is indicated when similarity acceptance criteria are met or if the differences observed do not preclude a demonstration of highly similar.

Parameter	Quality Attribute	Test Method	Number of Batches U.S.-Lantus (cartridge): MYL-1501D (cartridge)		U.S.-Lantus (cartridge) Min-Max Range (QR: Mean±3SD)	MYL-1501D (cartridge) Min-Max Range	Support a Demonstration of Highly Similar between MYL-1501D and U.S.-Lantus
Protein content	Protein content/ Assay	RP-HPLC (% Assay: U/mL)	22:10		95.0~107.2 (QR: 87.9~111.1) (lot 4F1270A is 107.2, making QR wide)	97.2~102.1	Yes
Metabolic activity	IR-B binding kinetics	Surface Plasmon Resonance (SPR) k_a (1/Ms) k_d (1/s) K_D (nM)	8:8	k_a	6.82E+05~7.55E+05 (QR: 6.18E+05 ~8.06E+05)	6.41E+05~ 7.54E+05	Yes
				k_d	0.011~0.015 (QR: 0.008~0.017)	0.011~0.014	
				K_D	15.36~20.40 (QR: 11.63~23.73)	15.81~18.37	
	IR-B auto-phosphorylation	IR-B auto-phosphorylation assay (relative potency)	22:10		0.94~1.21 (QR: 0.88~1.26)	0.97~1.18	Yes
	IR auto-phosphorylation	IR auto-phosphorylation assay using HepG2 cells (relative potency)	22:10		0.86~1.18 (QR: 0.80~1.25)	0.91~1.14	Yes
	Glucose uptake activity	Glucose uptake assay in 3T3-L1 cells (relative potency)	8:8		0.94~1.12 (QR: 0.86~1.21)	0.97~1.18	Yes
	Adipogenesis assay	Adipogenesis assay using 3T3-L1 cells (relative potency)	8:8		0.89~1.80 (QR: 0.25~1.99) (lot 4F1270A is 1.80, resulted in wide QR)	0.71~1.10	Yes
	Inhibition of stimulated lipolysis assay	Inhibition of stimulated lipolysis assay using 3T3-L1 cells (relative potency)	8:8		0.574~1.550 (QR: 0.00~1.87) (lot 4F1270A is 1.550, resulted in wide QR)	0.749~1.350	Yes
Mitogenic activity	IR-A binding kinetics	SPR k_a (1/Ms) k_d (1/s) K_D (nM)	8:8	k_a	1.18E+06~1.70E+06 (QR:1.00E+06~2.02E+06)	1.33E+06~ 1.88E+06	Yes
				k_d	0.023~0.036 (QR: 0.017~0.043)	0.026~0.041	
				K_D	17.62~22.75 (QR: 14.37~25.36)	18.80~23.29	
	IR-A auto-phosphorylation	IR-A auto-phosphorylation assay (relative potency)	22:10		0.97~1.17 (QR: 0.89~1.24)	0.95~1.19	Yes
	IGF-1 receptor binding kinetics	SPR k_a (1/Ms) k_d (1/s) K_D (nM)	22:10	k_a	1.47E+05~1.96E+05 (QR:1.37E+05~2.05E+05)	1.53E+05~ 1.76E+05	Yes
				k_d	0.04578~0.05421 (QR: 0.04352~0.05556)	0.046~0.051	

Parameter	Quality Attribute	Test Method	Number of Batches U.S.-Lantus (cartridge): MYL-1501D (cartridge)		U.S.-Lantus (cartridge) Min-Max Range (QR: Mean±3SD)	MYL-1501D (cartridge) Min-Max Range	Support a Demonstration of Highly Similar between MYL-1501D and U.S.-Lantus
				K_D	0.26~0.34 (QR: 0.22~0.36)	0.27~0.32	
	Cell proliferation assay	Cell proliferation assay in Saos-2 cells (relative potency)	8:8		0.92~1.19 (QR: 0.72~1.35)	0.88~1.12	Yes
Size variant	High Molecular Weight Protein (HMWP)/ Aggregates	SEC-HPLC (% HMWP)	22:10		LOD: 0.015%, LOQ: 0.050%		Yes
					BQL~0.06 (QR: 0.04~0.06)	BQL~0.06	
		SEC-MALS	10: 10	Mass fraction (%)	100 (QR:100~100)	100	Yes
				Mw/Mn	1.001~1.006 (QR: 0.999~1.007)	1.002~1.005	
				Mz/Mn	1.002~1.012 (QR: 0.997~1.016)	1.004~1.010	
		AUC–sedimentation velocity	3:9	Monomer sedimentation coefficient (S)	1.61~1.64 (QR: 1.59~1.65)	1.60~1.65	Yes
				Total aggregate fraction (%)	0.0~3.2 (QR: 0~5.9)	0.0~3.9	
Product variant	Glyceridic ester of Glutamic acid	RP-HPLC (%) LOD: 0.015% LOQ: 0.040%	22: 10	RRT: 0.96~0.98	0.14~0.34 (QR: 0.05~0.45)	0.11~0.30	Yes
	Insulin glargine			RRT: 1	98.42~99.24 (QR: 97.93~99.66)	98.85~99.60	
	A15 deamidation			RRT: 1.02~1.03	0.16~0.42 (QR: 0.01~0.57)	0.10~0.29	
	Des R & B3 deamidation			RRT: 1.04~1.08	0.17~0.40 (QR: 0.04~0.56)	0.05~0.22	
	Des TRR			RRT: 1.14~1.18	BDL~0.10 (QR: 0.00~0.11)	BDL	
	Citrate conjugate			RRT: 1.16~1.25	BDL~0.09 (QR: 0.03~0.10)	BDL~0.06	
	Acetylation			RRT: 1.24~1.34	BQL~0.06 (QR: 0.03~0.07)	BDL~0.04	
Isoelectric point (pI)	Isoelectric point (pI)	Capillary Iso-Electric Focusing (cIEF)	15:10		7.00~7.06 (QR: 6.98~7.09)	7.00~7.06	Yes
Primary structure & disulfide confirmation	Intact mass	ESI-MS Mass spectrometry (Da)	22:10		6063.5~6063.9	6063.4~6063.7	Yes
	Intact mass of chain A and chain B	Reduced ESI-MS by DTT to separate into chain A and chain B (Da)	22: 10	Chain A	2326.8~2327.4	2326.9~2327.1	Yes
				Chain B	3742.9~3743.2	3742.8~3743.0	
	Disulfide confirmation	Non-reduced peptide mass fingerprinting (PMF) using Glu-C analyzed with LC-MS and MS-MS (Da)	22: 10	Fragment 4	417.1	417.1	Yes
				Fragment 3	1428.7~1429.4	1428.6~1428.8	
				Fragment 2	1320.5~1320.6	1320.5~1320.6	
				Fragment 1	2969.1~2970.6	2969.1~2969.9	
		Reduced (DTT) PMF using Glu-C analyzed with LC-MS and MS-MS (Da)	22: 10	Fragment 6	456.0~456.1	456.0	Yes
				Fragment 5	417.1	417.1	
				Fragment 4	1428.7~1429.2	1428.7~1428.8	
				Fragment 3	1482.7~1482.8	1482.7~1482.8	
				Fragment 2	867.3~867.4	867.3	
				Fragment 1	1490.5~1490.7	1490.5~1490.7	
Secondary structure	Secondary structure (α-helix, β-sheets, β-turns and random coil)	Far UV-CD Spectra	22: 10	α-helix %	18.7~28.7 (QR: 17~33)	26.6~30.2	Yes
				β-sheet %	33.1~54.1 (QR: 25~59)	45.0~49.9	
				β-turn %	5.9~18.8 (QR: 3~22)	6.2~9.9	
				Random coil %	17.9~22.9 (QR: 15~25)	15.0~17.5	
				α-helix %	22~33 (QR: 19~36)	23~31	Yes

Parameter	Quality Attribute	Test Method	Number of Batches U.S.-Lantus (cartridge): MYL-1501D (cartridge)		U.S.-Lantus (cartridge) Min-Max Range (QR: Mean±3SD)	MYL-1501D (cartridge) Min-Max Range	Support a Demonstration of Highly Similar between MYL-1501D and U.S.-Lantus
		Fourier Transform Infrared (FT-IR) Spectroscopy	22:10	β-sheet %	20~33 (QR: 16~36)	23~31	
				β-turn %	21~23 (QR: 20~24)	21~22	
				Random coil %	23~25 (QR: 22~27)	23~24	
				Amide I (cm^{-1})	1646.91~1650.77 (QR: 1644.97~1654.11)	1646.91~1648.84	
				Amide II (cm^{-1})	1536.99~1540.85 (QR: 1536.41~1543.01)	1538.92~1540.85	
Higher order structure	Higher order structure	Nuclear Magnetic Resonance (2D-NMR)	1:2		Similar 2D-NMR spectra were observed between MYL-1501D and U.S.-Lantus. The disulfide linkages between A6-A11, A7-B7 and A20-B19 were confirmed.		Yes
		Intrinsic Fluorescence (λ_{max}: nm)	10:10		300.93~302.03 (QR: 299.76~302.54)	300.00~302.03	Yes
		Extrinsic Fluorescence (λ_{max}: nm)	22:10		473~483 (QR: 468.3~487.3)	474~478	Yes
		Near UV-CD Spectra	22:10		Similar near UV-CD spectra were observed between MYL-1501D and U.S.-Lantus.		Yes
	Thermal stability	Differential Scanning Calorimetry (DSC) (Tm: °C)	10:10		68.40~73.48 (QR: 66.41~75.79)	70.21~73.85	Yes
	Crystal structure	X-Ray Crystallography	1:2		The 3D-structures of US-Lantus and MYL-1501D are similar to each other and to the previously determined 3D-structures of insulin glargine.		Yes
Excipient	Zinc content	Atomic Absorption Spectrometry (AAS) (µg/100 U)	22:10		27.8~30.5 (QR: 27.3~31.2)	27.9~33.0 (Zinc content is 33.0 for lot BS15005876, and 31.8 for BS15002330)	Yes

Assessor's Comment: *Results for zinc content do not meet the similarity acceptance criteria. However, the observed difference does not preclude a demonstration that MYL-1501D is highly similar to US-Lantus, as discussed in section 3.2.R.4.3.5 Zinc Content by Atomic Absorption Spectrometry (AAS) of this memo.*

Lots used in the comparative analytical assessment between MYL-1501D cartridges and US-Lantus cartridges

The lots of products used in the analytical similarity comparison are listed in Table 6 below.

Table 6: List of MYL-1501D, EU-approved Lantus and US-licensed Lantus lots (cartridge) used for CAA.

Sl. No	EU-approved Lantus® Lots*		US-approved Lantus® Lots*		MYL-1501D Lots*	
	Lot Number	Expiry date	Lot Number	Expiry date	Lot Number	Manufacturing date
					Using Process V DS	
1	4F789A	Sep-17	4F1179A	Mar-17	BS15005851	Nov-15
2	5F035A	Dec-17	4F1227A	Aug-17	BS15005852	Nov-15
3	5F1325A	Jul-17	4F1270A	Jul-17	BS15005853	Nov-15
4	5F1446A	Jul-17	5F1296A	Aug-17	BS15002330	July-15
5	5F1709A	Oct-17	5F1357A	Aug-17	Using Process VI DS	
					BS15005866	Dec-15
6	5F1895A	Dec-17	5F1492A	Apr-17	BS15005867	Dec-15
7	5F2004A	Jan-18	5F1524A	Aug-17	BS15006714	Jan-16
8	5F2014A	Jan-18	5F1568A	Mar-17	BS15009374	Mar-16
9	5F2228A	Dec-17	5F1710A	Sep-17	BS15009375	Mar-16
10	5F2251A	Feb-18	5F1739A	Oct-17	BS15009376	Apr-16
11	4F209A	Apr-17	3F420A	May-16		
12	5F869B	Jan-18	3F393A	May-16		
13	5F1792A	Dec-17	3F425A	May-16		
14	5F1991A	Dec-17	4F924A	Jun-16		
15	5F1953A	May-17	4F723A	Sep-16		
16	5F1972A	Jan-18	3F417A	May-16		
17	5F1511A	Mar-17	3F072A	May-16		
18	3F105A	Mar-16	4F1023A	Apr-17		
19	3F124A	May-16	4F658A	Apr-17		
20	5F1324A	Jul-17	4F1050A	May-17		
21	5F038A	Dec-17	4F614A	May-17		
22	4F173A	Dec-16	4F655A	Jun-17		
23			1F759A	Jun-14		
24			1F767	Jun-14		

* All MYL-1501D, EU-approved Lantus® and US-approved lots were tested within their expiry

Detailed information for MYL-1501D cartridge lots used above is listed in the following table (assessor modified, Mfg: manufacturing).

MYL-1501D (cartridge) Lot #	DP Lot Size	DP Mfg Date & Site	Use of MYL-1501D Cartridge Lot	From DS Batch #	DS Batch Size	DS Mfg Process	DS Mfg Date & Site

					(b) (4)		
BS15005851	20 L	Nov-2015 Bangalore, India (II)	• Comparative Safety/Efficacy study (MYL-1501D-3004) for product from Process VI or V • Representative batch for Phase 1 clinical study; • Used in toxicity study U-16176	BS14002199 (DS dispatch lot # BS15005781)			Mar-2014 Biocon, India (L1)
BS15005852	20 L	Nov-2015 Bangalore, India (II)	• 3-way PK/PD study (MYL-1501D-1001) using DP from Process V, VI and Lantus US • Comparative PK/PD study (MYL-1501D-1003) for product from Process VI and V	BS14002200 (DS dispatch lot # BS15005782)		V	Mar-2014 Biocon, India (L1)
BS15005853	20 L	Nov-2015 Bangalore, India (II)	• Comparative Safety/Efficacy study (MYL1501D-3004) for product from Process VI and Process V	ED-B13-01001454			Oct-2013 Biocon, India (L1)
BS15002330	50 L	July-2015 Bangalore, India (II)	• Safety and efficacy study in T1DM patients (MYL-GAI-3001) • Safety and efficacy study (MYLGAI-3003)	BS14002199			Mar-2014 Biocon, India (L1)
BS15005866	900 Kg	Dec-2015 Biocon, Malaysia (L2)	• Representative batch with process intended for commercialization; • stability study; comparability; analytical similarity assessment; • Representative batch for Phase 1 clinical study	BS15005128			Nov-2015 Biocon, Malaysia (L2)
BS15005867	900 Kg	Dec-2015 Biocon, Malaysia (L2)	• Representative batch with process intended for commercialization; • stability study; comparability; analytical similarity assessment; • Representative batch for Phase 1 clinical study	BS15005256			Nov-2015 Biocon, Malaysia (L2)
BS15006714	900 Kg	Jan-2016 Biocon, Malaysia (L2)	• Representative batch with process intended for commercialization; • stability study; comparability; analytical similarity assessment; • Representative batch for Phase 1 clinical study	BS15005423		VI	Nov-2015 Biocon, Malaysia (L2)
BS15009374	900 Kg	Mar-2016 Biocon, Malaysia (L2)	• Process validation batch, stability; Representative batch for Phase 1 clinical study • Comparative PK/PD study (MYL-1501D-1004) for vial and cartridge presentation	BS15006908			Jan-2016 Biocon, Malaysia (L2)
BS15009375	900 Kg	Apr-2016 Biocon, Malaysia (L2)	• Comparative Safety/Efficacy study (MYL1501D-3004) for product from Process VI and Process V • Comparative PK/PD study (MYL-1501D-1003) for product from Process VI and V • Process validation batch, stability; Representative batch for Phase 1 clinical study	BS15007049			Jan-2016 Biocon, Malaysia (L2)
BS15009376	900 Kg	Apr-2016 Biocon, Malaysia (L2)	• Process validation batch, stability; Representative batch for Phase 1 clinical study • Toxicity study U-16176 • 3-way PK/PD study (MYL-1501D-1001) using DP from Process V or VI and US-Lantus	BS15006908 BS15007170			Jan-2016 Biocon, Malaysia (L2)

Site L1: Biocon Biologics Limited, 20th K. M. Hosur Road, Electronics City, Bengaluru-560100, India (FEI# 3015283245)
Site II: Biocon Biologics Limited, Special Economic Zone, Plot No: 2, 3, 4 & 5, Phase – IV, Bommasandra-Jigani Link Road, Bommasandra Post, Bengaluru, Karnataka, 560099, India (FEI# 3003981475)
Site L2: Biocon Sdn. Bhd. (930330-U), No.1, Jalan Bioteknologi 1, Kawasan Perindustrian SiLC, 79200 Iskandar Puteri, Johor, Malaysia. (FEI# 3011248248).

***Assessor's Comment**: The Applicant did not provide detailed information about MYL-1501D lots used in CAA studies in the original submission. Upon our request (OBP IR #2 sent on 02/09/2021), on 02/16/2021, the Applicant provided the above table with detailed information (such as manufacturing*

scale, site, date, use of the lot, DS batch # and manufacturing information) about MYL-1501D lots used. The IR response provided by the Applicant is acceptable.
U.S.-licensed Lantus lots used for the comparative analytical studies are within and span across the 36 month shelf life. The age of U.S.-Lantus and MYL-1501D lots at analysis allows for a meaningful comparison to support the demonstration of similarity therefore are acceptable.

The 10 MYL-1501D cartridge lots used in the CAA included lots used in the clinical PK/PD similarity studies, comparative clinical studies, and lots representative of the clinical and the proposed commercial drug product. The 10 MYL-1501D cartridge lots included 6 lots manufactured using Process VI (proposed commercial manufacturing process) drug substance (DS) and 4 lots manufactured using Process V DS. Comparability between lots manufactured using DS Process V and VI has been established. Some differences between Process V and VI were identified in the comparison of glycosylated variants and the A15 deamidation variant; however, residual uncertainty was mitigated by additional information and data to support no meaningful impact on biological behavior of the molecule (Refer to NDA-/deemed BLA-210605 CDTL Review and Division Summary Memo for Regulatory Action, June 11, 2020; NDA-/deemed BLA-210605 OPQ Executive Summary, May 22, 2020; NDA-/deemed BLA-210605 OPQ Executive Summary, April 5, 2018).

The proposed presentations of MYL-1501D include a 10 ml vial and a pre-filled pen integrated with a 3 ml cartridge. The cartridge is the primary container closure system of the pre-filled pen DP and the assembly process of the cartridge into the pen was demonstrated to have no impact on the quality attributes of MYL-1501D. Therefore, it is acceptable to include MYL-1501D cartridge lots in the comparative analytical assessment of MYL-1501D and U.S.-licensed Lantus.

The Applicant refers to the US-Lantus lots as 'cartridge' lots throughout the CAA reports. US-Lantus is marketed as a vial and a pre-filled pen integrated with a cartridge. The Applicant clarified in the submission that the U.S.-Lantus pre-filled pens are referred to as cartridges in the CAA. For the sake of consistency with the BLA, this memo also refers to these U.S.-Lantus pre-filled pen lots as 'cartridge' lots.

3.2.R.4.3.1 Protein Content/ Assay

The concentration of insulin glargine (mg/mL) and assay in units (U) in MYL-1501D and U.S.-licensed Lantus is determined using RP-HPLC method by comparing to standard solution each time. 10 lots of MYL-1501D in cartridge (age from 1 to 7 month at analysis) were compared to 22 lots of U.S.-licensed Lantus (age from 15 to 30 month at analysis).
The representative overlay of chromatogram is provided in the following Figure 2. Scatter plot representing the distribution of protein content (mg/mL)/ Assay (Units/mL) for U.S.-licensed Lantus and MYL-1501D is shown in Figure 3 and 4 below, respectively. Equivalence testing is conducted by Mylan between MYL-1501D and U.S.-licensed Lantus but not discussed here.

Figure 2: Representative Overlay of the RP-HPLC Chromatograms for Protein content of MYL-1501D, EU-Approved Lantus® and US-approved Lantus®

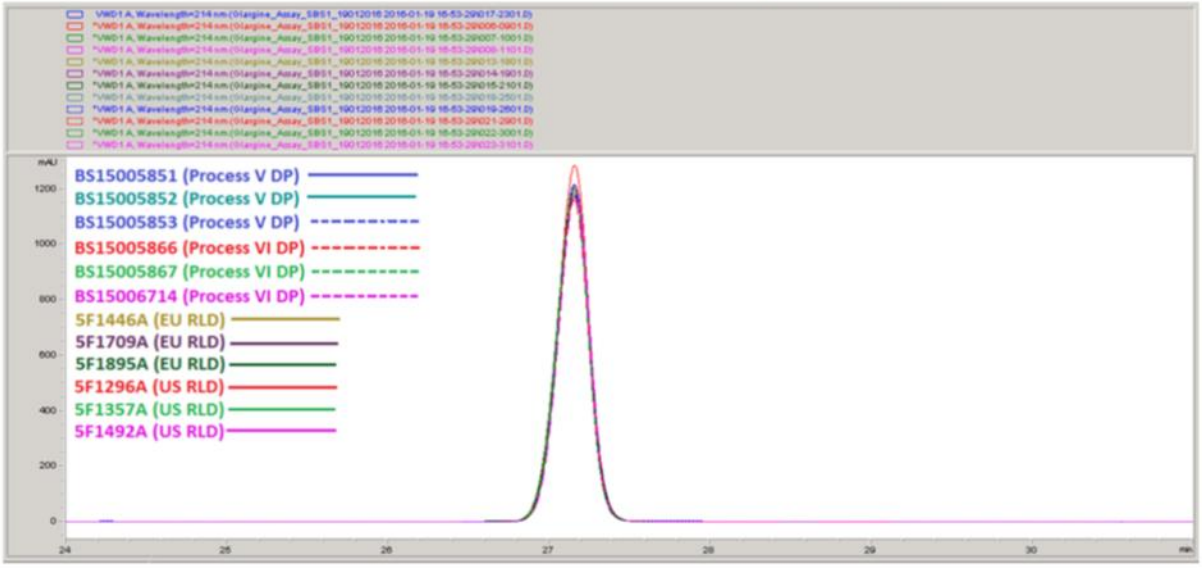


Figure 3: Scatter Plot Distribution for Content (mg/mL) of MYL-1501D, EU- and US-approved Lantus®

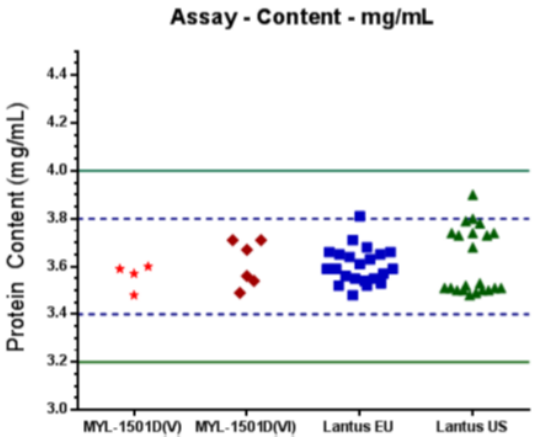
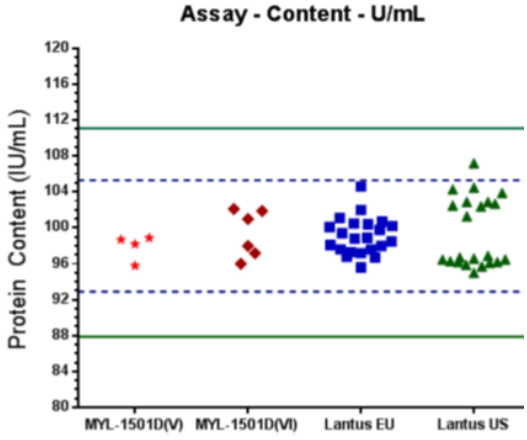


Figure 4: Scatter Plot Distribution for Assay (Units/mL) of MYL-1501D, EU- and US-approved Lantus®.



Data plots of MYL-1501D are displayed in two groups according to the DS manufacturing process (V in red or VI in dark red). The solid lines in Green represent the QR which has been set based on mean ± 3SD obtained from the observed data of the U.S.-licensed Lantus lots. The dotted lines in Blue represent QR obtained from E.U.-approved Lantus lots. The same pattern and color code apply to all the following tables and figures unless otherwise stated.

***Assessor's Comment**: Mylan did not provide information about reference standard used in this assay in the original submission. Upon our IR (OBP IR #2 02/09/2021), Mylan provided such information on 02/16/2021, indicating there were two RS* (b) (4) *used here for U.S.-Lantus and MYL-1501D lots. They also presented summary of bridging study (discussed in section 3.2.R.4.2 Quality Attributes/ Criticality Risk Ranking/ Reference Standards of this memo) which indicated these RS performed very similarly to the common reference standard EPCRS LOT 1.0, supporting the pooling of data from various runs in this assay.*

The representative HPLC chromatograms of MYL-1501D lots are highly similar to that of U.S.-licensed Lantus lots. The protein content/Assay results of MYL-1501D lots are 100% within the quality range

established for U.S.-Lantus lots, supporting a demonstration of highly similar between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation in terms of protein content/Assay.

3.2.R.4.3.2 Functional and Biological Similarity Assessment

The biological and functional similarity assessment of MYL-1501D against U.S.-licensed Lantus was carried out using multiple assays to measure biological activity using *in-vivo* and *in-vitro* bioassays. *In-vitro* bioassays performed include receptor auto-phosphorylation, receptor binding kinetics, metabolic and mitogenic activity. The *in-vivo* assessment of potency is measured by USP<121> Rabbit Bioassay.

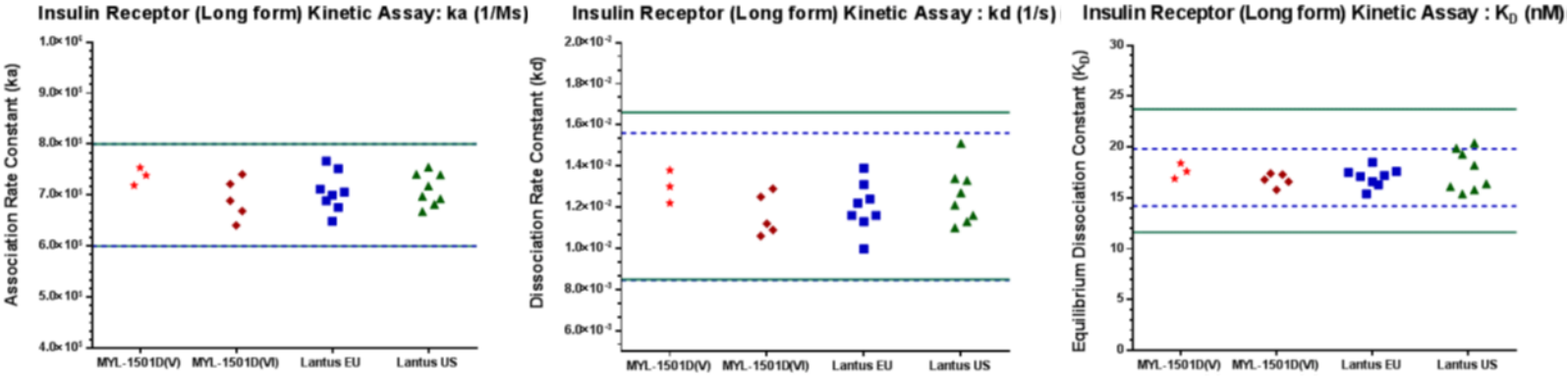
***Assessor's Comment**: The Applicant used an appropriate panel of tests for assessing the functional and biological similarity.*

3.2.R.4.3.2.1 Metabolic Activity

2.1a Insulin Receptor IR-B (long form) Binding Kinetics

The human Insulin receptor is expressed as two isoforms as a result of alternative splicing. The mature protein insulin receptor-B (IR-B, long form) differs from insulin receptor-A (IR-A, short form) by the presence of additional 12 amino acids, downstream of the carboxy-terminal sequence which is essential for ligand binding. IR-B is expressed in normal adult tissues. Comparative IR-B receptor binding affinity of ligand (MYL-1501D or U.S.-licensed Lantus) has been studied by Surface Plasmon Resonance (SPR). 8 lots of MYL-1501D in cartridge (age from 1 to 3 month at analysis) were compared to 8 lots of U.S.-licensed Lantus (age from 17 to 26 month at analysis). Representative sensorgrams for MYL-1501D and U.S.-licensed Lantus are provided in CAA report 1 but not shown here for brevity. Scatter plots distribution of the data for binding affinity to IR-B in terms of rate of association (ka), rate of dissociation (kd) and Dissociation Constant (KD) are provided in Figure 9 below.

Figure 9: Scatter Plot Distribution for IR-B binding kinetic constants (ka, kd and KD) of MYL-1501D, E.U.-approved Lantus and U.S.-licensed Lantus.



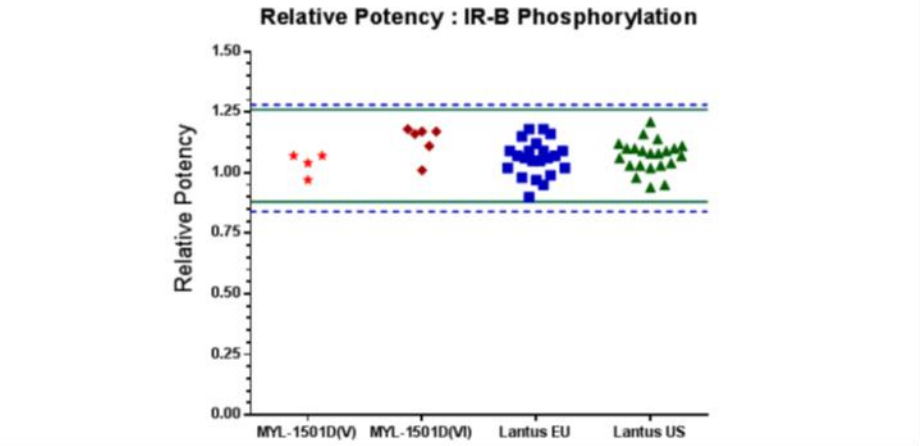
***Assessor's Comment**: The representative sensorgrams of IR-B binding kinetics for MYL-1501D lots are similar to that of U.S.-licensed Lantus. The association rate constant (k_a), dissociation rate constant (k_d), and equilibrium dissociation constant (K_D) of MYL-1501D lots are 100% within the quality range of U.S.-Lantus lots, demonstrating that the IR-B binding kinetics is highly similar between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.*

2.1b Insulin Receptor IR-B (long form) Auto-phosphorylation Assay

Insulin binding to the α-subunit induces auto-phosphorylation of the β-subunit cytoplasmic domain on multiple tyrosine residues. This auto-phosphorylation results, both *in vivo* and *in vitro*, in the activation

of the receptor kinase activity towards substrates. The activation process involves a series of conformational changes induced by ligand binding and by auto-phosphorylation, which correlate with the capacity of the receptor to phosphorylate substrates *in vitro*. Therefore, assay has been conducted to determine the phosphorylation of IR-B receptor once ligand (MYL-1501D or U.S.-licensed Lantus) binds to receptor.
10 lots of MYL-1501D in cartridge (age from 1 to 7 month at analysis) were compared to 22 lots of U.S.-licensed Lantus (age from 15 to 31 month at analysis). Representative dose response curves from each group is provided in CAA report 1 but not shown here. The insulin receptor-B phosphorylation activity data along with descriptive statistics is also provided in the report. The scatter plot representing the distribution of data is shown in the following Figure 13. Equivalence testing is conducted by Mylan between MYL-1501D and U.S.-licensed Lantus but not discussed here.

Figure 13: Scatter Plot Distribution for Relative potency (IR-B phosphorylation activity) of MYL-1501D, EU-approved Lantus® and US-approved Lantus®

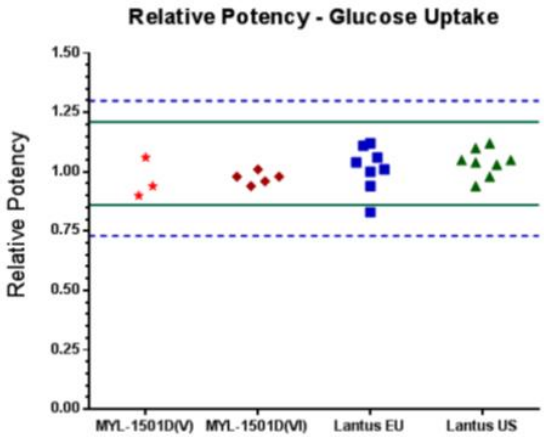


***Assessor's Comment**: The values of relative IR-B auto-phosphorylation activity for all MYL-1501D lots are 100% within the quality range of U.S.-licensed Lantus lots, demonstrating that the IR-B phosphorylation activity is highly similar between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.*

2.1c Glucose Uptake Assay in 3T3-L1 Cells

This assay measures glucose uptake in differentiated mouse 3T3-L1 adipocyte cells using the glucose oxidase/peroxidase (GOPOD) assay, which measures residual glucose left in the medium using a colorimetric method. The uptake of glucose by adipocytes results in decrease of glucose content in the medium. The remaining glucose concentration is directly proportional to the dose of insulin given which can be measured using GOPOD reagent. GOPOD forms a different gradient of pink color in proportion to the glucose concentration present. The intensity of the pink color is measured by absorbance at 550 nm using a spectrophotometer. Relative Potency analysis is performed, using obtained OD values in Parallel Line Assay software (PLA 3.0) by Stegmann Systems.
8 lots of MYL-1501D in cartridge (age from 1 to 3 month at analysis) were compared to 8 lots of U.S.-licensed Lantus in cartridge (age from 17 to 26 month at analysis). Representative dose response curves (PLA) for MYL-1501D and U.S.-licensed Lantus are provided in CAA report 1 but not shown here. The scatter plot representing the distribution of data is shown in Figure 18 below.

Figure 18: Scatter Plot Distribution for Relative potency (Glucose Uptake) of MYL-1501D, EU-Approved Lantus® and US-approved Lantus®

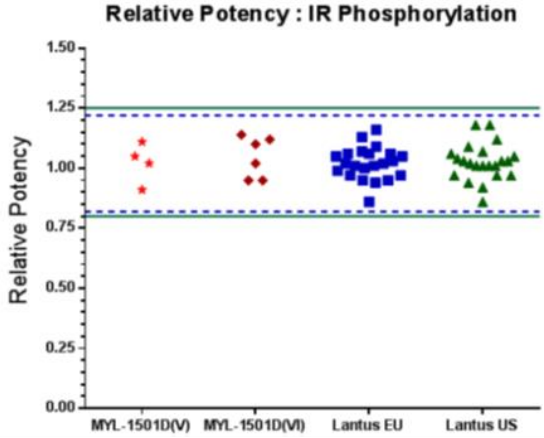


***Assessor's Comment**: The relative potency values of glucose uptake assay for MYL-1501D lots are 100% within the quality range of U.S.-licensed Lantus lots, demonstrating that the activity of stimulating glucose uptake in 3T3-L1 cells is highly similar between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.*

2.1d Insulin Receptor Phosphorylation Assay Using HepG2 Cell Lysates

Insulin receptor (IR) is a glycoprotein consisting of two 130-kDa α-subunits and two 95-kDa transmembrane β-subunits. Insulin binding to the α-subunit induces auto-phosphorylation of the β-subunit cytoplasmic domain on multiple tyrosine residues. This auto-phosphorylation results, both *in vivo* and *in vitro*, in the activation of the receptor kinase activity towards substrates. The activation process involves a series of conformational changes induced by ligand binding and by auto-phosphorylation, which correlate with the capacity of the receptor to phosphorylate substrates in vitro. The AlphaScreen SureFire INSR p-Tyr1150/1151 assay is used to measure the auto-phosphorylation of endogenous IR in cellular lysates of HepG2 cells which are prior stimulated with different doses of insulin glargine.
10 lots of MYL-1501D in cartridge (age from 1 to 7 month at analysis) were compared to 22 lots of U.S.-licensed Lantus (age from 15 to 31 month at analysis). Representative dose response curves are provided in CAA report 1 but not shown here. The scatter plot demonstrating distribution of the relative potency data is shown in Figure 22 below. Equivalence testing is conducted but not discussed here.

Figure 22: Scatter Plot Distribution for relative potency (IR phosphorylation) of MYL-1501D, EU-approved Lantus® and US-approved Lantus®



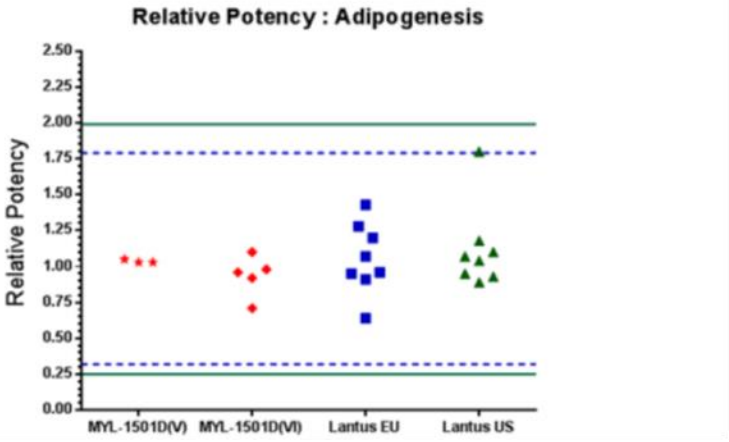
***Assessor's Comment**: The relative potency values of IR auto-phosphorylation for MYL-1501D lots are 100% within the quality range of U.S.-licensed Lantus lots, demonstrating that the IR phosphorylation activity is highly similar between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.*

2.1e Adipogenesis Assay Using 3T3-L1 Cells

Insulin is a potent adipogenesis hormone that triggers an induction of a series of transcription factors governing differentiation of pre-adipocytes into mature adipocytes, this process is known as adipogenesis. In this adipogenesis assay, 3T3-L1 cells were seeded in 96-well plates and incubated for 48 hrs. On day 3 the initiation of differentiation (adipogenesis) was carried out using the Insulin Glargine. Eight-point dilutions were prepared in adipocyte maintenance medium. This is represented as day 1 of differentiation. Post 48 hours of incubation, the preadipocyte medium were replaced by adipocyte maintenance medium (minus insulin), and the plates were incubated for additional 6 days. On day 7 of differentiation, the plates were prepared as per the assay procedure described in the BioVision kit protocol and read at Ex/Em =535/590 nm on EnVision. The relative potency 100% of standard run in every plate was calculated using SoftMax Pro 5.4.1 software.

8 lots of MYL-1501D in cartridge (age from 11 to 16 month at analysis) were compared to 8 lots of U.S.-licensed Lantus (age from 31 to 36 month at analysis). Representative dose response curves for MYL-1501D and U.S.-licensed Lantus are provided in CAA report 1 but not shown here. The scatter plot representing the distribution of relative potency values is shown in Figure 27 below.

Figure 27: Scatter Plot Distribution for relative potency (Adipogenesis) of US-approved Lantus®, EU-approved Lantus® and MYL-1501D



***Assessor's Comment**: The relative adipogenesis potency values of MYL-1501D lots are 100% within the quality range of U.S.-licensed Lantus lots, demonstrating the adipogenesis activity is highly similar between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.*

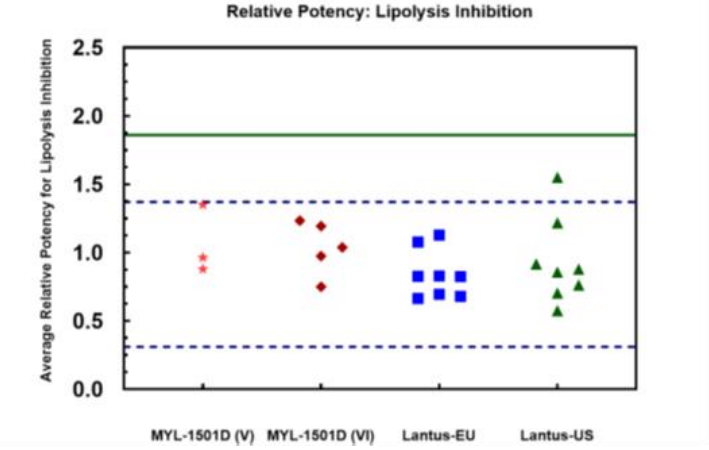
2.1f Inhibition of Stimulated Lipolysis Assay Using 3T3-L1 Cells

The key physiological function of insulin as the major anabolic hormone in the body is to restrain lipolysis and promote fat storage in adipose tissues. In an in vitro setting 3T3-L1 cells, insulin inhibits adipolysis/lipolysis in a dose dependent manner. Lipolysis is measured by quantification of the free fatty acid released from the cells.

In this lipolysis inhibition assay, 3T3-L1 cells were seeded in 96-well plates and incubated in pre-adipocytes media for 48 hrs. On day 3, differentiation media containing IBMX +dexamethasone +Insulin +0.1µM rosiglitazone were added and the plate was further incubated for 3 days. On day 6, media

changed to adipocytes maintenance media minus dexamethasone, and the plate was incubated for 3 more days. On day 10, MEM alpha starvation was done for overnight (with 1nM Human Insulin). Treatment of cells with increasing concentration of Insulin Glargine in KRB-Pyruvate containing 1% BSA for 1hr, followed by stimulation of lipolysis with 3nM of isoproterenol (IP) for 2hrs. Free fatty acid assay was performed with collected supernatant, and the plate was read for absorbance at 570 nm.
8 lots of MYL-1501D in cartridge (age from 14 to 19 month at analysis) were compared to 8 lots of U.S.-licensed Lantus (age from 29 to 35 month at analysis). Representative dose response curves for MYL-1501D and U.S.-licensed Lantus are provided in CAA report 1 but not shown here. The scatter plot representing the distribution of relative potency values is shown in Figure 31 below.

Figure 31: Scatter Plot Distribution of Relative Potency (Inhibition of Stimulated Lipolysis Assay) of US-licensed Lantus®, EU-approved Lantus® and MYL-1501D



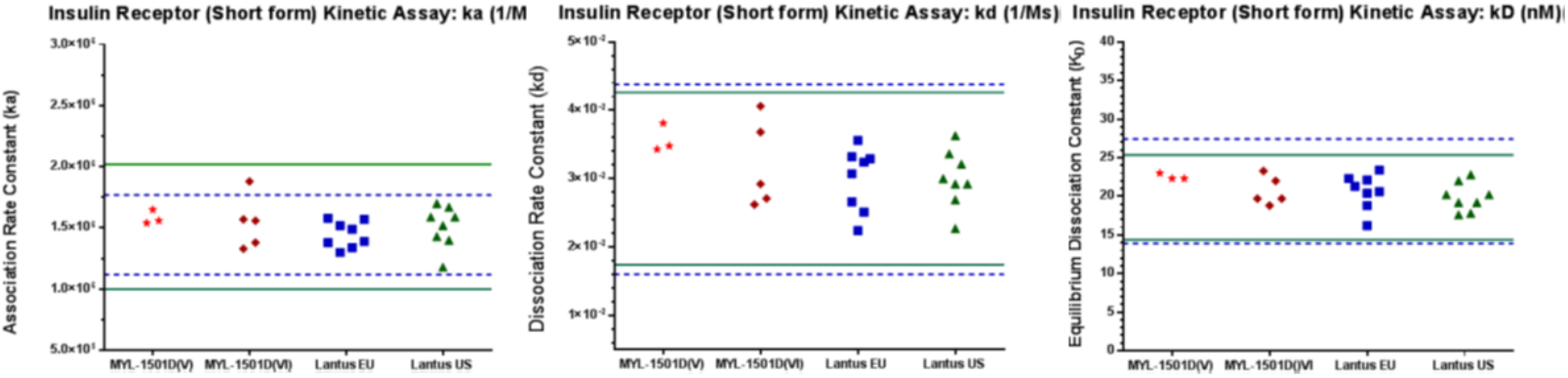
***Assessor's Comment**: The relative potency values of lipolysis inhibition for MYL-1501D lots are 100% within the quality range of U.S.-licensed Lantus lots, demonstrating that the lipolysis inhibition activity is highly similar between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.*

3.2.R.4.3.2.2 Mitogenic Activity

2.2a Insulin Receptor IR-A (short form) Binding Kinetics

The two mature proteins IR-A (short form) and IR-B (long form) of human insulin receptor differ by the presence or absence of 12 amino acids encoded by exon 11 at the C-terminus of the extracellular α-subunit, downstream of the C-terminal sequence that is essential for ligand binding. IR-A appears to be expressed predominantly in fetal tissues and cancer. In addition, a role of the isoform IR-A has been discussed for hybrid receptors, as increased expression of IR-A/IGF1R hybrids has been found in tumors. Therefore, it is important to determine the receptor binding activities of insulin glargine to IR-A. Comparative binding affinity to IR-A has been studied using Surface Plasmon Resonance (SPR).
8 lots of MYL-1501D in cartridge (age from 1 to 3 month at analysis) were compared to 8 lots of U.S.-licensed Lantus (age from 17 to 26 month at analysis). Representative sensorgrams of IR-A binding affinity for MYL-1501D and U.S.-licensed Lantus are provided in CAA report 1 but not shown here. The IR-A binding affinity data in terms of rate of association (k_a), rate of dissociation (k_d) and Dissociation Constant (K_D) are shown in scatter plots in Figure 51 below.

Figure 51: Scatter plot distribution of Insulin receptor IR-A (short form) binding kinetic constants of MYL-1501D, EU-approved Lantus® and US-approved Lantus®

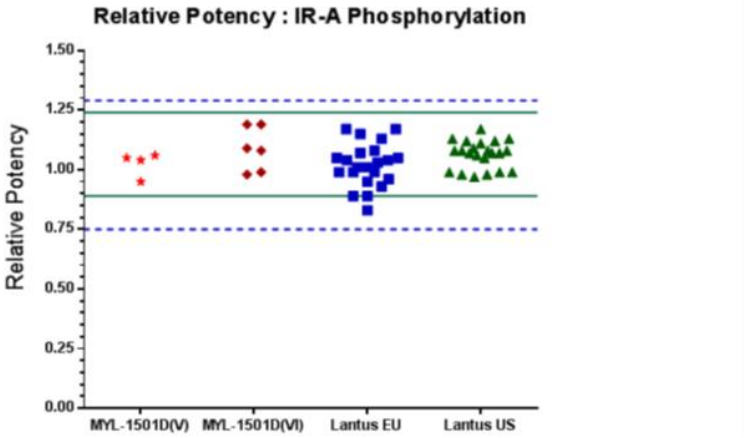


***Assessor's Comment**: The representative sensorgrams of IR-A binding kinetics for MYL-1501D lot are similar to that of U.S.-licensed Lantus lot. The association rate constant (k_a), dissociation rate constant (k_d), and equilibrium dissociation constant (K_D) of MYL-1501D lots are 100% within the quality range of U.S.-licensed Lantus lots. It can be concluded that the IR-A binding kinetics is highly similar between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.*

2.2b Insulin Receptor IR-A Phosphorylation Assay

The auto-phosphorylation of IR-A when insulin glargine binds with IR-A receptor has also been compared with 10 lots of MYL-1501D in cartridge (age from 1 to 7 month at analysis) and 22 lots of U.S.-licensed Lantus (age from 15 to 31 month at analysis). Representative dose response curves for MYL-1501D and U.S.-licensed Lantus are provided in CAA report 1 but not shown here. The scatter plot representing the distribution of the data is shown in Figure 42 below. Equivalence testing is conducted by Mylan but not discussed here.

Figure 42: Scatter Plot Distribution for Relative potency (IR-A phosphorylation) of MYL-1501D, EU-Approved Lantus® and US-approved Lantus®



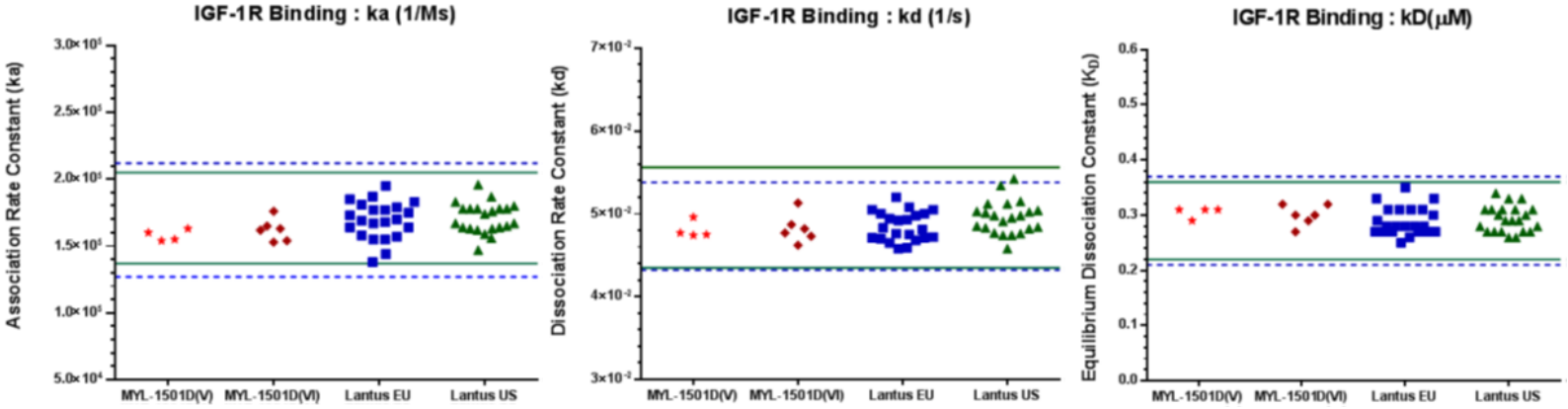
***Assessor's Comment**: The relative potency values of IR-A auto-phosphorylation for MYL-1501D lots are 100% within the quality range of U.S.-Lantus lots, demonstrating that the IR-A phosphorylation activity is highly similar between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.*

2.2C Insulin Growth Factor-1 Receptor (IGF-1R) Binding Kinetics

Surface Plasmon Resonance (SPR) based assay is used to evaluate the binding of insulin glargine to purified recombinant human IGF-1 receptor, using BIAcore. The ligand IGF-1 receptor is immobilized and the analyte, insulin glargine, is allowed to flow on the surface. As the analyte binds to the ligand, the accumulation of protein on the surface results in an increase in the refractive index. The binding affinity is determined in terms of rate of association (k_a), rate of dissociation (k_d) and Dissociation Constant (K_D) which are used to compare MYL-1501D and U.S.-licensed Lantus.

10 lots of MYL-1501D in cartridge (age from 1 to 7 month at analysis) were compared to 22 lots of U.S.-licensed Lantus (age from 15 to 31 month at analysis). Representative sensorgrams for MYL-1501D and U.S.-licensed Lantus are provided in CAA report 1 but now shown here. Scatter plots demonstrating the distribution of the data are shown in Figure 35 below. Equivalence testing is conducted based on these data but not discussed here.

Figure 35: Scatter Plot Distribution for IGF-1R binding kinetic constants of MYL-1501D, EU-approved Lantus® and US-approved Lantus®.



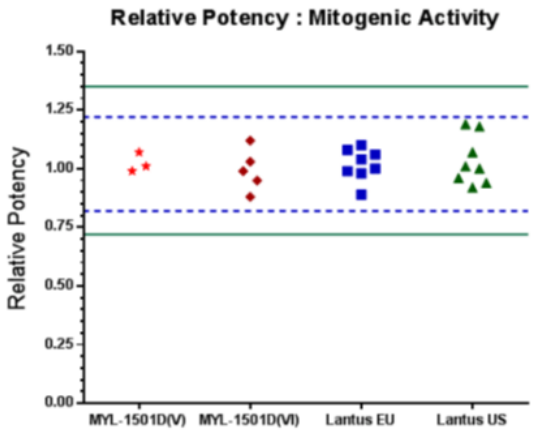
***Assessor's Comment**: The representative sensorgrams of IGF-1R binding kinetics for MYL-1501D lot are similar to that of U.S.-Lantus lot. The IGF-1R association rate constant (k_a), dissociation rate constant (k_d), and equilibrium dissociation constant (K_D) of MYL-1501D lots are all 100% within the quality range of U.S.-licensed Lantus lots, demonstrating that the IGF-1R binding activity is highly similar between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.*

2.2d Mitogenic Activity Using Saos-2 Cells-Based Assay

The scientific basis for the study is that different insulin products mediate variable increases in mitogenic activity, which can be used to calculate potency. The proliferation of Saos-2 cells exposed to different lots of MYL-1501D or U.S.-Lantus was measured calorimetrically using the redox indicator dye Alamar Blue. The relative fluorescence unit (RFU) obtained is directly proportional to the increase in cell number. Mitogenic activity is measured in terms of Relative Potency using Parallel Line Assay software by Stegmann Systems.

8 lots of MYL-1501D in cartridge (age from 1 to 3 month at analysis) were compared to 8 lots of U.S.-licensed Lantus (age from 17 to 26 month). Representative dose response curves (PLA) for each group are provided in CAA report 1. The scatter plot representing the distribution of data is shown in the following Figure 47.

Figure 47: Scatter Plot Distribution of Relative Potency (Mitogenic Assay) of MYL-1501D, EU-approved Lantus® and US-approved Lantus®



***Assessor's Comment**: The relative potency values of mitogenic activity in Saos-2 cells for MYL-1501D lots are 100% within the quality range of U.S.-licensed Lantus lots, demonstrating the mitogenic activity is highly similar between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.*

3.2.R.4.3.2.3 In-vivo Rabbit Bioassay (per USP<121>)

The direct manifestation of insulin glargine administration is an abrupt decrease in blood glucose, which is the basis for the *in-vivo* rabbit bioassay. The method determines the potency of insulin glargine against the USP insulin glargine standard and USP human insulin standard. The assay is carried out according to USP <121> and USP <111>. The data are tabulated in Table 15 below.

(b) (4)

Assessor's Comment*: The Applicant did not provide age information for each drug product lot used in this rabbit bioassay in the original submission, therefore an IR (OBP IR #2) was sent on 02/09/2021 regarding this. In an IR response on 02/16/2021, the Applicant provided the above Table 15 with age information added for each drug product lot used. This response is acceptable.*
The Applicant provided results of in-vivo potency determined by the rabbit bioassay method. Due to the high variability of the assay, the rabbit bioassay is not amenable to statistical evaluation. The results indicate that the MYL-1501D and U.S.-Lantus lots are comparable and compliant with the USP <121> acceptance criterion of 'NLT 15 U/mg'. However, per current OBP recommendation, the rabbit bioassay is not recommended for demonstration of similarity of insulin products. Therefore, the above described results are not included in our assessment of highly similar between MYL-1501D and U.S.-Lantus. The similarity of potency is assessed by other assays including content, metabolic assays and mitogenic assays.

Summary of Functional and Biological Assays:
Results from multiple orthogonal analytic studies to assess functional activities and biological activities support a highly similar demonstration between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation with respect to functional and biological activities

3.2.R.4.3.3 Purity and Impurity

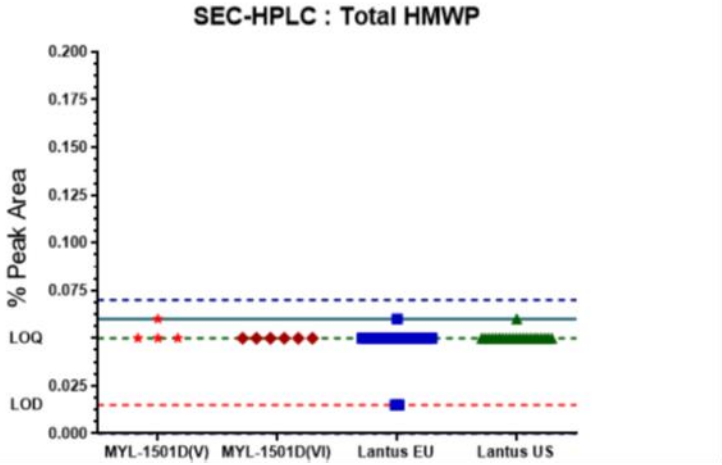
3.2.R.4.3.3.1 Size Variant- High Molecular Weight Protein (HMWP)/Aggregates

Size variants such as high molecular weight impurities (HMWP) species including aggregates, formed due to association of two or more molecules of the monomer or fragments, are primarily estimated by Size Exclusion Chromatography (SEC-HPLC). Orthogonal methods such as Size-Exclusion Chromatography with Multi-Angle Light Scattering (SEC-MALS) and Analytical Ultracentrifuge (AUC) have also been used to assess size-based variants. Results for each assay are discussed below.

3.1a HMWP Assessment Using SEC-HPLC

10 lots of MYL-1501D in cartridge (age from 1 to 7 month at analysis) were compared to 22 lots of U.S.-licensed Lantus (age from 13 to 26 month at analysis). Representative overlaid SEC-HPLC chromatograms for size-based quality attributes are provided in CAA report 1 but not shown here. The scatter plot representing the distribution of data is provided in Figure 53 below (LOD=0.015%, LOQ=0.050%).

Figure 53: Scatter Plot distribution of HMWP in MYL-1501D, EU-approved Lantus® and US-approved Lantus®



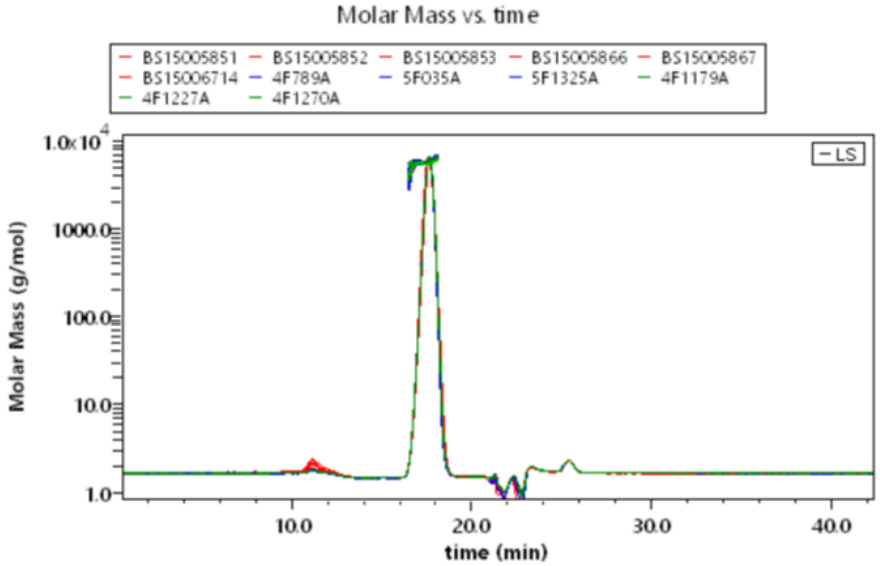
***Assessor's Comment**: The representative overlaid chromatograms of MYL-1501D lots are similar to that of U.S.-licensed Lantus lots. The total HMWP content for most of the MYL-1501D and U.S.-Lantus lots were observed to be below the quantification limit (LOQ: 0.05%) by SEC-HPLC method. The HMWP content values of all tested MYL-1501D lots are within the QR established for U.S.-Lantus, hence MYL-1501D cartridge presentation is highly similar to U.S.-Lantus cartridge presentation in HWMP profile.*

3.1b HMWP Assessment Using SEC-MALS

SEC-MALS is an orthogonal tool to assess and characterize the size variants. The multiple angle light scattering detection in conjunction with size-exclusion chromatography (SEC-MALS), estimates the molar mass of the monomer and the higher oligomeric species. Exponential/polynomial fitting of results helps in obtaining the predominant molar mass.

10 lots of MYL-1501D in cartridge (age from 1 to 10 month at analysis) were compared to 10 lots of U.S.-licensed Lantus (age from 18 to 26 month at analysis). Representative overlaid molar mass (g/mol) vs time plots are shown in Figure 54 below.

Figure 54: Representative Overlaid Molar mass chromatogram by SEC-MALS for MYL-1501D, EU-approved Lantus® and US-approved Lantus®



The SEC-MALS analysis data for MYL-1501D and U.S.-Lantus lots are tabulated in Table 52 and 53 but not shown in a scatter plot in CAA report 1. The following table contains summarized data from Table 52 and 53 (assessor generated).

Molar mass measured with SEC-MALS	U.S.-Lantus (cartridge) Min - Max range	MYL-1501D (cartridge) Min - Max range
Mass fractions (%)	100 (mean: 100, QR: 100~100)	100 (mean: 100)
Mw/Mn	1.001~1.006 (mean: 1.003, QR: 0.999~1.007)	1.002~1.005 (mean: 1.004)
Mz/Mn	1.002~1.011 (mean: 1.006, QR: 0.997~1.016)	1.004~1.010 (mean: 1.008)

***Assessor's Comment**: SEC-MALS analysis of MYL-1501D and U.S.-Lantus lots indicates that a similar size range is obtained for the monomer across both products. A single predominant peak of monomer is observed in all samples with a similar distribution of molar mass. The content of multimers or aggregate is low in both products. These data support the conclusion obtained from SEC-HPLC method above that HMWP profile is highly similar between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.*

3.1c HMWP Assessment Using AUC– Sedimentation Velocity

Analytical ultracentrifuge (AUC) is an alternative tool to obtain information on protein homogeneity and distribution of stable aggregates. Sedimentation velocity measured by the AUC, provides information on the protein heterogeneity and state of association or aggregation. Aggregates can be detected based on their different sedimentation coefficients. The method is also sensitive to conformational changes in proteins that alters the sedimentation coefficients.

9 lots of MYL-1501D in cartridge (age from 1 to 6 month at analysis) were compared to 3 lots of U.S.-licensed Lantus (age from 20 to 25 month at analysis). Representative normalized sedimentation coefficient distribution graphs are presented in Figure 55, 57, and 58 below.

Figure 55: Representative Normalized sedimentation coefficient distribution for US-approved Lantus®

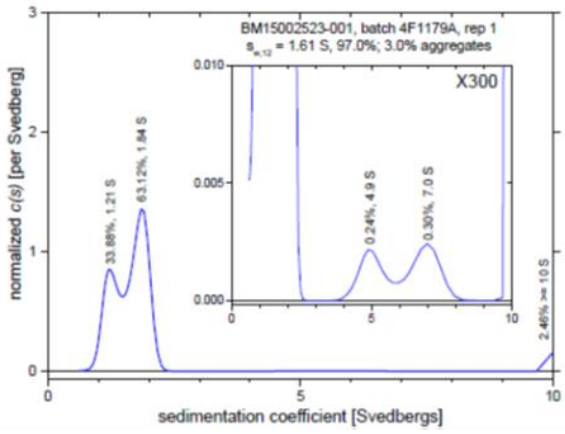


Figure 57: Representative Normalized sedimentation coefficient distribution for MYL-1501D (Process V)

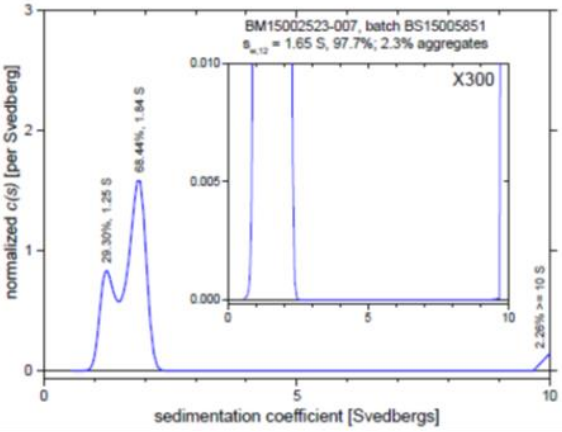
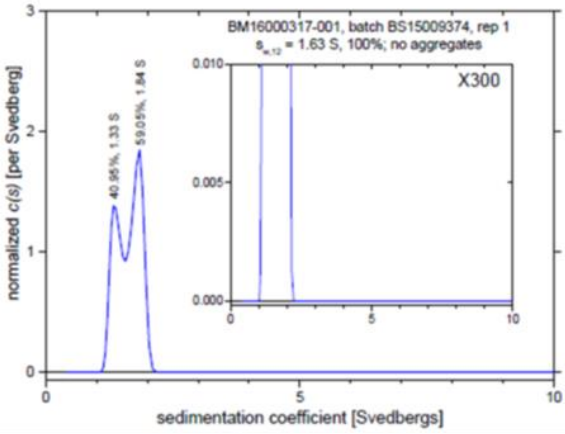


Figure 58: Representative Normalized sedimentation coefficient distribution for MYL-1501D (Process VI)



The AUC analysis data are tabulated in Table 54 to Table 56 but not shown in a scatter plot in CAA report 2. The following table contains summarized data obtained from Table 54 to 56 (assessor generated).

Size variant measured using AUC	U.S.-Lantus (cartridge) Min - Max range	MYL-1501D (DS V) Min - Max range	MYL-1501D (DS VI) Min - Max range
Monomer sedimentation coefficient (S)	1.61~1.64 (mean: 1.62) (QR:1.59~1.65)	1.61~1.65 (mean: 1.62)	1.58~1.63 (mean: 1.61)
Total aggregate fraction (%)	0.0~3.2 (mean: 1.8) (QR: 0~5.9)	2.3~3.9 (mean: 3.4)	0.0~3.9 (mean: 1.2)

***Assessor's Comment**: The Applicant proposed assessment of AUC results by profile comparison/ overlay and data table. Since an orthogonal method of evaluation of HMWP by SEC using quality range statistical approach was also applied (discussed in section 3.1a HMWP Assessment Using SEC-HPLC above), the evaluation of AUC by profile comparison is acceptable. Additionally, the Applicant's AUC method seems to have high variability, making it not amenable to meaningful quantitative analyses. The AUC profiles of MYL-1501D and U.S.-Lantus lots are comparable, data tables show comparable monomer sedimentation coefficients and aggregate fractions, which together support a highly similar*

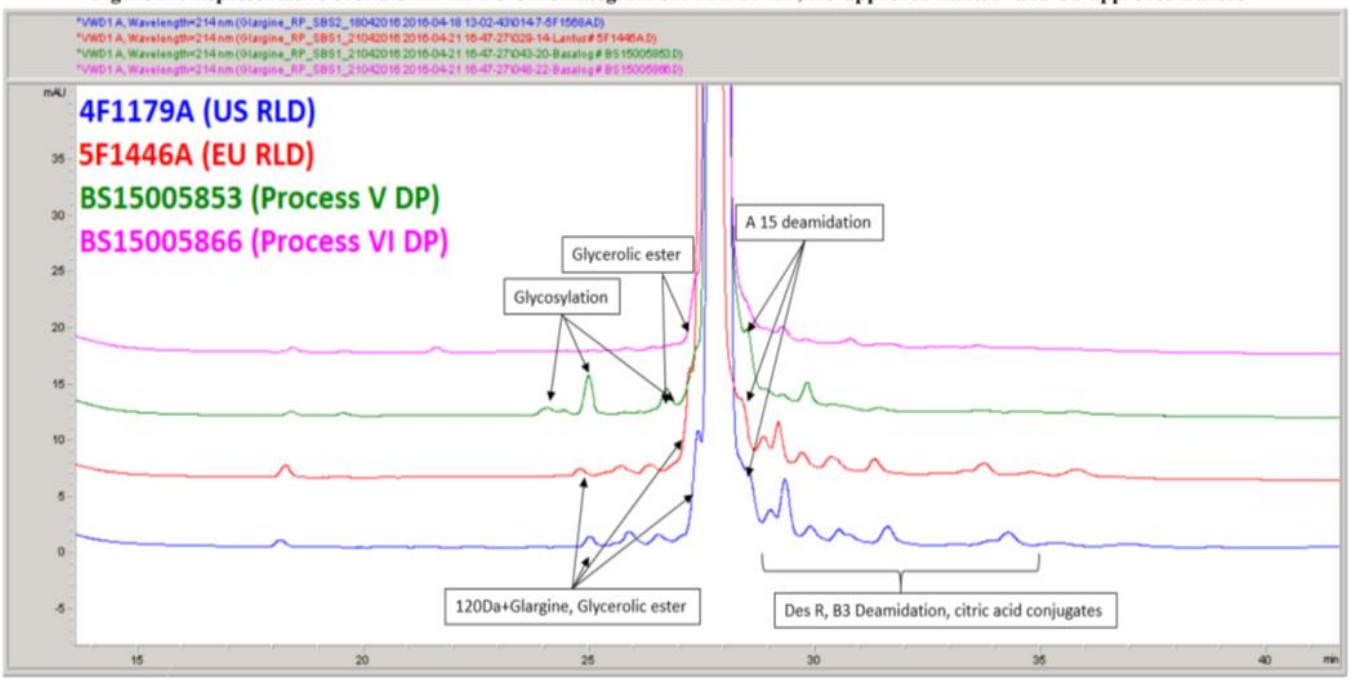
demonstration of HWMP profile between MYL-1501D cartridge presentation and U.S.-Lantus cartridge presentation.

3.2.R.4.3.3.2 Product Variants by RP-HPLC

Modifications such as deamidation, oxidation and reduction resulting in hydrophobic variants are key chemical modifications of amino acids. Deamidation is the most prominent non-enzymatic degradation reaction of insulin and insulin analogues that occurs due to loss of the amide –NH2 groups. The product related variants generated by deamidation/ clipping of the B-chain C-terminal amino acids, mis-cleavage of precursor by trypsin are monitored by RP-HPLC.

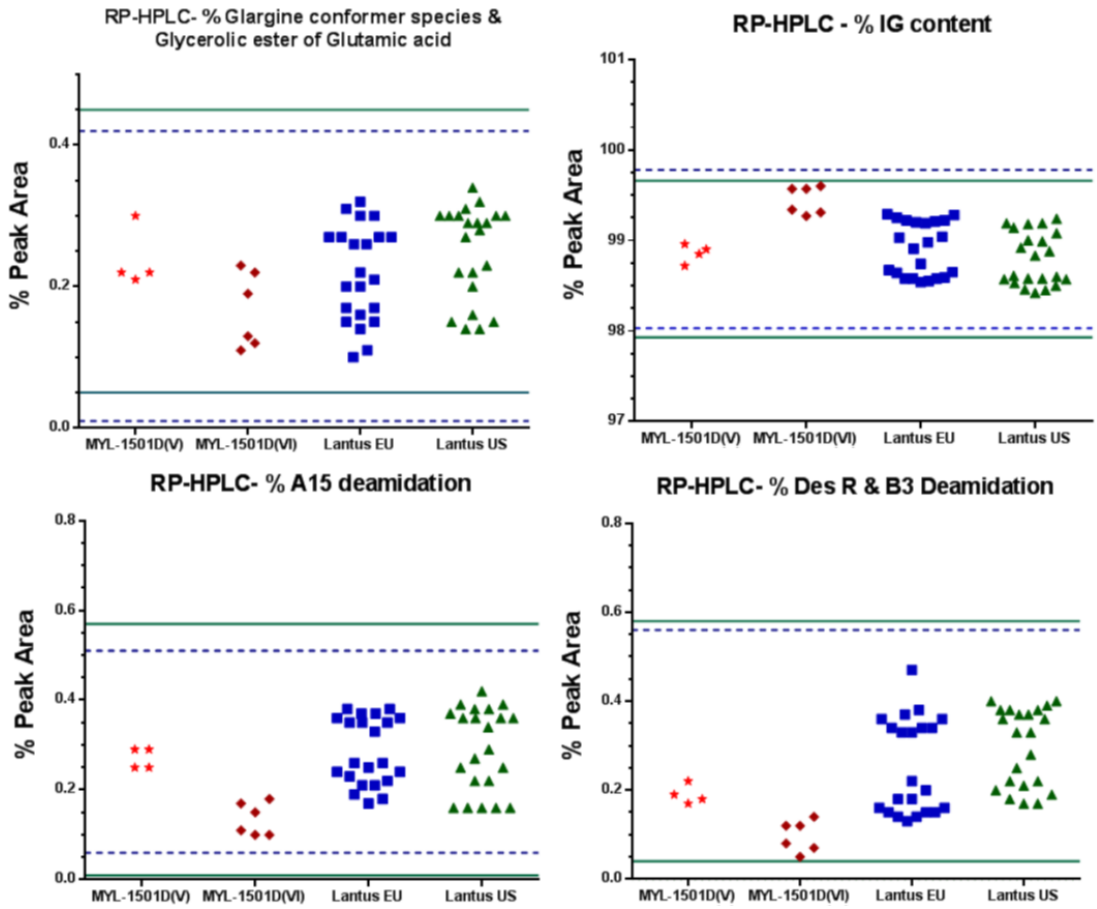
10 lots of MYL-1501D in cartridge (age from 1 to 9 month at analysis) were compared to 22 lots of U.S.-licensed Lantus (age from 13 to 26 month at analysis). Representative overlaid RP-HPLC chromatograms are shown in Figure 59 below.

Figure 59: Representative overlaid RP-HPLC Chromatogram of MYL-1501D, EU-approved Lantus® and US-approved Lantus®



RP-HPLC data for U.S.-Lantus and MYL-1501D for product variants is tabulated in Table 57 and 59 in CAA report 1 but not shown here. Scatter plots distribution of the data for individual product variants are provided in Figure 60 below.

Figure 60: Scatter Plot distribution of Hydrophobic variants of MYL-1501D, EU-Approved Lantus and US-approved Lantus (LOQ: 0.04%, LOD: 0.015%)



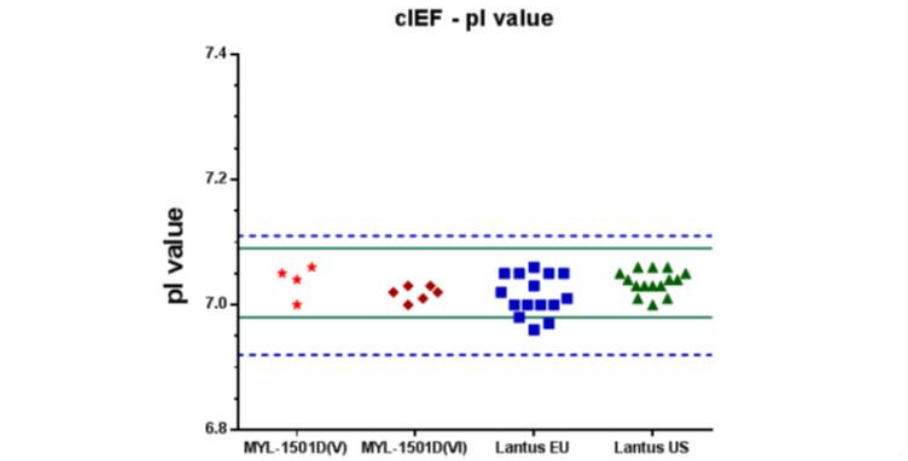
***Assessor's Comment**: The overlaid chromatograms in Figure 59 indicate the product variant profiles and levels are overall similar between MYL-1501D and U.S.-Lantus cartridge presentation.*
Data in Figure 60 show that product variants measured by RP-HPLC for all MYL-1501D lots are within the QR established for U.S.-Lantus and therefore demonstrate highly similar. The data above shows variant levels of MYL 1501D Process V and Process VI lots in separate clusters. As previously stated, the difference in impurities and variants between MYL-1501D lots from DS Process V and Process VI has been acknowledged previously in the review of NDA-210605 and mitigated by clinical studies; however, lots from both Process V and VI are within the quality ranges of U.S.-Lantus. Levels of other product variants (citrate conjugates, acetylated insulin glargine, iso-glargine) are low and similar between MYL-1501D and U.S.-Lantus lots (data not shown in scatter plots here). MYL-1501D Process VI lots have below detection limit or undetected levels of glycosylated variants.
Overall, the results from product related variants support a demonstration of highly similar between MYL-1501D cartridge presentation and U.S.-Lantus cartridge presentation.

3.2.R.4.3.3.3 Capillary Isoelectric Focusing to Assess the Isoelectric Point (pI)

The capillary electrophoretic method (cIEF) to measures pI (isoelectric point) of the protein which is unique to each protein and hence can provide information about identity and purity. cIEF separates charge variants and provides information about the protein pI, which depends on the amino acid sequence of a protein.
10 lots of MYL-1501D in cartridge (age from 2 to 11 month at analysis) were compared to 15 lots of U.S.-licensed Lantus (age from 8 to 29 month at analysis). Representative overlay of the cIEF profile is

provided in CAA report 1 but not shown here. The scatter plot distribution of pI values is provided in Figure 62 below.

Figure 62: Scatter plot distribution for pI value for MYL-1501D, EU-approved Lantus® and US-approved Lantus®



Assessor's Comment: *The representative cIEF profiles for MYL-1501D lots are similar to that of U.S.-licensed Lantus. The calculated pI values for the main peak of MYL-1501D lots are 100% within the QR observed for U.S.-licensed Lantus lots, demonstrating the pI value is highly similar between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.*

Summary of Purity, Impurity, and Product related variants:
Results from multiple orthogonal analytic studies to assess the purity and impurities, size variants, product variants, pI, indicate that MYL-1501D cartridge presentation is highly similar to U.S.-licensed Lantus cartridge presentation with respect to purity, impurity, and product variant profiles and levels.

3.2.R.4.3.4 Primary, Secondary and Higher Order Structure
3.2.R.4.3.4.1 Primary Structure and Disulfide Linkage
The test methods used for assessing similarity of primary structure and disulfide linkage are presented in Table 63 below.

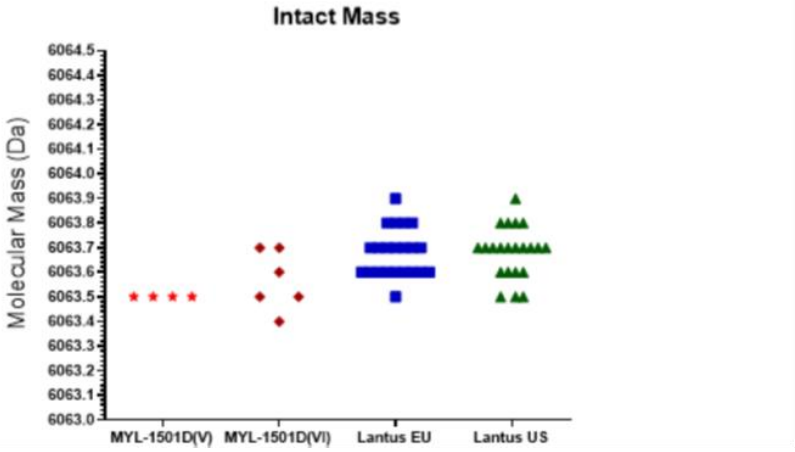
Table 63: Test Methods used for Primary Structure Similarity Assessment

Analytical Test	Description
Intact mass	Intact mass by ESI-MS Mass spectrometry
Reduced mass	Reduced by DTT to separate into two chains, Chain A and Chain B
Non-Reduced PMF	Peptide mass fingerprinting using GLU-C analysed using LC-MS and MS-MS
Reduced PMF	Peptide mass fingerprinting using GLU-C reduced with DTT analysed using LC-MS and MS-MS.

4.1a Intact Mass Analysis
The intact mass analysis not only confirms the identity of the molecule but also forms the first evidence of primary structure and hence primary sequence. 10 lots of MYL-1501D in cartridge (age from 1 to 9 month) and 22 lots of U.S.-licensed Lantus (age from 16 to 33 month) were analyzed for intact mass on a C18 column using RP-HPLC connected to an ESI-mass spectrometer.

Representative UV chromatograms and corresponding intact mass are provided in CAA report 1 but not shown here. Scatter plot representing the distribution of intact mass is shown in Figure 64 below.

Figure 64: Scatter plot distribution for Intact Mass of MYL-1501D, EU-approved Lantus® and US-approved Lantus®



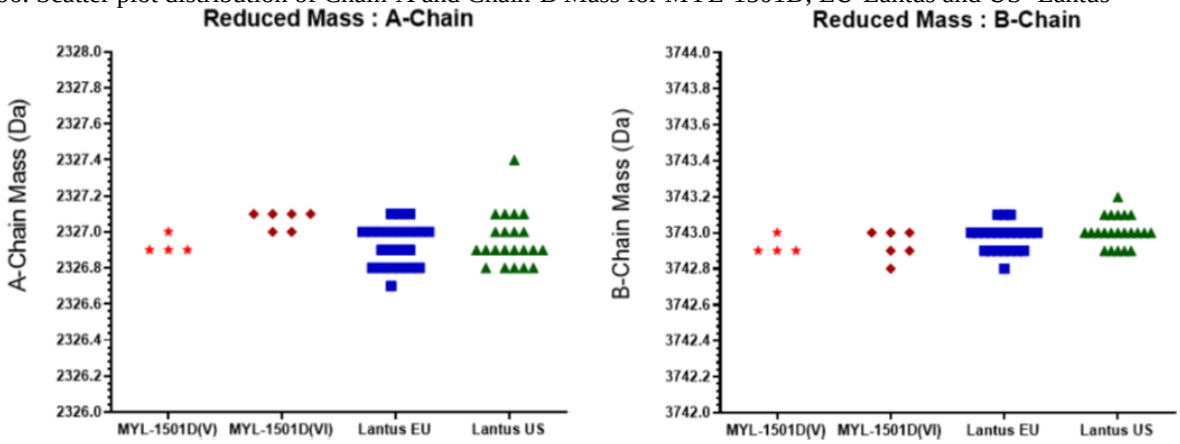
Assessor's Comment: *Representative intact mass UV profiles of MYL-1501D lots are similar to that of U.S.-Lantus. The observed intact mass for the cartridge presentation of U.S.-Lantus (mean: 6063.7) and MYL-1501D (mean: 6063.5) are all highly similar to the expected theoretical mass ([M+H] ± 1 Da) of 6063.9 Da. This result supports the similarity in primary sequence between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.*

4.1b Reduced Mass analysis by RP-HPLC-ESI Mass Spectrometry

Mass analysis of the DTT reduced insulin glargine product gives rise to the constituent two chains of the molecule namely Chain-A and Chain-B. The samples were first reduced with DTT and then separated on a C8 column and detected on ESI mass spectrometer connected to the RP-HPLC. Reduced mass analysis not only confirms the characteristics of the two chains but also confirms the identity of the individual chains at the level of the primary structure.

10 lots of MYL-1501D in cartridge (age from 1 to 9 month at analysis) were compared to 22 lots of U.S.-licensed Lantus (age from 16 to 33 month at analysis). Representative UV chromatograms of Chain-A and Chain-B are provided in CAA report 1 but not shown here. Scatter plots representing the distribution of mass values are provided in Figure 66 below.

Figure 66: Scatter plot distribution of Chain-A and Chain-B Mass for MYL-1501D, EU-Lantus and US- Lantus



Assessor's Comment: *Representative UV profiles of Chain A and Chain B for MYL-1501D lots are similar to that of U.S.-Lantus lots. The observed mass of Chain A and Chain B for the cartridge presentation of U.S.-Lantus (mean: 2327.0 for A and 3743.0 for B) and MYL-1501D (mean: 2327.0 for A and 3742.9 for B) are highly similar to the expected theoretical mass ([M+H] ± 1 Da) of 2327.6 Da for Chain A and 3743.3 Da for Chain B. This result also supports the similarity in primary sequence between MYL-1501D cartridge presentation and U.S.-Lantus cartridge presentation.*

4.1c Disulfide Linkage by Non-Reduced Peptide Mass Fingerprinting Analysis

Peptide mapping is an analytical technique for protein identification where, the protein of interest is first cleaved into smaller peptides, whose absolute masses, as determined with a mass spectrometer, are compared to their respective theoretical masses. Specific enzymes selectively cleave the protein at specific site, for example the V8 Protease selectively acts upon the glutamic acid residues in the peptide chain and hence cleaves the amide bond after glutamic acid from the C-terminus. In insulin glargine, 4 glutamic acid residues (at positions A4, A17, B13 and B21) gives rise to 4 peptide fragments which could be analyzed by the LC-MS technique to generate mass fingerprint (PMF). Under non-reducing condition the disulfide bonds are still intact and hence PMF gives rise to A-B chain connected peptide providing the confirmation of disulfide linkages. The expected theoretical fragments on Glu C digestion of insulin glargine under non-reducing conditions along with their respective masses is tabulated in Table 70 below.

Table 70: List of Disulphide linked Peptide Fragments and Their Masses Monitored by Non-Reduced Glu-C Peptide Mass Fingerprinting

Fragment number	Fragment No. / Location	Amino acid Sequence	Theoretical mass $(M+H)^+ \pm 1Da$
4	A (1-4)	GIVE	417.2
3	B (22-32)	RGFFYTPKTRR	1428.8
2	A (18-21) & B (14-21)	(NYCG) & (ALYLVCGE)	1320.49
1	A(5-17) & B (1-13)	(QCCTSICSLYQLE) & (FVNQHLCGSHLVE)	2969.36

10 lots of MYL-1501D (age from 1 to 9 month) and 22 lots of U.S.-licensed Lantus (age from 16 to 33 month) in cartridge presentation were subjected to proteolysis with Endoproteinase Glu C. The peptides were then detected on an ESI-mass spectrometer as they were separated on a C18 column connected to RP-HPLC.

The non-reduced PMF analysis data for U.S.-Lantus and MYL-1501D are provided in Table 71 and 73 in CAA report 1 and are summarized in the table below (assessor generated). Representative overlaid UV-chromatograms are also provided but not shown here.

Peptide mass measured with non-reducing PMF	U.S.-Lantus (cartridge) Min – Max range	MYL-1501D (cartridge) Min – Max range
Fragment 4 (Da)	417.1 (mean: 417.1)	417.1 (mean: 417.1)
Fragment 3 (Da)	1428.7~1429.4 (mean: 1429.0)	1428.6~1428.8 (mean: 1428.7)
Fragment 2 (Da)	1320.5~1320.6 (mean: 1320.5)	1320.5~1320.6 (mean: 1320.5)
Fragment 1 (Da)	2969.1~2970.6 (mean: 2969.6)	2969.1~2969.9 (mean: 2969.5)

Assessor's Comment: *Representative UV profiles of 4 fragments for MYL-1501D lots are similar to that of U.S.-Lantus. The observed mass values measured by non-reducing PMF for the cartridge presentation of MYL-1501D and U.S.-licensed Lantus are highly similar to each other and to the expected theoretical mass ([M+H] ± 1 Da) for fragment 1/2/3/4, supporting a demonstration of highly similar in primary sequence and disulfide linkages between MYL-1501D cartridge presentation and U.S.-Lantus cartridge presentation.*

4.1d Reducing Peptide Mass Fingerprinting Analysis

The difference between peptide mass fingerprinting (PMF) under reduced condition and non-reduced condition is that DTT is used to disrupt the disulfide bond under reduced condition. Specific enzyme- V8 protease which cleaves insulin glargine at the C terminus of glutamic acid to give rise to four peptide fragments was further reduced with the help of DTT to disrupt the disulfide bonds, and subsequently subjected to MS analysis for sequence confirmation.

In the reducing PMF analysis of insulin glargine, the following six peptide fragments are expected (shown in Table 74 below) after digestion with Glu-C and are sequenced for confirmation.

Table 74: Expected theoretical fragments for Glu C digestion of Insulin Glargine under reduced conditions along with their respective masses

Fragment number	Fragment No. / Location	Amino Acid Sequence	Theoretical mass $(M+H)^+$ ±1Da
1	A(5-17)	QCCTSICSLYQLE	1490.6
2	B (14-21)	ALYLVCGE	867.4
3	B (1-13)	FVNQHLCGSHLVE	1482.7
4	B (22-32)	RGFFYTPKTRR	1428.8
5	A (1-4)	GIVE	417.2
6	A (18-21)	NYCG	456.1

10 lots of MYL-1501D in cartridge (age from 1 to 9 month) and 22 lots of U.S.-licensed Lantus (age from 16 to 33 month) were subjected to PMF analysis under reducing condition. The reducing PMF analysis data are provided in Table 75 and 77 in CAA report 1 and are summarized in the table below (assessor generated). Representative overlaid UV-chromatograms are also provided but not shown here.

Peptide mass measured with non-reducing PMF	U.S.-Lantus (cartridge) Min – Max range	MYL-1501D (cartridge) Min–Max range
Fragment 6 (Da)	456.0~456.1 (mean: 456.0) (QR: 455.9~456.1)	456.0 (mean: 456.0)
Fragment 5 (Da)	417.1 (mean: 417.1) (QR: 417.1~417.1)	417.1 (mean: 417.1)
Fragment 4 (Da)	1428.7~1429.2 (mean: 1428.8) (QR: 1428.3~1429.2)	1428.7~1428.8 (mean: 1428.7)
Fragment 3 (Da)	1482.7~1482.8 (mean: 1482.7) (QR: 1482.6~1482.8)	1482.7 (mean: 1482.7)
Fragment 2 (Da)	867.3~867.4 (mean: 867.3) (QR: 867.2~867.4)	867.3 (mean: 867.3)
Fragment 1 (Da)	1490.5~1490.7 (mean: 1490.6) (QR: 1490.4~1490.7)	1490.5~1490.7 (mean: 1490.6)

Assessor's Comment: *Representative UV profiles of 6 fragments for MYL-1501D lots are similar to that of U.S.-Lantus. The observed peptide mass values measured by reducing PMF for the cartridge presentation of U.S.-licensed Lantus and MYL-1501D are all highly similar to each other and to the expected theoretical mass ([M+H] ± 1 Da) for fragment 1/2/3/4/5/6. These data, together with the data obtained from non-reduced PMF analysis above, demonstrate a highly similar primary sequence and disulfide linkage numbers between MYL-1501D cartridge presentation and U.S.-Lantus cartridge presentation. In order to pinpoint the position of disulfide linkages, NMR studies have been carried out on representative batches of U.S.-licensed Lantus and MYL-1501D. Refer to the following section 4.2c Disulfide Linkage Confirmation by Solution-State 2D NMR Spectroscopy for more details.*

3.2.R.4.3.4.2 Secondary and Tertiary Structure Confirmation

The test methods used for assessing similarity of secondary and tertiary structure are presented in Table 78 below.

Table 78: Test Methods used for Higher order Structure Similarity Assessment

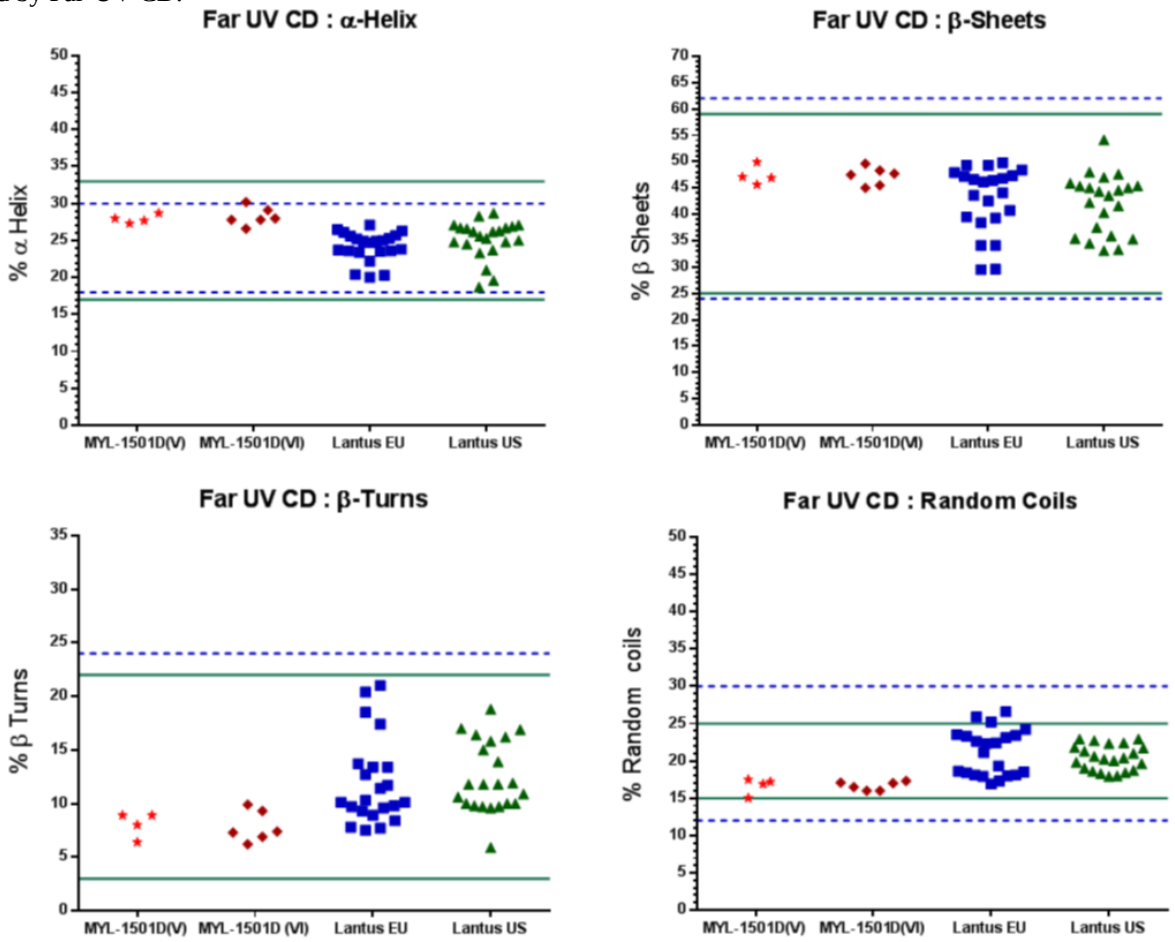
Analytical Test method	Description
Secondary Structure	Far-UV-CD Spectra
	Fourier Transform Infrared Spectroscopy
Higher Order Structure	Near-UV-CD Spectra
	Intrinsic Fluorescence
	Extrinsic Fluorescence
	Nuclear Magnetic Resonance (2D-NMR)
Thermal stability	Differential Scanning Calorimetry
Crystal structure	X-Ray Crystallography

4.2a Far UV CD Spectroscopic Analysis

Circular Dichroism (CD) refers to the differential absorption of left and right circularly polarized light and the spectrum obtained due to this phenomenon is called CD spectrum in which the CD signal is represented in terms of Milli-degrees (mdeg). Wavelength scans, using a CD spectrometer, in the "far-UV" spectral region (200-260 nm) and the "near-UV" spectral region (260-360 nm) result in CD spectra that are characteristic of the secondary and tertiary structure of a protein. Secondary structure of a protein can be determined by CD spectroscopy in the "far-UV" spectral region (190-260 nm).

10 lots of MYL-1501D in cartridge (age from 1 to 10 month at analysis) were compared to 22 lots of U.S.-licensed Lantus (age from 16 to 33 month at analysis). Representative overlaid far-UV CD profiles are provided in CAA report 1 but not shown here. The far-UV CD spectra were then deconvoluted by Yang's reference fit to estimate the secondary structural components such as α-helix, β-sheets, β-turns and random coil. Data distribution of the secondary structures are represented as scatter plots in Figure 70 below.

Figure 70: Scatter plot distribution for secondary structure of EU-approved Lantus®, US-approved Lantus® and MYL-1501D assessed by Far-UV CD.



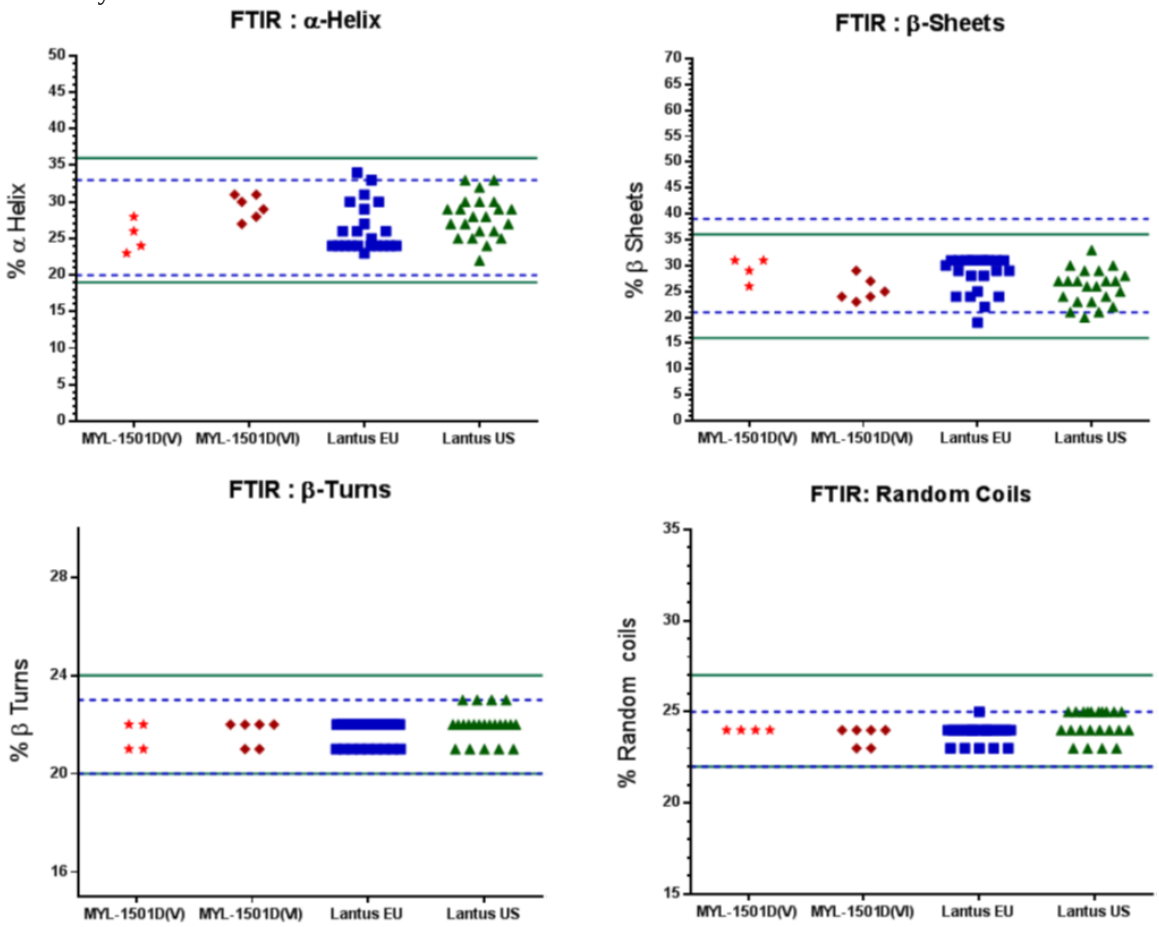
Assessor's Comment: *Representative Far-UV CD spectra of MYL-1501D lots are similar to that of U.S.-licensed Lantus. The secondary structural contents (α-helix, β-sheets, β-turns and random coil) for all MYL-1501D lots are 100% within the quality range established for U.S.-Lantus, supporting a demonstration of highly similar secondary structure between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation. Similarity of secondary structure is also supported by orthogonal FTIR method as discussed below.*

4.2b Fourier Transform Infrared Spectroscopy (FTIR)

FTIR is used as an orthogonal tool for secondary structure estimation. It is a non-destructive technique which provides information about the secondary structure composition of proteins.

10 lots of MYL-1501D in cartridge (age from 1 to 10 month at analysis) were compared to 22 lots of U.S.-licensed Lantus (age from 14 to 33 month at analysis). Representative overlaid FTIR spectra are provided in CAA report 1 but not shown here. Data distribution for the secondary structures (α-helix, β-sheets, β-turns and random coil) are represented as scatter plots in Figure 72 below.

Figure 72: Scatter plot distribution for Secondary structures for EU-approved Lantus®, US-approved Lantus® and MYL-1501D assessed by FTIR



Assessor's Comment: *The representative FTIR spectra profiles of MYL-1501D lots are similar to that of U.S.-licensed Lantus. The secondary structure (α-helix, β-sheets, β-turns and random coil) estimations for all MYL-1501D lots are 100% within the quality range established for U.S.-Lantus, supporting a demonstration of highly similar secondary structure between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.*

Overall, the assessment of secondary structure by Far UV spectroscopy (section 4.2a above) and FTIR supports a demonstration of highly similar secondary structure between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.

4.2c Disulfide Linkage Confirmation by Solution-State 2D NMR Spectroscopy

Disulfide linkages are critical for the stability and conservation of the 3D structure of a protein. Insulin and its analogues are an example where the disulfide linkages maintain the globular fold of the protein thus conserving their activity. In Insulin Glargine the A- and B chains are crosslinked by two disulfide bridges (A20–B19 and A7–B7). A third intra-chain disulfide linkage exists in the A-chain (A6–A11). As shown in following Figure 73 to Figure 75, the presence of disulfide linkages in MYL-1501D (lot BS15005851 and BS15009374) and U.S.-Lantus (lot 4F1179A) is confirmed by solution-state 2D NMR spectroscopy studies.

Figure 73: NMR spectra: a) 2D [^{1}H, ^{1}H] TOCSY and b) 2D [^{1}H, ^{1}H] NOESY of MYL-1501D (Process V; BS15005851)

The vertical dotted lines indicate the spectral assignments for the Cysteines at positions A6, A7, A11, A20, B7 and B19. The horizontal dotted lines show one of the NOE connectivity's arising due to the disulphide linkage indicated as hyphenated residue numbers near the lines

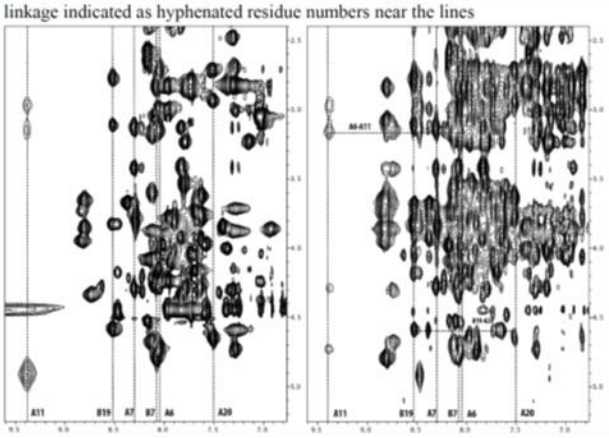


Figure 74: NMR spectra: a) 2D [^{1}H, ^{1}H] TOCSY and b) 2D [^{1}H, ^{1}H] NOESY of MYL-1501D (Process VI; BS15009374)

The vertical dotted lines indicate the spectral assignments for the Cysteines at positions A6, A7, A11, A20, B7 and B19. The horizontal dotted lines show one of the NOE connectivity's arising due to the disulphide linkage indicated as hyphenated residue numbers near the lines

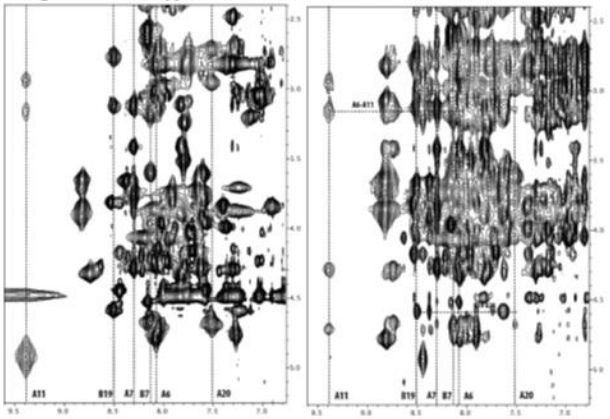
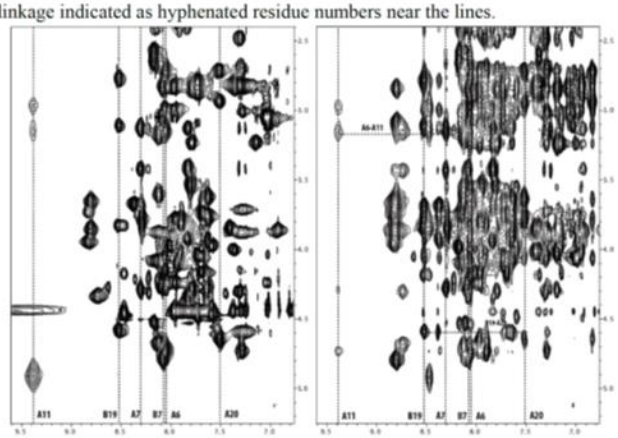


Figure 75: NMR spectra: a) 2D [^{1}H, ^{1}H] TOCSY and b) 2D [^{1}H, ^{1}H] NOESY of US-approved Lantus® (4F1179A)

The vertical dotted lines indicate the spectral assignments for the Cysteines at positions A6, A7, A11, A20, B7 and B19. The horizontal dotted lines show one of the NOE connectivity's arising due to the disulphide linkage indicated as hyphenated residue numbers near the lines.



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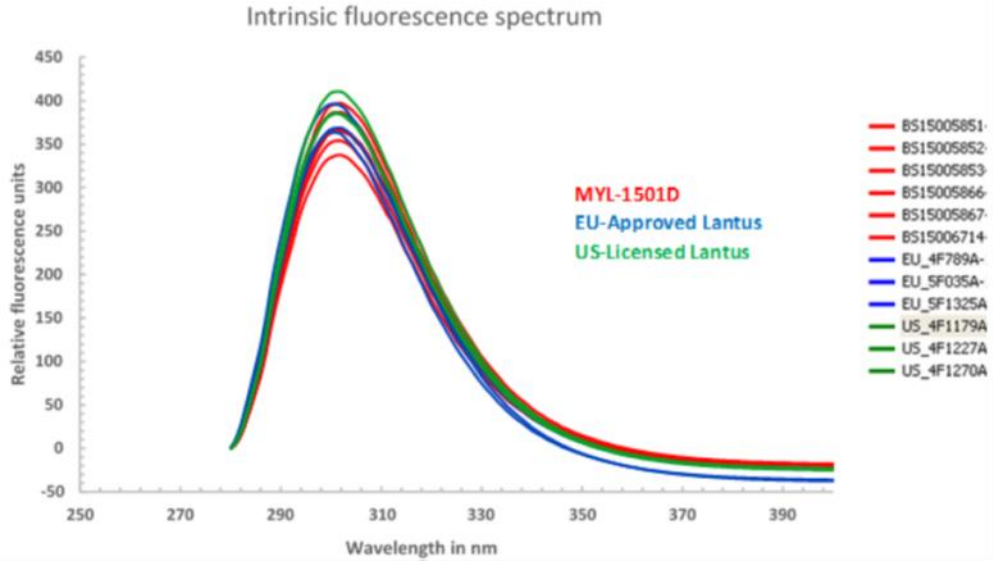
Assessor's Comment: *The 2D NMR spectra profiles of MYL-1501D lots are similar to that of U.S.-licensed Lantus. Cysteines at positions 6,7,11 and 20 of the A-chain and cysteines at positions 7 and 19 of the B chain were identified and assigned. The disulfide linkages between A6-A11, A7-B7 and A20-B19 were conformed in MYL-1501D and U.S.-Lantus lots. The minor changes in chemical shifts, peak splitting and extra peaks observed here could be due to differences in NMR buffer conditions. Since the peaks and connectivities that correspond to the disulfide linkages do not show any major change in the chemical shifts, these data support a demonstration of highly similar disulfide linkages between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.*

4.2d Intrinsic Fluorescence

Intrinsic fluorescence of a folded protein is a mixture of the fluorescence from individual aromatic amino acids, mostly due to tryptophan residues, with some due to tyrosine and phenylalanine and is used as a tool indicative of conformational state of a protein. The fluorescence emission depends on the type, number of aromatic residues, and their solvent exposure. The wavelength of the emitted light is an additional indicator of the fluorophore environment.

10 MYL-1501D lots (age from 1 to 10 month) were analyzed side by side with 10 U.S.-Lantus lots (age from 18 to 25 month) to measure the peak maximum (λ_{max}). Representative overlaid intrinsic fluorescence spectra are provided in Figure 77 below.

Figure 77: Overlay of intrinsic fluorescence spectra of EU-approved Lantus®, US-approved Lantus® and MYL-1501D



The observed λ_{max} values for U.S.-Lantus and MYL-1501D are provided in Table 85 and 87 in CAA report 1 and are summarized in the table below (assessor generated).

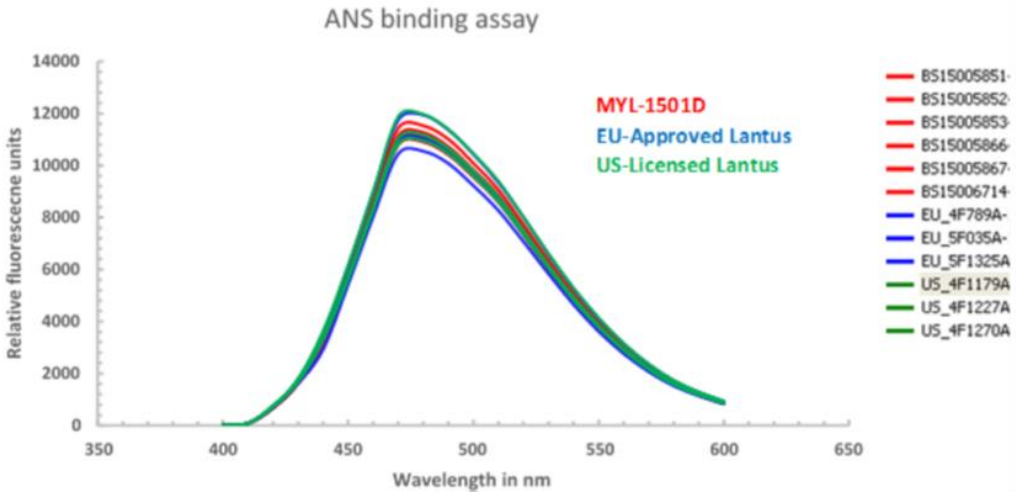
Intrinsic fluorescence	U.S.-Lantus (cartridge) Min – Max range	MYL-1501D (cartridge) Min – Max range
λ_{max} (nm)	300.93~302.03 (mean: 301.15) (QR: 299.76~302.54)	300.00~302.03 (mean: 301.28)

Assessor's Comment: *The intrinsic fluorescence spectra of MYL-1501D cartridge lots are similar to that of U.S.-licensed Lantus. The emitted peak maximum (λ_{max}) values for MYL-1501D lots are also 100% within the quality range established for U.S.-Lantus. These data support a demonstration of highly similar structural conformation between the cartridge presentation of MYL-1501D and U.S.-Lantus.*

4.2e Extrinsic Fluorescence

Fluorescence spectroscopy techniques with non-covalent, extrinsic fluorescent dyes are commonly used to monitor protein conformational variants, e.g. environmental stress or chemical induced protein change (oxidation or deamidation), or by protein aggregation. 8-Anilinonaphthalene-1-sulfonic acid (ANS) is an organic fluorescent compound containing both a sulfonic acid and an amine group used as a fluorescent molecular probe. ANS binds with high affinity to the hydrophobic surfaces of proteins and the interaction is mediated by formation of ion pairs. The emission maximum of ANS undergoes a blue shift and fluorescence intensity increases significantly upon binding to the hydrophobic pockets in the protein molecule. The fluorescence emission is very sensitive to solvent polarity, viscosity and temperature.
10 MYL-1501D lots (age from 1 to 9 month) and 22 U.S.-Lantus lots (age from 16 to 33 month) were analyzed using ANS binding assay to measure the peak maximum (λ_{max}). The fluorescence spectra for both products were acquired in formulation buffer, with the excitation at 388 nm and the emission was scanned from 400-660 nm. Representative overlaid extrinsic fluorescence spectra are provided in Figure 78 below.

Figure 78: Representative Overlay of extrinsic fluorescence spectra using ANS binding assay of EU-approved Lantus®, US-approved Lantus® and MYL-1501D



The observed λ_{max} values for U.S.-Lantus and MYL-1501D are provided in Table 88 and 90 in CAA report 1 and are summarized in the table below (assessor generated).

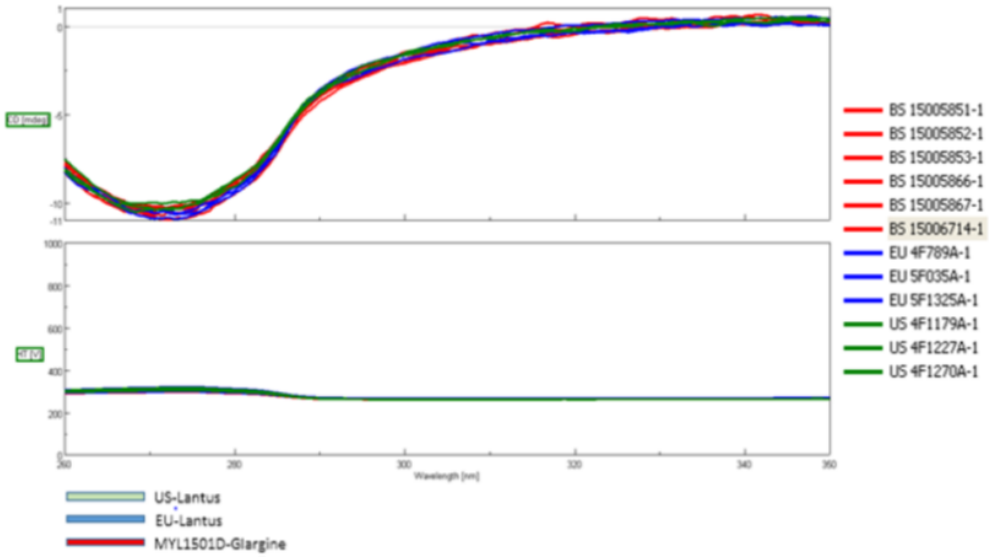
Extrinsic fluorescence	U.S.-Lantus (cartridge) Min – Max range	MYL-1501D (cartridge) Min – Max range
λ_{max} (nm)	473~483 (mean: 477.8) (QR: 468.3~487.3)	474~478 (mean: 475.9)

Assessor's Comment: *The extrinsic fluorescence spectra of MYL-1501D lots are similar to that of U.S.-licensed Lantus. The emitted peak maximum (λ_{max}) values for MYL-1501D lots are 100% within the quality range established for U.S.-Lantus. These data also support a demonstration of highly similar structural conformation between the cartridge presentation of MYL-1501D and U.S.-Lantus.*

4.2f Near UV CD Spectral Analysis

Circular Dichroism (CD) refers to the differential absorption of left and right circularly polarized light and the spectrum obtained due to this phenomenon is called CD spectrum in which the CD signal is represented in terms of Milli-degrees (mdeg). Wavelength scans, using a CD spectrometer, in the "near-UV" spectral region (260-360 nm) result in CD spectra that are characteristic of the tertiary structure of a protein. This methodology, also called near-UV CD spectral analysis, can detect changes in the tertiary structure which includes environment around aromatic residues and disulfide linkages in the protein.
10 lots of MYL-1501D were compared to 22 lots of U.S.-licensed Lantus. Representative overlaid near UV-CD spectra of 6 MYL-1501D lots (age from 4 to 6 month) and 3 U.S.-licensed Lantus lots (age from 21 to 25 month) are provided in Figure 79 below. The near UV CD spectra profiles are compared visually for any conformational changes.

.Figure 79: Representative Overlay of Near UV CD profile for tertiary structure of EU-approved Lantus®, US-approved Lantus® and MYL-1501D



Assessor's Comment: *The age information for MYL-1501D and U.S.-Lantus lots used in near UV CD spectral analysis was missing in the original submission. In response to the Agency's IR (OBP IR #2) sent on 02/09/2021, Mylan provided age information for all lots displayed in Figure 79 on 02/16/2021. Mylan's response is acceptable.*

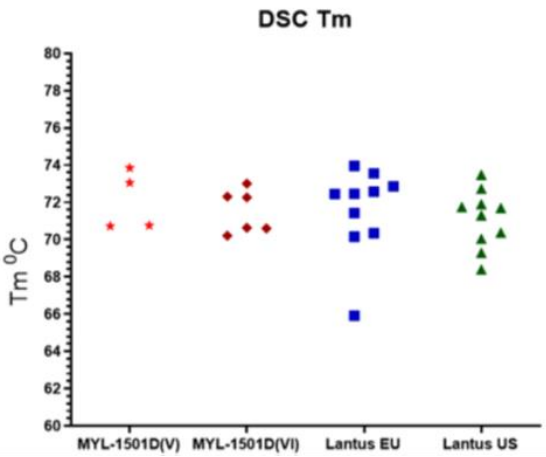
Representative near-UV CD spectra (260 – 350 nm) of MYL-1501D and U.S.-licensed Lantus lots all exhibit a similar pattern with a broad negative CD band around 270 nm and a shoulder at 300 – 310 nm, supporting a demonstration of highly similar tertiary structure between the cartridge presentation of MYL-1501D and U.S.-Lantus.

4.2g Thermal Stability by Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) illustrates the structure of a protein from a thermodynamic perspective. DSC measures the heat capacity required to induce a change in the structure of a molecule. The temperature at which half of the protein molecules are unfolded is called the melting temperature (mid-point of DSC peak, Tm). This thermodynamic difference would indicate structural differences. Similar Tm values for different sample would indicate similarity of protein structure within the samples.

The thermal properties and structural-phase transitions of 10 U.S.-Lantus lots (age from 20 to 28 month) and 10 MYL-1501D lots (age from 3 to 12 month) were evaluated side-by-side by DSC. The conformational changes can be visualized by profile comparison in addition to the Tm values. Representative overlaid DSC profiles and observed Tm values are provided in CAA report 1 but not shown here. The scatter plot representing the distribution of data is presented in Figure 84 below.

Figure 84: Scatter plot distribution for Tm Values Using DSC for EU-approved Lantus®, US-approved Lantus® and MYL-1501D



U.S.-Lantus Tm (°C):
Min-Max: 68.40~73.48
Mean: 71.10
QR: 66.41~75.79

MYL-1501D Tm (°C):
Min-Max: 70.21~73.85
Mean: 71.75

Assessor's Comment: *The representative DSC profiles for MYL-1501D lots are similar to that of U.S.-licensed Lantus. The measured melting temperature (Tm) values for MYL-1501D are 100% within the quality range established for U.S.-Lantus (as indicated by the notes on right side of Figure 84 above). These results support a demonstration of highly similar thermal stability and conformation between MYL-1501D cartridge presentation and U.S.-Lantus cartridge presentation.*

4.2h X-Ray Crystallography

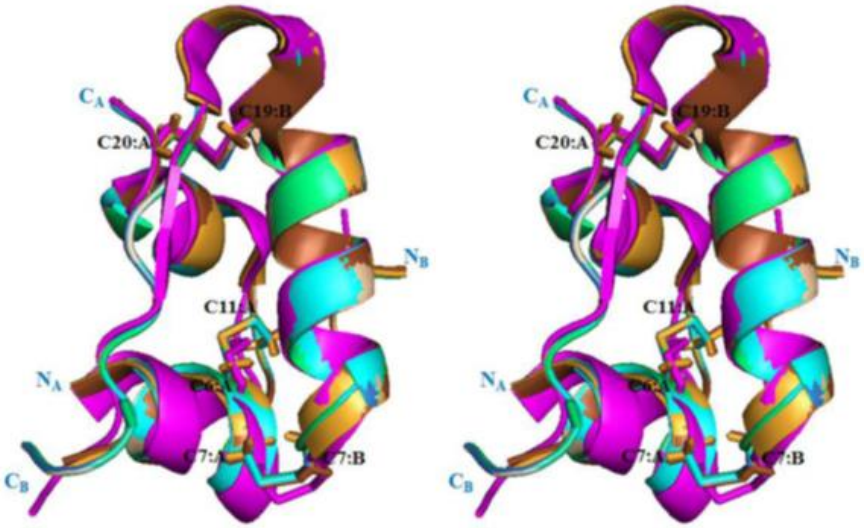
The higher order structures of intact proteins are key for the characterization of biologics, which may provide potential clues to any observed biological and/or immunological differences between proteins and variant forms (i.e., proteins with PTMs). X-ray crystallography, which is an orthogonal method to near UV CD, can provide more details of the 3D structure of a protein.

Insulin glargine extracted samples from the cartridge presentation of U.S.-Lantus lot (4F1179A), MYL-1501D Process V lot (BS15005851), and MYL-1501D Process VI lot (BS15009374) were used for crystallization, X-ray diffraction experiments, structure determination and comparative structural analysis. The structures were determined by molecular replacement using the human insulin structure as the phasing model. However, only the polypeptide was used in molecular replacement calculations, and positions of water molecules were independently determined using difference Fourier maps. The resulting structures of these insulin glargine samples were refined, and the refinement statistics reflect the quality of diffraction data collected and the quality of the final maps.

The 3D structure of MYL-1501D and U.S.-licensed Lantus are compared to each other and to the previously determined 3D structures of insulin glargine and human insulin, as shown in the following Figure 85.

Figure 85: Superposition of the EU-approved Lantus®, US-approved Lantus® and MYL-1501D with the published insulin glargine structure from Protein Data bank, the left panel shows superimposed structure with insulin as base and right panel shows superimposed structure with glargine as the base.

In this stereo representation, the seven structures viz., EU-approved Lantus® (light green), US-approved Lantus® (Wheat), MYL-1501D-Process V (sky blue), MYL-1501D-Process VI (Cyan), 4IYD (Bright orange), 4IYF (Brown) and 3W7Y (Magenta) EU-approved Lantus® (light green), US-approved Lantus® (tan), MYL-1501D-Process V (sky blue), MYL-1501D-Process VI (plum), 4IYD (Salmon) and 4IYF (Light green) are shown. The molecules superpose well with an overall RMSD of 0.146 Å.



MYL-1501D cartridge lot BS15005851 (V) (sky blue)

MYL-1501D cartridge lot BS15009374 (VI) (Cyan)

U.S.-Lantus cartridge lot 4F1179A (wheat)

E.U.-Lantus cartridge lot 4F789A (light green)

4IYD (bright orange): Insulin glargine crystal structure 1 in PDB database

4IYF (brown): Insulin glargine crystal structure 2 in PDB database

3W7Y (magenta): structure of human insulin in PDB database

Assessor's Comment: *The Applicant indicated there is a five-degree shift between the left and right figure showing above. The 3D structures show an overlay of the analyzed insulin glargine samples with the published structure of human insulin and insulin glargine. The overlay closely resembles in terms of polypeptide fold, oligomeric organization and thermal parameters. All the molecules superpose well with an overall RMSD of 0.146 Å. Overall, the X-ray structure of MYL-1501D and U.S.-licensed Lantus lot is highly similar to each other and to the previously determined 3D structures of insulin glargine, supporting a demonstration of highly similar 3D structure between MYL-1501D cartridge presentation and U.S.-Lantus cartridge presentation.*

Summary of Primary, Secondary and Higher Order Structure:

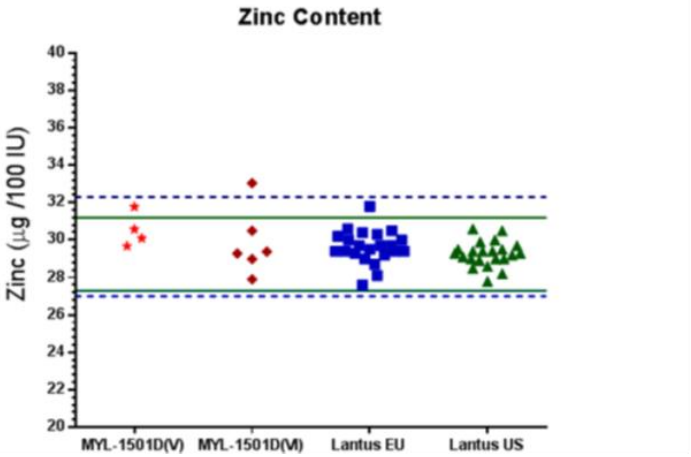
Results from multiple orthogonal analytic studies to assess the amino acid sequence, disulfide linkage, secondary and tertiary structure support a demonstration of highly similar primary, secondary, and higher order structure between MYL-1501D cartridge presentation and U.S.-licensed Lantus cartridge presentation.

3.2.R.4.3.5 Zinc Content by Atomic Absorption Spectrometry (AAS)

Zinc is an important functional excipient which influences the release of insulin glargine from the injection site. The stabilization of the insulin- glargine hexamer and higher aggregates influences the nature of the precipitate, the rate of its dissolution, and the absorption from the site of injection. Animal studies indicated that the addition of zinc as a hexamer-stabilizing agent delays the onset and further increases the duration of action of insulin glargine in a concentration-dependent manner resulting in delayed and prolonged absorption from the injection site after subcutaneous administration.

10 MYL-1501D lots (age from 1 to 7 month) and 22 U.S.-Lantus lots (age from 15 to 30 month) were analyzed using Atomic Absorption Spectrometry (AAS). The scatter plot of Zinc content data is presented in Figure 86 below.

Figure 86: Scatter plot distribution of Zinc content in EU-approved Lantus®, US-approved Lantus® and MYL-1501D



Assessor's Comment: *Zinc content values for 80% of MYL-1501D lots are within the quality range obtained for U.S.-Lantus. Two lots of MYL-1501D have marginally higher level of Zinc (31.8 µg/100 IU for lot BS15002330 and 33 µg/100 IU for lot BS15005867) than the upper quality range observed for U.S.-Lantus (31.2 µg/100 IU). Zinc impacts stability, and the higher order structure of insulin, thereby affecting the pharmacokinetic profile. The observed difference does not preclude a demonstration that MYL-1501D is highly similar to U.S.-Lantus, since MYL-1501D cartridge lots have similar higher order structure, functional and biological activity to U.S.-Lantus cartridge, as demonstrated by assays discussed above as well as comparable stability profiles (discussed below). Additionally, the levels of Zinc are controlled in drug substance and drug product at release and stability.*

3.2.R.4.3.6 Comparative Forced Degradation Study for MYL-1501D (cartridge) and U.S.-Lantus (cartridge)

A comparative forced-degradation (FD) study was performed to establish the similarity of degradation profiles between MYL-1501D cartridge presentation and U.S-Lantus cartridge presentation. Protocols and results for this FD study can be found in eCTD Section 3.2.P.8 Stability (pre-filled pen) in the application. The batch details of MYL-1501D cartridge, U.S-Lantus and E.U.-Lantus cartridge used in this study are provided in the table below (assessor modified based on Table 3.2.P.8.1/10 in eCTD Section 3.2.P.8.1 Stability Summary and Conclusion).

Sample	Lot Number	Product Age at Start of FD Study	Expiry or Manufacturing Date	Used in Other CAA Studies
U.S.-Lantus pre-filled pen	5F1966A	13 months	Unknown	No
E.U.-Lantus cartridge	4F789A	17 months	September 2017 (Expiry)	Yes
MYL-1501D cartridge (Process VI DS)	BS15006714	3 months	January 2016	Yes
MYL-1501D cartridge (Process V DS)	BS15005851	4 months	November 2015	Yes

In this FD study, all DP cartridges were placed under identical degradation conditions to compare the product degradation rate, mechanisms and impurity profiles. These multiple degradation conditions, including elevated temperature, variable pH (acidic and alkaline), photo exposure, mechanical stress (agitation), and oxidation were implemented on all batches. The testing conditions and protocols are detailed in Table 3.2.P.8.1/ 11 below. The analytical methods are the same as those presented in eCTD Section 3.2.P.5.2 Analytical Procedures (pre-filled pen).

Table 3.2.P.8.1/ 11: Testing Protocol –Comparative Forced Degradation Study

Degradation Factor	Condition	Time-points	% HMWP by SE-HPLC	% Total impurities and any individual impurity by RP-HPLC	Assay by RP-HPLC
pH stress	pH 2	0, 1, 3, 8 days	√	√	√
	pH 10	0, 1, 3 and 6 hours	√	√	√
Chemical Treatment	Oxidation (3% H_2O_2)	0, 1, 6 and 12 hours	√	√	√
Photo Treatment	Photo exposure	0, 0.6, 1.2 Million lux hours	√	√	√
Mechanical Stress	Agitation at 250 RPM at 25°C	0, 1, 3, 7,15 days	√	√	√
Temp. Stress	60°C	0, 1, 3, 7,15 days	√	√	√
	2-8°C (Control)	0, 1, 3, 8,15 days	√	√	√
Initial time point (control)	Control (initial time-point)	0 hours	√	√	√

Assessor's Comment: *On 02/16/2021, in a response to our IR (OBP IR #2), Mylan clarified that the mechanical stress condition is agitation at 250 rpm under 25°C ± 3°C and updated relevant tables in eCTD Section 3.2.P.1 Stability Summary and Conclusion and Section 3.2.P.3. Stability Data. Table 3.2.P.8.1/ 11 here is the updated version.*

Results for this FD study under various stress conditions are presented in eCTD Section 3.2.P.8.3 Stability Data (pre-filled pen) and are summarized in the table below (assessor generated). Data obtained from initial time-point and end time-point of MYL-1501D cartridge (from Process VI or V DS) and U.S-Lantus pre-filled pen are shown here. Data obtained from E.U.-Lantus cartridge are provided by the Applicant but not shown here.

Summary results of initial/end time point under various stress conditions for MYL-1501D and U.S.-Lantus

Forced degradation factors	Condition	Initial/ End time point	% HMWP by SE-HPLC			% Total impurities by RP-HPLC			% Any individual impurity by RP-HPLC			% Assay by RP-HPLC		
			MYL-VI (cart)	MYL-V (cart)	US-Lantus (PFP)	MYL-VI (cart)	MYL-V (cart)	US-Lantus (PFP)	MYL-VI (cart)	MYL-V (cart)	US-Lantus (PFP)	MYL-VI (cart)	MYL-V (cart)	US-Lantus (PFP)
Initial time point (control)		**Time 0**	**0.03**	**0.04**	**0.03**	**0.35**	**0.94**	**1.00**	**0.15**	**0.24**	**0.25**	**98.6**	**98.6**	**102.7**
Temperature stress	2-8°C (control)	15 days	0.02	0.05	0.04	0.34	0.90	0.95	0.14	0.27	0.32	98.6	99.9	101.8
	60°C	15 days	0.77	0.86	0.49	12.57	13.49	13.80	7.12	6.72	5.70	84.3	84.4	84.2
Photo stress	Photo exposure	1.2M lux hrs	13.80	13.33	19.18	4.54	4.44	6.07	1.05	1.23	1.43	82.8	84.3	81.5
Oxidative stress	3% H_2O_2	12 hours	1.14	0.89	0.70	13.95	12.79	12.84	8.34	7.94	8.55	71.6	72.0	72.0
pH stress	pH 2	8 days	0.04	0.04	0.04	1.37	1.96	2.04	0.49	0.60	0.59	94.3	94.7	95.2
	pH 10	6 hours	0.08	0.10	0.09	0.58	1.35	1.12	0.25	0.40	0.40	95.0	97.4	97.9
Mechanical stress	Agitation at 250rpm & 25°C	15 days	0.05	0.09	0.05	0.94	1.41	1.62	0.41	0.44	0.48	94.5	98.2	99.9

MYL-VI (cart): MYL-1501D cartridge manufactured with Process VI DS (lot #: BS15006714, 3-month old at FD study)
MYL-V (cart): MYL-1501D cartridge manufactured with Process V DS (lot #: BS15005851, 4-month old at FD study)
US-Lantus (PFP): U.S.-licensed Lantus pre-filled pen (lot #: 5F1966A, 13-month old at FD study)

Assessor's Comment: *Mylan did not provide information about individual impurities species and levels in all above FD studies in the original submission for the Agency to compare the degradation pathways between different products. An IR (OBP IR #2) was sent on 02/09/2021 regarding this issue. Mylan provided response on 02/19/2021 with tabulated results for each impurity species under all tested stress conditions in eCTD Section 1.11.1 Quality Information Amendment - Response to Information Request Dated February 9, 2021 - Comment 7a. Their IR response is acceptable. These results, together with the forced degradation data presented in eCTD Section 3.2.P.8.3 Stability Data (pre-filled pen) summarized above, are discussed in the following section a/b/c/d/e.*

a. Temperature Stress

Assessor's Comment: *All products under the control temperature condition of 2°C~8°C remained stable, showing no meaningful change during the whole testing period with very low levels of all individual impurity species. Under the stressed temperature condition of 60°C, increases in HMWP, total impurity, and any individual impurity were observed in both MYL-1501D lots and U.S.-Lantus lot and similar levels were seen during the whole testing period of 15 days. When comparing individual impurity species and levels, the major degradation species are A15 deamidation and DesR & B3 deamidation, whose levels are similar across all products at all tested time points, indicating the degradation pathways are similar between MYL-1501D lots and U.S.-Lantus lot under 60°C. Overall, the data presented here support a demonstration of similar stability and degradation pathways under 60°C between MYL-1501D cartridge presentation and U.S-Lantus cartridge presentation.*

b. Photo Exposure

Assessor's Comment: *MYl-1501D and U.S.-Lantus lots showed a similar degradation profile under light exposure up to 1.2 million lux hours. Increases in HMWP, and impurities, primarily Des TRR, with some other minor species like citrate conjugate and A15 deamidation, were observed across all products at all tested time points, indicating the degradation pathways under photo-stress are similar between MYL-1501D lots and U.S.-Lantus lot. MYL-1501D lots appear to have a lower rate of degradation under light stress compared to U.S.-Lantus. These results might indicate a slightly enhanced stability of the MYL-1501D DP compared to U.S.-Lantus or may be attributed to the younger age (3~4 months) of MYL-1501D lots used in this study, when compared to U.S-Lantus lot (13 month). Overall, the study showed that MYL-1501D cartridge lots and US-Lantus lots degrade under photo exposure conditions via similar degradation pathways.*

c. Oxidative Stress

Assessor's Comment: *MYL-1501D lots displayed similar levels of HMWP, total impurity, and any individual impurity to that of U.S.-Lantus lot during the whole testing period of 12 hours under the tested oxidative stress condition (3% H_2O_2). When comparing individual impurity species and levels, the major degradation species is acetylation & glargine conformer species (RRT 1.24- 1.34), whose levels are similar across all products at all tested time points. Overall, the data provided in the application support a demonstration of highly similar stability under oxidative stress of 3% H_2O_2 between MYL-1501D cartridge presentation and U.S.-Lantus cartridge presentation.*

d. pH Stress

Assessor's Comment: *All tested samples showed similarly low level of degradation under the testing conditions at pH 2 for up to 8 days or at pH 10 for up to 6 hours, with very low levels of all individual*

impurity species, supporting a demonstration of highly similar stability under tested pH stress conditions between MYL-1501D cartridge presentation and U.S.-Lantus cartridge presentation.

e. Mechanical Stress

Assessor's Comment: *On 02/16/2021, in a response to our IR (OBP IR #2), Mylan clarified that the mechanical stress condition is agitation at 250 rpm (not 230 rpm as shown before) and updated Table 3.2.P.8.3/ 101 in eCTD Section 3.2.P.3 Stability Data (pre-filled pen).*
All tested samples showed almost minimal degradation under the testing condition of 250 rpm and 25°C of up to 15 days, with very low levels of all individual impurity species, supporting a demonstration of highly similar stability under tested mechanical stress condition between MYL-1501D cartridge presentation and U.S.-Lantus cartridge presentation.

Summary of Comparative Forced Degradation Study:
Comparative forced degradation studies under thermal stress, photo exposure, oxidative stress, pH and mechanical stress conditions showed that MYL-1501D cartridge presentation and U.S.-Lantus cartridge presentation have similar degradation pathways and profiles.
The stability of MYL-1501D cartridge presentation and U.S.-Lantus cartridge presentation are also similar under accelerated condition (25°C ± 2°C/60% ± 5% RH), refer to the aforementioned NDA-210605 Review 1 (dated 4/5/2018) and NDA-210605 Review 2 (dated 8/22/2019) for detailed assessment about comparative accelerated stability study.

Summary of Overall Similarity between MYL-1501D (cartridge) and U.S.-licensed Lantus (cartridge):
Results from multiple orthogonal analytic methods demonstrate that MYL-1501D cartridge presentation is highly similar to U.S.-licensed Lantus cartridge presentation with respect to functional and biological activities, purity and impurities, product variants, primary, secondary, and higher order structure and degradation pathways.

3.2.R.4.4 Comparative Analytical Assessment between U.S.-Lantus Vials and Cartridges

The U.S.-licensed Lantus is presented in cartridges (contained in pre-filled injection pens) and vials. The formulation of vials has an additional excipient (polysorbate 20 at target concentration of 20 µg/mL) in comparison with cartridge/pre-filled pen formulation. The same as U.S.-Lantus vials, MYL-1501D DP presented in vials also has the additional excipient polysorbate 20 at a concentration of 20 µg/mL in comparison to MYL-1501D cartridges. The Applicant conducted an assessment to demonstrate a similarity between the two presentations of U.S.-licensed Lantus- vials and cartridges. Data used for this assessment are obtained from either side-by-side testing or stand-alone analysis conducted at different times during MYL-1501D product development. Equivalence testing is not performed for this similarity comparison.

Assessor's Comment: *The data for U.S.-Lantus cartridges presented here in CAA report 2 are the same as the data for U.S.-Lantus cartridges shown in CAA report 1. According to Mylan, the testing for U.S.-Lantus vials was conducted either side-by-side with U.S.-Lantus cartridges or stand-alone during MYL-1501D development. On 02/16/2021, Mylan provided information of reference standards used in each assay and results for bridging studies if different reference standards were used in an assay in response to the Agency's IR (OBP IR #2) sent on 02/09/2021. The information provided by Mylan support the pooling of the data from various runs of the corresponding assays, as discussed in section 3.2.R.4.2 Quality Attributes/ Criticality Risk Ranking/ Reference Standards previously, therefore is acceptable. The CAA results, as discussed in the following sections, demonstrate similarity between the vial presentation*

and the cartridge presentation of U.S.-Lantus. These CAA data, obtained from U.S.-Lantus vials or cartridges, are then combined to establish the U.S.-Lantus QR for the similarity assessment between MYL-1501D vial presentation and U.S.-Lantus (vial + cartridge). Based on the demonstrated similarity between U.S.-Lantus cartridges and vials as discussed ahead, this strategy of establishing a combined QR from U.S.-Lantus cartridge and vial lots for comparison with MYL-1401D vial lots is acceptable.

A summary of the analytical similarity results for U.S.-licensed Lantus (vial) vs. US-licensed Lantus (cartridge) are provided in the following table (assessor generated based on CAA report CDL/TR/LR.19.0091/20/002, also referred as CAA report 2 in the following context, QR: quality range). For attributes that are evaluated using quality ranges, when at least 90% of U.S.-Lantus vials are within the U.S.-Lantus cartridge QR, the results are deemed to support a demonstration of highly similar. In the following table, 'Yes' is indicated when similarity acceptance criteria are met or if the differences observed do not preclude a demonstration of highly similar.

Parameter	Quality Attribute	Test Method	Number of Lots U.S.-Lantus (cartridge): U.S.-Lantus (vial)		U.S.-Lantus (cartridge) Min-Max Range (QR: Mean±3SD)	U.S.-Lantus (vial) Min-Max Range	Support a Demonstration of Highly Similar between U.S.-Lantus (vial) and U.S.-Lantus (cartridge)
Protein content	Protein content/ Assay	RP-HPLC (% Assay: U/mL)	22:10		95.0~107.2 (QR: 87.9~111.1) (lot 4F1270A is 107.2, resulted in wide QR)	99.6~102.8	Yes
Metabolic activity	IR-B binding kinetics	Surface Plasmon Resonance (SPR) k_a (1/Ms) k_d (1/s) K_D (nM)	8:5	k_a	6.82E+05~7.55E+05 (QR: 6.18E+05 ~8.06E+05)	5.82E+05~7.39E +05	Yes
				k_d	0.011~0.015 (QR: 0.008~0.017)	0.013~0.016	
				K_D	15.36~20.40 (QR: 11.63~23.73)	21.62~28.24 (2 vial lots are out of the cartridge QR)	
	IR-B auto-phosphorylation	IR-B auto-phosphorylation assay (relative potency)	22:5		0.94~1.21 (QR: 0.88~1.26)	0.88~1.12	Yes
	IR auto-phosphorylation	IR auto-phosphorylation assay using HepG2 cells (relative potency)	22:5		0.86~1.18 (QR: 0.80~1.25)	0.99~1.15	Yes
	Glucose uptake activity	Glucose uptake assay in 3T3-L1 cells (relative potency)	8:5		0.94~1.12 (QR: 0.86~1.21)	0.87~1.10	Yes
Mitogenic activity	IR-A binding kinetics	SPR k_a (1/Ms) k_d (1/s) K_D (nM)	8:5	k_a	1.18E+06~1.70E+06 (QR: 1.00E+06~2.02E+06)	1.15E+06~1.65E +06	Yes
				k_d	0.023~0.036 (QR: 0.017~0.043)	0.022~0.031	
				K_D	17.62~22.75 (QR: 14.37~25.36)	18.61~23.20	
	IR-A auto-phosphorylation	IR-A auto-phosphorylation assay (relative potency)	22:5		0.97~1.17 (QR: 0.89~1.24)	1.05~1.14	Yes
	IGF-1 receptor binding kinetics	SPR k_a (1/Ms) k_d (1/s) K_D (nM)	22:5	k_a	1.47E+05~1.96E+05 (QR:1.37E+05~2.05E+05)	1.68E+05~1.81E +05	Yes
				k_d	0.04578~0.05421 (QR: 0.04352~0.05556)	0.5010~0.5018	
				K_D	0.26~0.34 (QR: 0.22~0.36)	0.28~0.30	

Parameter	Quality Attribute	Test Method	Number of Lots U.S.-Lantus (cartridge): U.S.-Lantus (vial)		U.S.-Lantus (cartridge) Min-Max Range (QR: Mean±3SD)	U.S.-Lantus (vial) Min-Max Range	Support a Demonstration of Highly Similar between U.S.-Lantus (vial) and U.S.-Lantus (cartridge)
	Saos-2 cell proliferation	Cell proliferation assay in Saos-2 cells (relative potency)	8:5		0.92~1.19 (QR: 0.72~1.35)	1.02~1.13	Yes
Size variant	High Molecular Weight Protein (HMWP)/ Aggregates	SEC-HPLC (% HMWP)	22:10		LOD: 0.015%, LOQ: 0.050%		Yes
					BQL~0.06 (QR: 0.04~0.06)	BQL~0.08	
		SEC-MALS	10:10	Mass fraction%	100 (QR:100~100)	100	Yes
				Mw/Mn	1.001~1.006 (QR: 0.999~1.007)	1.000~1.003	
				Mz/Mn	1.002~1.012 (QR: 0.997~1.016)	1.000~1.007	
		AUC–sedimentation velocity	3:3	Monomer sedimentation coefficient (S)	1.61~1.64 (QR: 1.59~1.65)	1.60~1.63	Yes
				Total aggregate fraction %	0.0~3.2 (QR: 0~5.9)	0.6~3.1	
Product variant	Glyceridic ester of Glutamic acid	RP-HPLC (%) LOD: 0.015% LOQ: 0.040%	22:10	RRT: 0.96~0.98	0.14~0.34 (QR: 0.05~0.45)	0.24~0.28	Yes
	Insulin glargine			RRT: 1	98.42~99.24 (QR: 97.93~99.66)	98.48~98.95	
	A15 deamidation			RRT: 1.02~1.03	0.16~0.42 (QR: 0.01~0.57)	0.16~0.42	
	Des R & B3 deamidation			RRT: 1.04~1.08	0.17~0.40 (QR: 0.04~0.56)	0.29~0.42	
	Des TRR			RRT: 1.14~1.18	BDL~0.10 (QR: 0.00~0.11)	0.05~0.10	
	Citrate conjugate			RRT: 1.16~1.25	BDL~0.09 (QR: 0.03~0.10)	0.05~0.08	
	Acetylation			RRT: 1.24~1.34	BQL~0.06 (QR: 0.03~0.07)	BDL~BQL	
Isoelectric point (pI)	Isoelectric point (pI)	Capillary Iso-Electric Focusing (cIEF)	15:10		7.00~7.06 (QR: 6.98~7.09)	7.00~7.07	Yes
Primary structure & disulfide confirmation	Intact mass	ESI-MS Mass spectrometry (Da)	22:10		6063.5~6063.9	6063.9	Yes
	Intact mass of chain A and chain B	Reduced ESI-MS by DTT to separate into chain A and chain B(Da)	22:10	Chain A	2326.8~2327.4	2327.02	Yes
				Chain B	3742.9~3743.2	3742.9	
	Disulfide confirmation	Non-reduced peptide mass fingerprinting (PMF) using Glu-C analyzed with LC-MS and MS-MS (Da)	22:10	Fragment 4	417.1	417.1	Yes
				Fragment 3	1428.7~1429.4	1429.2~1429.6	
				Fragment 2	1320.5~1320.6	1320.5~1320.7	
				Fragment 1	2969.1~2970.6	2969.3~2970.4	
		Reduced (DTT) PMF using Glu-C analyzed with LC-MS and MS-MS (Da)	22:10	Fragment 6	456.0~456.1	456.0~456.1	Yes
				Fragment 5	417.1	417.1	
				Fragment 4	1428.3~1429.2	1428.7~1429.6	
				Fragment 3	1482.7~1482.8	1482.7~1482.9	
				Fragment 2	867.3~867.4	867.4	
				Fragment 1	1490.5~1490.7	1490.6~1490.7	
		Far UV-CD Spectra		α-helix %	18.7~28.7 (QR: 17~33)	23.7~26.6	Yes

Parameter	Quality Attribute	Test Method	Number of Lots U.S.-Lantus (cartridge): U.S.-Lantus (vial)		U.S.-Lantus (cartridge) Min-Max Range (QR: Mean±3SD)	U.S.-Lantus (vial) Min-Max Range	Support a Demonstration of Highly Similar between U.S.-Lantus (vial) and U.S.-Lantus (cartridge)
Secondary structure	Secondary structure (α-helix, β-sheets, β-turns and random coil)		22:10	β-sheet %	33.1~54.1 (QR: 25~59)	41.3~44.9	
				β-turn %	5.9~18.8 (QR: 3~22)	10.6~14	
				Random coil%	17.9~22.9 (QR: 15~25)	18.1~20.1	
		Fourier Transform Infrared (FT-IR) Spectroscopy	22:10	α-helix %	22~33 (QR: 19~36)	23~30	Yes
				β-sheet %	20~33 (QR: 16~36)	24~32	
				β-turn %	21~23 (QR: 20~24)	21~22	
				random coil %	23~25 (QR: 22~27)	23~24	
				Amide I cm^{-1}	1646.91~1650.77 (QR: 1644.97~1654.11)	1646.91~1650.77	
				Amide II cm^{-1}	1536.99~1540.85 (QR: 1536.41~1543.01)	1536.99~1538.92	
Higher order structure	Higher order structure	Nuclear Magnetic Resonance (2D-NMR)	1:1		Similar 2D-NMR spectra were observed between U.S.-Lantus vial 5F193A and U.S.-Lantus cartridge 4F1179A. The disulfide linkage between A6-A11, A7-B7 and A20-B19 were confirmed.		Yes
		Intrinsic Fluorescence (λ_{max}: nm)	10:10		300.93~302.03 (QR: 299.76~302.54)	301.07~302.00	Yes
		Extrinsic Fluorescence (λ_{max}: nm)	22:10		473~483 (QR: 468.3~487.3)	474~479	Yes
		Near UV-CD Spectra	22:10		Similar near UV-CD spectra were observed U.S.-Lantus vials and U.S.-Lantus cartridges.		Yes
	Thermal stability	Differential Scanning Calorimetry (DSC) (Tm: °C)	10:10		68.40~73.48 (QR: 66.41~75.79)	70.07~72.99	Yes
	Crystal structure	X-Ray Crystallography	1:1		The 3D-structures of U.S.-Lantus vial 5F193A and U.S.-Lantus cartridge 4F1179A are similar to each other and to the previously determined 3D-structures of insulin glargine.		Yes
Excipient	Zinc content	Atomic Absorption Spectrometry (AAS) (µg/100 U)	22:10		27.8~30.5 (QR: 27.3~31.2)	28.6~30.7	Yes

Assessor's Comment: *The results for IR-B binding kinetics did not meet the similarity acceptance criteria. However, the observed differences do not preclude a demonstration that U.S.-Lantus vial presentation is highly similar to the cartridge presentation, as discussed in subsection 2.1a Insulin Receptor IR-B (long form) Binding Kinetics of section 3.2.R.4.4.2.1 Metabolic Activity in this memo.*

The batches used in the analytical similarity comparison between U.S.-Lantus cartridges and vials are listed in Table 5 below.

Table 5: List of US-licensed Lantus lots (cartridges & vials) used for CAA.

Sl. No	US-Approved Lantus® Lots* (Cartridges)		US-Approved Lantus® Lots* (Vials)	
	Lot Number	Expiry date	Lot Number	Expiry date
1	4F1179A	Mar-17	4F126A	Mar-17
2	4F1227A	Aug-17	A4789	Jun-17
3	4F1270A	Jul-17	A4803	Jul-17
4	5F1296A	Aug-17	A4825	Aug-17
5	5F1357A	Aug-17	4F148A	Sep-17
6	5F1492A	Apr-17	4F169A	Oct-17
7	5F1524A	Aug-17	5F412A	Feb-18
8	5F1568A	Mar-17	A5892	Mar-18
9	5F1710A	Sep-17	A5921	Jun-18
10	5F1739A	Oct-17	5F193A	May-18
11	3F420A	May-16		
12	3F393A	May-16		
13	3F425A	May-16		
14	4F924A	Jun-16		
15	4F723A	Sep-16		
16	3F417A	May-16		
17	3F072A	May-16		
18	4F1023A	Apr-17		
19	4F658A	Apr-17		
20	4F1050A	May-17		
21	4F614A	May-17		
22	4F655A	Jun-17		
23	1F759A	Jun-14		
24	1F767	Jun-14		

* US-Approved lots were tested within their expiry (Cartridges & Vials)

***Assessor's Comment**: The Applicant refers to the US-Lantus lots as 'cartridge' lots throughout the CAA reports. US-Lantus is marketed as a vial and a pre-filled pen integrated with a cartridge . The Applicant clarified in the submission that the US-Lantus pre-filled pens are referred to as cartridges in the CAA. For the sake of consistency with the BLA, this memo also refers to these U.S.-Lantus pre-filled pen lots as 'cartridge' lots. Lots of U.S.-Lantus cartridges used here are the same as those presented in CAA report 1 for similarity comparison between MYL-1501D cartridge presentation and U.S.-Lantus cartridge presentation (discussed earlier in this memo). The lots of US-Lantus cartridges and vials used in this CAA are acceptable.*

3.2.R.4.4.1 Protein Content/ Assay

The concentration of insulin glargine (mg/mL) and assay in units (U) in U.S.-licensed Lantus (vials and cartridges) is determined using RP-HPLC method by comparing to standard solution each time. 10 lots of U.S.-Lantus in vial (age from 19 to 34 month at analysis) were compared to 22 lots of U.S.-Lantus in cartridge (age from 15 to 30 month at analysis).

Representative overlaid chromatograms are provided in the following Figure 2. Scatter plot representing the distribution of protein content (mg/mL)/ Assay (Units/mL) for U.S.-licensed Lantus cartridges and vials is shown in Figure 3 and 4 below, respectively.

Figure 2: Representative Overlay of the RP-HPLC Chromatograms for Protein content of US-Approved Lantus® (Cartridge & Vial)

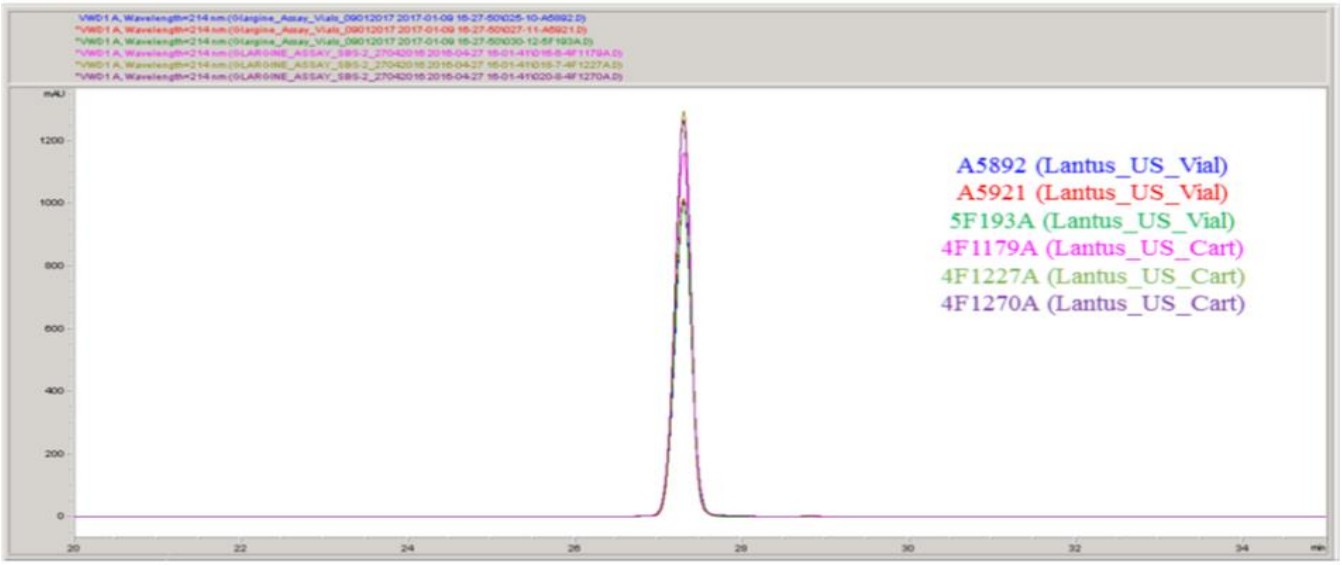


Figure 3: Scatter Plot Distribution for Content (mg/mL) of US-approved Lantus® & Vial)

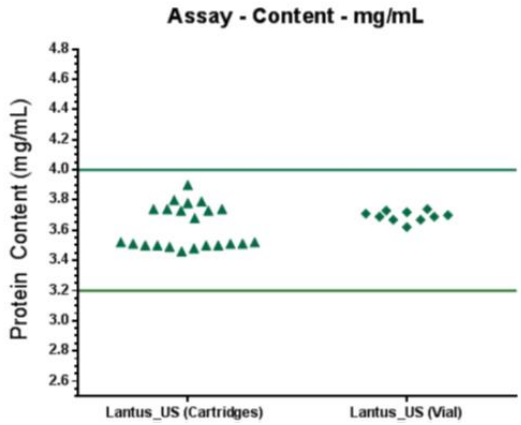
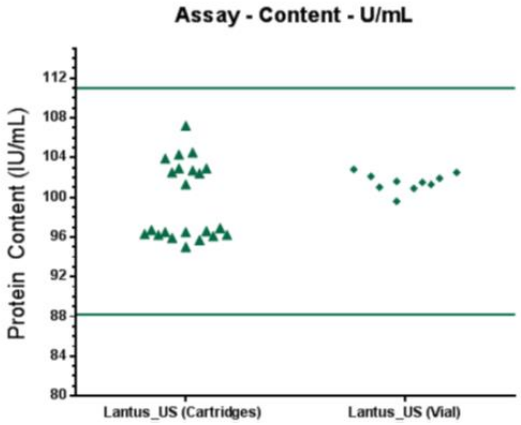


Figure 4: Scatter Plot Distribution for Assay (Units/mL) of US-approved Lantus® (Cartridges & Vial).



U.S.-Lantus cartridges are shown as green triangles. ▲
U.S.-Lantus vials are represented by green diamonds. ◆
The solid lines in Green represent the QR which has been set based on mean ± 3SD obtained from the observed data of the U.S.-Lantus lots (cartridges). The same pattern and color code apply to all following tables and figures unless otherwise stated.

***Assessor's Comment**: Mylan did not provide information about reference standard used in this assay in the original submission. Upon our IR (OBP IR #2 02/09/2021), Mylan provided such information on 02/16/2021, indicating there were three RS* (b) (4) *used here for U.S.-Lantus vials and cartridges. They also presented summary of bridging study (discussed in section 3.2.R.4.2 Quality Attributes/ Criticality Risk Ranking/ Reference Standards of this review memo previously), which indicated these RS performed very similarly to the*

common reference standard EPCRS LOT 1.0, supporting the pooling of data from various runs in this assay.
Representative HPLC chromatograms of U.S.-Lantus vials are similar to that of cartridges. The protein content values (mg/ml) and Assay (IU/mL) of U.S.-Lantus vials are 100% within the quality range of U.S.-Lantus cartridges, demonstrating that the protein content/Assay is highly similar between U.S.-Lantus vial presentation and cartridge presentation.

3.2.R.4.4.2 Functional and Biological Similarity Assessment

The biological and functional similarity assessments of U.S.-Lantus vials and cartridges were carried out using multiple assays. *In-vitro* bioassays performed include measuring receptor auto-phosphorylation, receptor binding kinetics, metabolic and mitogenic activity.

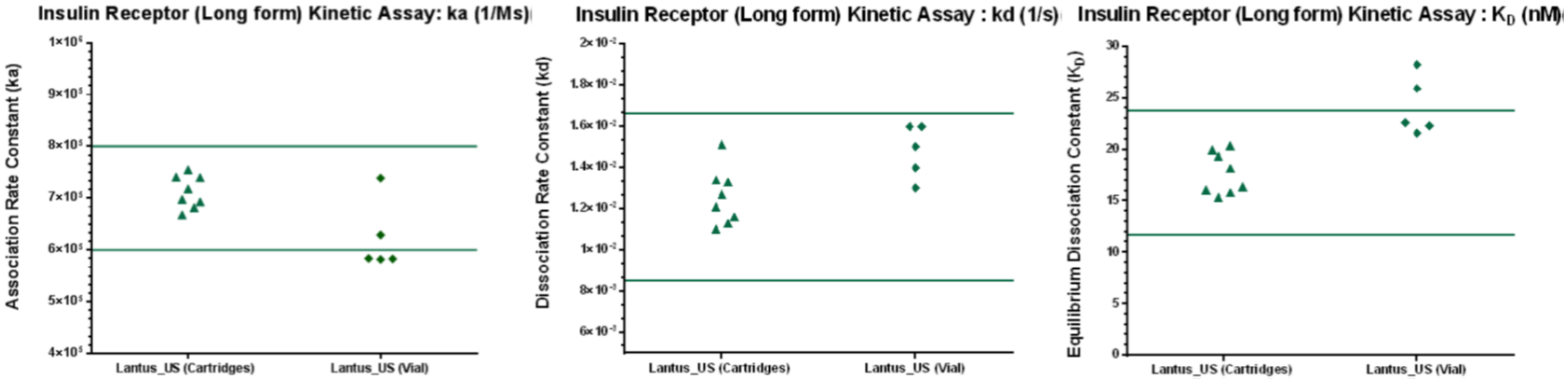
***Assessor's Comment**: The Applicant used an appropriate panel of tests for assessing functional and biological similarity.*

3.2.R.4.4.2.1 Metabolic Activity

2.1a Insulin Receptor IR-B (long form) Binding Kinetics

Comparative IR-B receptor binding affinity of U.S.-Lantus vials and cartridges has been studied by Surface Plasmon Resonance (SPR). 5 lots of U.S.-Lantus in vial (age from 20 to 28 month at analysis) were compared to 8 lots of U.S.-Lantus in cartridge (age from 17 to 26 month at analysis). Representative sensorgrams are provided in CAA report 2 but not shown here for brevity. A scatter plot distribution of the data for binding affinity to IR-B in terms of rate of association (ka), rate of dissociation (kd) and Dissociation Constant (KD) is provided in Figure 7 below.

Figure 7: Scatter Plot Distribution for Insulin receptor (Long form; IR-B) binding kinetic constants (k_a, k_d and K_D) of US-approved Lantus (Cartridge & Vial)

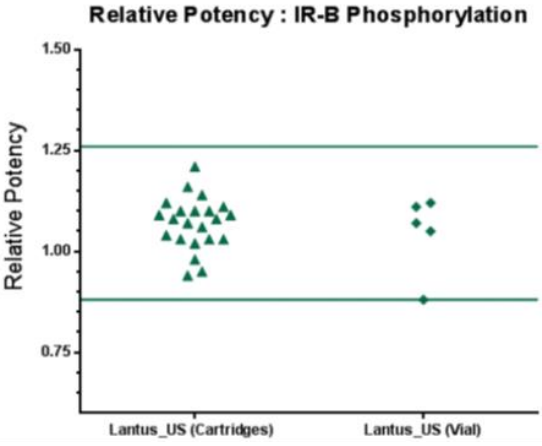


***Assessor's Comment**: Representative sensorgrams of IR-B binding kinetics for U.S.-Lantus vial lot are similar to that of cartridge lot. Insulin Receptor IR-B (long form) kinetic data above indicate that there are differences (k_a and K_D) in IR-B binding kinetics between U.S.-Lantus vials and cartridges. Three out of five lots of U.S.-Lantus vials are out of the quality range of the U.S.-Lantus cartridges. However, these differences in the kinetics are small and are not expected to have significant physiological effect until the differences are in log order. Additionally, metabolic data obtained from glucose uptake assay in 3T3-L1 cells, as well as Insulin receptor long-form phosphorylation, and Insulin receptor phosphorylation in HepG2 cells, as discussed in relevant section below, all support the similarity in functional activity between U.S.-Lantus cartridges and vials. Therefore, the observed differences in IR-B binding kinetics do not preclude a demonstration that U.S.-Lantus vial presentation is highly similar to U.S.-Lantus cartridge presentation.*

2.1b Insulin Receptor IR-B (long form) Auto-phosphorylation Assay

This assay is conducted to determine the phosphorylation of IR-B receptor once the ligand (U.S.-licensed Lantus vials or cartridges) binds to receptor. 5 lots of U.S.-Lantus in vial (age from 19 to 27 month at analysis) were compared to 22 lots of U.S.-Lantus in cartridge (age from 15 to 31 month at analysis). Representative dose response curves from each group are provided in CAA report 2 but not shown here. The Insulin receptor-B phosphorylation activity data along with descriptive statistics are also provided in the report. The scatter plot representing the distribution of data is shown in the following Figure 10.

Figure 10: Scatter Plot Distribution for Relative potency (IR-B phosphorylation activity) of US-approved Lantus® (Cartridge & Vial)



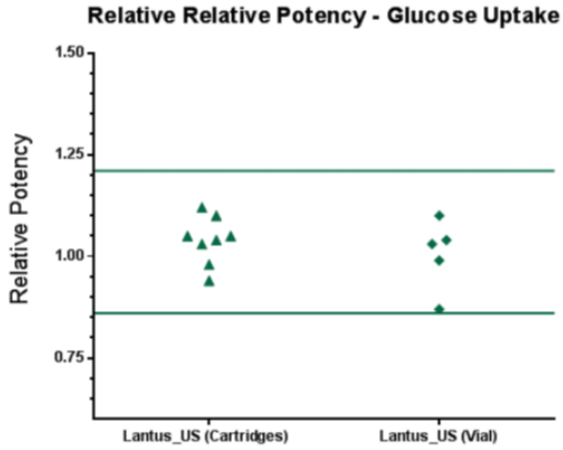
***Assessor's Comment**: The relative potency values of IR-B auto-phosphorylation for U.S.-Lantus vials are 100% within the quality range of U.S.-Lantus cartridges, demonstrating the IR-B auto-phosphorylation activity is highly similar between U.S.-Lantus vial and cartridge presentation.*

2.1c Glucose Uptake Assay in 3T3-L1 Cells

The assay measured glucose uptake in differentiated mouse 3T3-L1 adipocyte cells using the glucose oxidase/peroxidase (GOPOD) assay, which measures residual glucose left in the medium using a colorimetric method.

5 lots of U.S.-Lantus in vial (age from 19 to 27 month at analysis) were compared to 8 lots of U.S.-Lantus in cartridge (age from 17 to 26 month at analysis). Representative dose response curves (PLA) are provided in CAA report 2 but not shown here. The scatter plot representing the distribution of data is shown in Figure 13 below.

Figure 13: Scatter Plot Distribution for Relative potency (Glucose Uptake) of US-approved Lantus® (Cartridge & Vial)



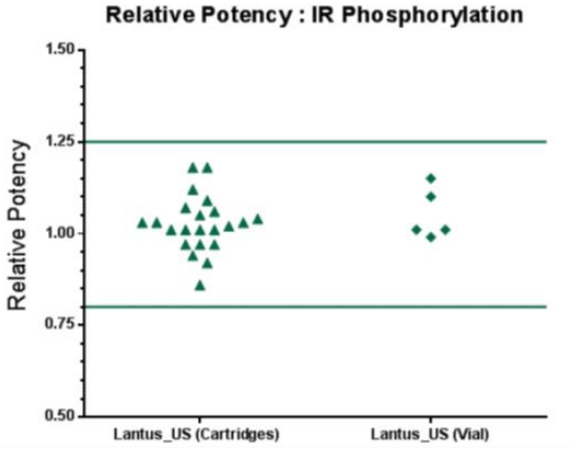
***Assessor's Comment**: The relative potency values of glucose uptake for U.S.-Lantus vials are 100% within the quality range of U.S.-Lantus cartridges, demonstrating a highly similar activity in stimulating 3T3-L1 cell glucose uptake between U.S.-Lantus vial presentation and cartridge presentation. These data also support that the observed differences of IR-B binding kinetics between U.S.-Lantus vial and cartridge presentation in subsection 2.1a above have minimal impact on the metabolic activity.*

2.1d Insulin Receptor Auto-phosphorylation Assay Using HepG2 Cell Lysates

The AlphaScreen SureFire INSR p-Tyr1150/1151 assay is used to measure the auto-phosphorylation of endogenous IR in cellular lysates of HepG2 cells which are pre-stimulated with different doses of U.S.-Lantus.

5 lots of U.S.-Lantus in vial (age from 19 to 27 month at analysis) were compared to 22 lots of U.S.-Lantus in cartridge (age from 15 to 31 month at analysis). Representative dose response curves are provided in CAA report 2 but not shown here. The scatter plot demonstrating distribution of the relative potency data is shown in Figure 16 below.

Figure 16: Scatter Plot Distribution for relative potency (IR phosphorylation) of US-approved Lantus® (Cartridge & Vial)



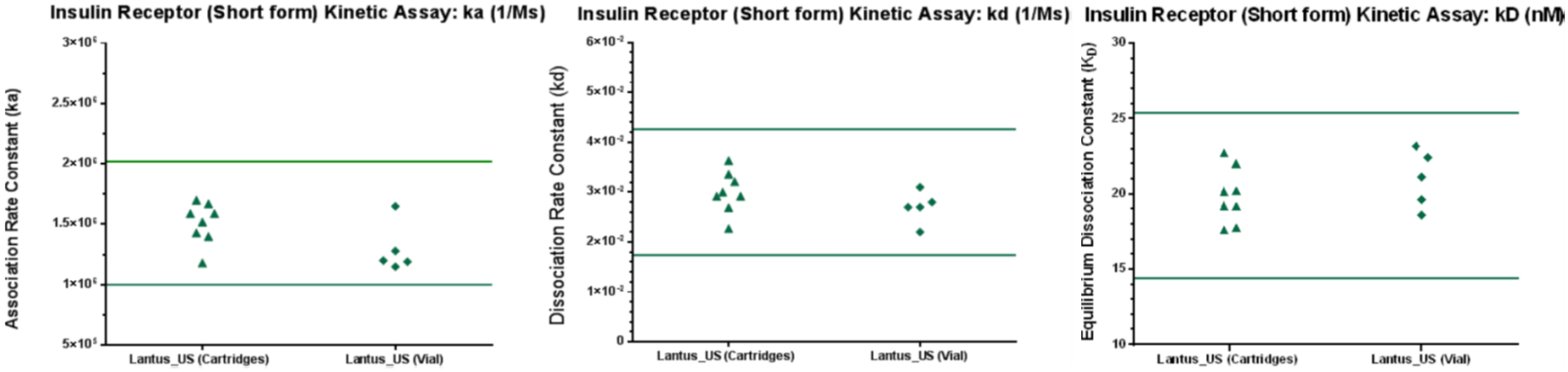
***Assessor's Comment**: The relative potency values of IR auto-phosphorylation for U.S.-Lantus vials are 100% within the quality range of U.S.-Lantus cartridges, demonstrating a highly similar IR phosphorylation activity between U.S.-Lantus vial presentation and cartridge presentation.*

3.2.R.4.4.2.2 Mitogenic Activity

2.2a Insulin Receptor IR-A (short form) Binding Kinetics

Comparative binding affinity to IR-A (short form) has been studied using SPR. 5 lots of U.S.-Lantus in vial (age from 20 to 28 month at analysis) were compared to 8 lots of U.S.-Lantus in cartridge (age from 17 to 26 month at analysis). Representative sensorgrams of IR-A binding affinity are provided in CAA report 2 but not shown here. The IR-A binding affinity data in terms of rate of association (k_a), rate of dissociation (k_d) and Dissociation Constant (K_D) are shown in scatter plots in Figure 28 below.

Figure 28: Scatter plot distribution of IR-A (short form) binding kinetic constants of US-Lantus (cartridge & vial)

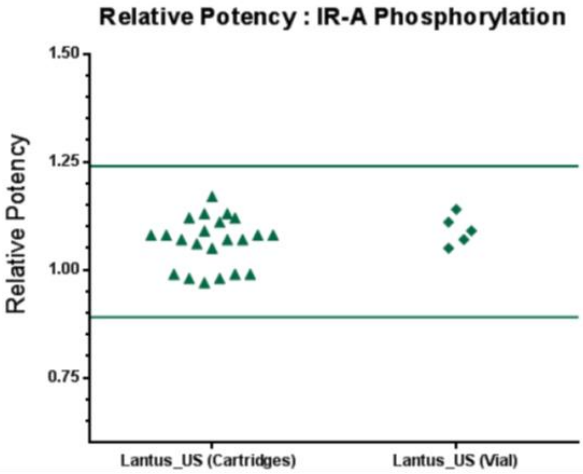


***Assessor's Comment**: Representative sensorgrams of IR-A binding kinetics for U.S.-Lantus vial are similar to that of the cartridge. The association rate constant (k_a), dissociation rate constant (k_d), and equilibrium dissociation constant (K_D) of U.S.-Lantus vials are 100% within the quality range of U.S.-Lantus cartridges. These data demonstrate the highly similar IR-A binding kinetics between U.S.-Lantus vial presentation and cartridge presentation.*

2.2b Insulin Receptor IR-A Phosphorylation Assay

The auto-phosphorylation of IR-A when ligand (U.S.-licensed Lantus) binds with IR-A receptor has also been compared with 5 lots of U.S.-Lantus in vial (age from 19 to 27 month at analysis) and 22 lots of U.S.-Lantus in cartridge (age from 15 to 31 month at analysis). Representative dose response curves are provided in CAA report 2 but not shown here. The scatter plot representing the distribution of the data is shown in Figure 22 below.

Figure 22: Scatter Plot Distribution for Relative potency (IR-A phosphorylation) of US-approved Lantus® (Cartridge & Vial)



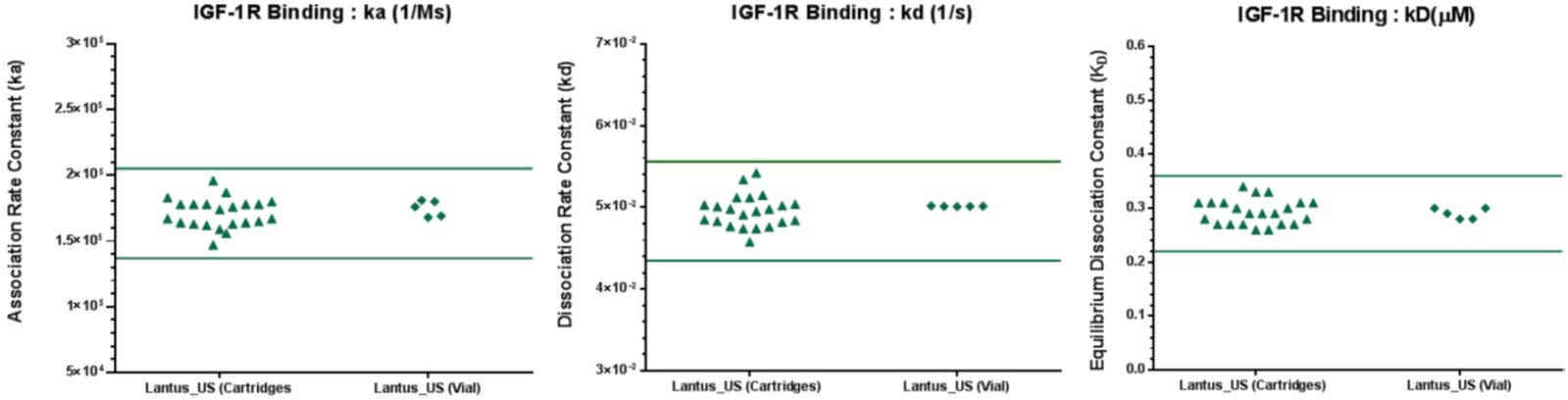
***Assessor's Comment**: The relative potency values of U.S.-Lantus vials are 100% within the quality range of U.S.-Lantus cartridges, demonstrating a highly similar IR-B auto-phosphorylation activity between U.S.-Lantus vial presentation and cartridge presentation.*

2.2C Insulin Growth Factor-1 Receptor (IGF-1R) Binding Kinetics

SPR based assay is used to evaluate the binding of insulin glargine to purified recombinant human IGF-1 receptor, using BIAcore. The binding affinity is determined in terms of rate of association (k_a), rate of dissociation (k_d) and Dissociation Constant (K_D) which are used to compare U.S.-Lantus vials and cartridges.

5 lots of U.S.-Lantus in vial (age from 18 to 26 month at analysis) were compared to 22 lots of U.S.-Lantus in cartridge (age from 15 to 31 month at analysis). Representative sensorgrams of IGF-1R binding affinity are provided in CAA report 2 but not shown here. Scatter plots demonstrating the distribution of the data are shown in Figure 19 below.

Figure 19: Scatter Plot Distribution for IGF-1R binding kinetic constants of US-approved Lantus (Cartridge & Vial).



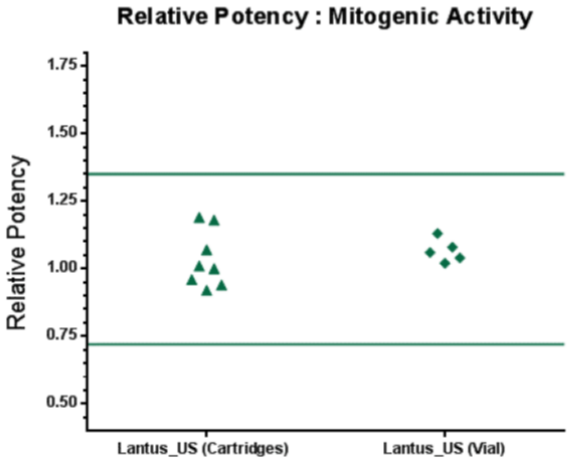
***Assessor's Comment**: Representative sensorgrams of IGF-1R binding kinetics for U.S.-Lantus vial are similar to that of the cartridge. The association rate constant (k_a), dissociation rate constant (k_d), and equilibrium dissociation constant (K_D) of U.S.-Lantus vials are 100% within the quality range of U.S.-*

Lantus cartridges, demonstrating the highly similar IGF-1R binding kinetics between U.S.-Lantus vial presentation and cartridge presentation.

2.2d Mitogenic Activity Using Saos-2 Cells-Based Assay

The proliferation of Saos-2 cells exposed to different lots of U.S.-Lantus was measured calorimetrically using the redox indicator dye Alamar Blue. The relative fluorescence unit (RFU) obtained is directly proportional to the increase in cell number. Mitogenic activity is measured in terms of Relative Potency using Parallel Line Assay software by Stegmann Systems.
5 lots of U.S.-Lantus in vial (age from 19 to 27 month at analysis) were compared to 8 lots of U.S.-Lantus in cartridge (age from 17 to 26 month at analysis). Representative dose response curves (PLA) for each group are provided in CAA report 2 but not shown here. The scatter plot representing the distribution of data is shown in the following Figure 25.

Figure 25: Scatter Plot Distribution of Relative Potency (Mitogenic Assay) of US-approved Lantus® (Cartridge & Vial)



***Assessor's Comment**: The relative values of mitogenic activity in Saos-2 cells for U.S.-Lantus vials are 100% within the quality range of U.S.-Lantus cartridges, demonstrating a highly similar mitogenic activity between U.S.-Lantus vial presentation and cartridge presentation.*

Summary of Functional and Biological Assays:
Results obtained from multiple orthogonal analytic methods to assess metabolic activity and mitogenic activity indicate that U.S.-Lantus vial presentation is highly similar to U.S.-Lantus cartridge presentation. The observed differences in IR-B binding kinetics between these two presentations pose a low risk with no observed impact on metabolic activity therefore they do not preclude a demonstration of highly similar functional and biological activities between U.S.-Lantus vial and cartridge presentation.

3.2.R.4.4.3 Purity and Impurity

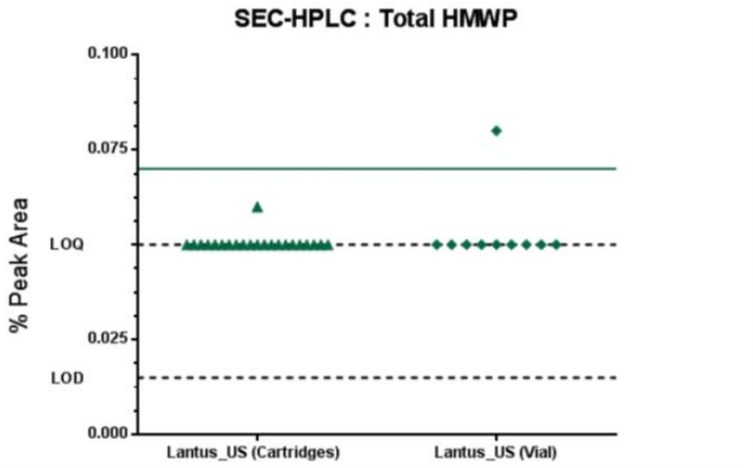
3.2.R.4.4.3.1 Size Variant- High Molecular Weight Protein (HMWP)/Aggregates

Size variants such as high molecular weight impurities (HMWP) species including aggregates, formed due to association of two or more molecules of the monomer or fragments, are primarily estimated by SEC-HPLC. Orthogonal methods such as SEC-MALS and AUC have also been used to assess size-based variants. Results for each assay are discussed below.

3.1a HMWP Assessment Using SEC-HPLC

10 lots of U.S.-Lantus in vial (age from 18 to 33 month at analysis) were compared to 22 lots of U.S.-Lantus in cartridge (age from 13 to 26 month at analysis). Representative overlaid SEC-HPLC chromatograms are provided in CAA report 2 but not shown here. The scatter plot representing the distribution of data is provided in Figure 30 below (LOD=0.015%, LOQ=0.050%).

Figure 30: Scatter Plot distribution of HMWP in US-approved Lantus® (Cartridge & Vial)

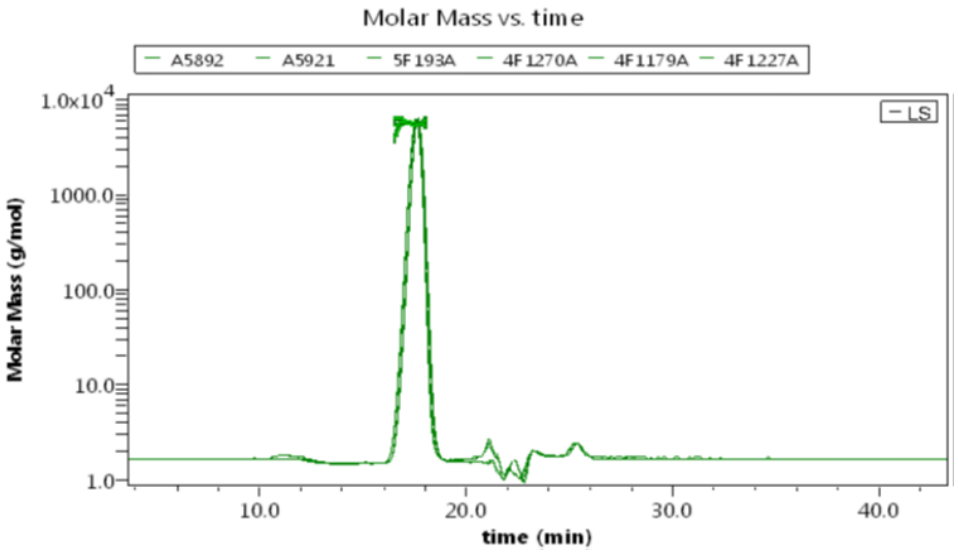


***Assessor's Comment**: Representative SEC-HPLC UV chromatograms of U.S.-Lantus vials are similar to that of cartridges. The total HMWP content for most of U.S.-licensed Lantus vials and cartridges were observed to be below the quantification limit (LOQ: 0.05%) by SEC-HPLC method. The HMWP content of 90% tested U.S.-Lantus vials are within the QR established for U.S.-Lantus cartridges, thereby demonstrating a similar HMWP content between U.S.-Lantus vial and cartridge presentation.*

3.1b HMWP Assessment Using SEC-MALS

SEC-MALS is an orthogonal tool to assess and characterize the size variants. 10 lots of U.S.-Lantus in vial (age from 17 to 32 month at analysis) were compared to 10 lots of U.S.-Lantus in cartridge (age from 18 to 26 month at analysis). Representative overlaid molar mass (g/mol.) vs time plots of U.S.-Lantus vial lots and cartridge lots are shown in Figure 31 below.

Figure 31: Representative Overlaid Molar mass chromatogram by SEC-MALS for US-approved Lantus® (Cartridge & Vial)



The SEC-MALS analysis data are tabulated in Table 28 and 29 but not shown in a scatter plot in CAA report 2. The following table contains summarized data from Table 28 and 29 (assessor generated).

Molar mass measured with SEC-MALS	U.S.-Lantus (cartridge) Min – Max range	U.S.-Lantus (vial) Min – Max range
Mass fractions (%)	100 (mean: 100, QR: 100~100)	100 (mean: 100)
Mw/Mn	1.001~1.006 (mean: 1.003, QR: 0.999~1.007)	1.000~1.003 (mean: 1.001)
Mz/Mn	1.002~1.011 (mean: 1.006, QR: 0.997~1.016)	1.000~1.007 (mean: 1.002)

***Assessor's Comment**: SEC-MALS data of U.S.-Lantus vials and cartridges indicate that a similar size range is obtained for the monomer across both products. A single predominant peak of monomer is observed in all samples with a similar distribution of molar mass. The content of multimers or aggregate is low in all to provide a measurement of molar mass. As an orthogonal method to SEC-HPLC, these data support the demonstration of a highly similar profile for size variants obtained from SEC-HPLC analysis in section 3.1a above between U.S.-Lantus vial and cartridge presentation.*

3.1c HMWP Assessment Using AUC– Sedimentation Velocity

Sedimentation velocity measured by the AUC, provides information on the protein heterogeneity and state of association or aggregation. Aggregates can be detected based on their different sedimentation coefficients.

3 lots of U.S.-Lantus in vial (age from 19 to 22 month at analysis) were compared to 3 lots of U.S.-Lantus in cartridge (age from 20 to 25 month at analysis). Representative normalized sedimentation coefficient distribution graphs are presented in Figure 32 and Figure 33 below.

Figure 32: Representative Normalized sedimentation coefficient distribution for US-approved Lantus® (Cartridge)

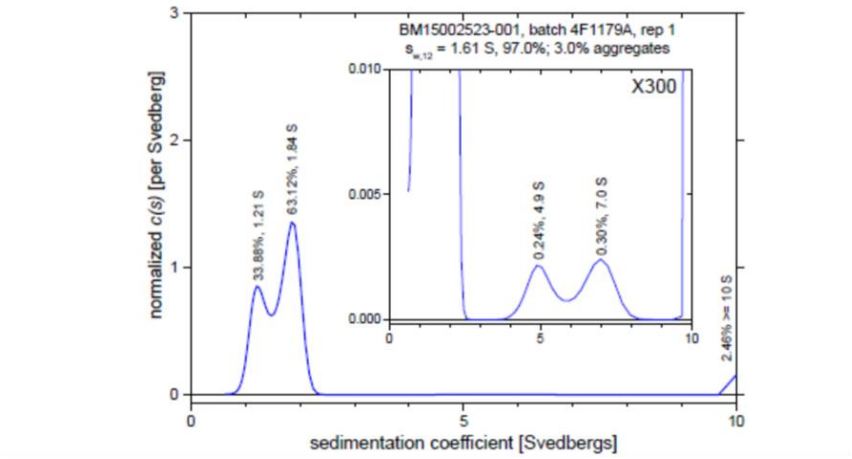
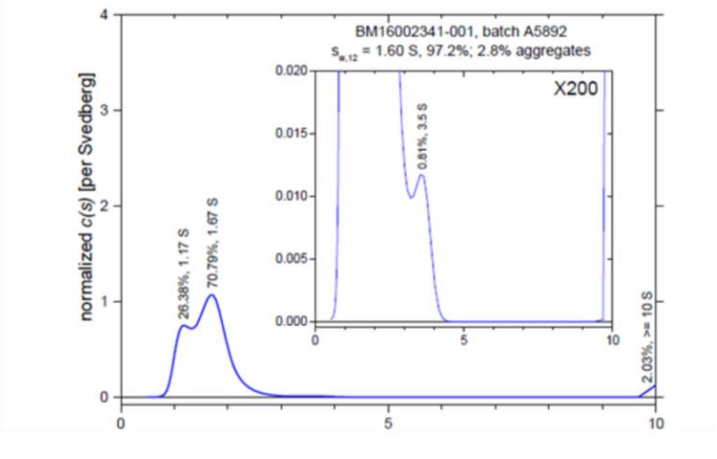


Figure 33: Representative Normalized sedimentation coefficient distribution for US-approved Lantus® (Vial)



The AUC analysis data are tabulated in Table 30 and Table 31 but not shown in a scatter plot in CAA report 2. The following table contains summarized data from Table 30 and Table 31 (assessor generated).

Size variant measured using AUC	U.S.-Lantus (cartridges) Min – Max range	U.S.-Lantus (vials) Min – Max range
Monomer sedimentation coefficient (S)	1.61~1.64 (mean: 1.62, QR: 1.59~1.65)	1.60~1.63 (mean: 1.62)
Total aggregate fraction (%)	0.0~3.2 (mean: 1.8, QR: 0~5.9)	0.6~3.1 (mean: 2.2)

***Assessor's Comment**: The AUC profile of U.S.-Lantus cartridges is similar to that of U.S.-Lantus vials. These data support the demonstration of a highly similar profile for size variants obtained from SEC-HPLC analysis in section 3.1a above between U.S.-Lantus vial and cartridge presentation.*

3.2.R.4.4.3.2 Product Variants by RP-HPLC

The product related variants generated by deamidation/clipping of the B-chain C-terminal amino acids, mis-cleavage of precursor by trypsin are monitored by RP-HPLC. 10 lots of U.S.-Lantus in vial (age from 19 to 34 month at analysis) were compared to 22 lots of U.S.-Lantus in cartridge (age from 13 to 26 month at analysis). Representative overlaid RP-HPLC chromatograms are shown in Figure 34 below.
RP-HPLC data for product variants of U.S.-Lantus vial lots and cartridge lots are tabulated in Table 32 and Table 33 in CAA report 2 but not shown here. Distribution of the data for individual product variant are shown as scatter plots in Figure 35 below.

Figure 34: Representative overlaid RP-HPLC Chromatogram of US-approved Lantus® (Cartridge & Vial)

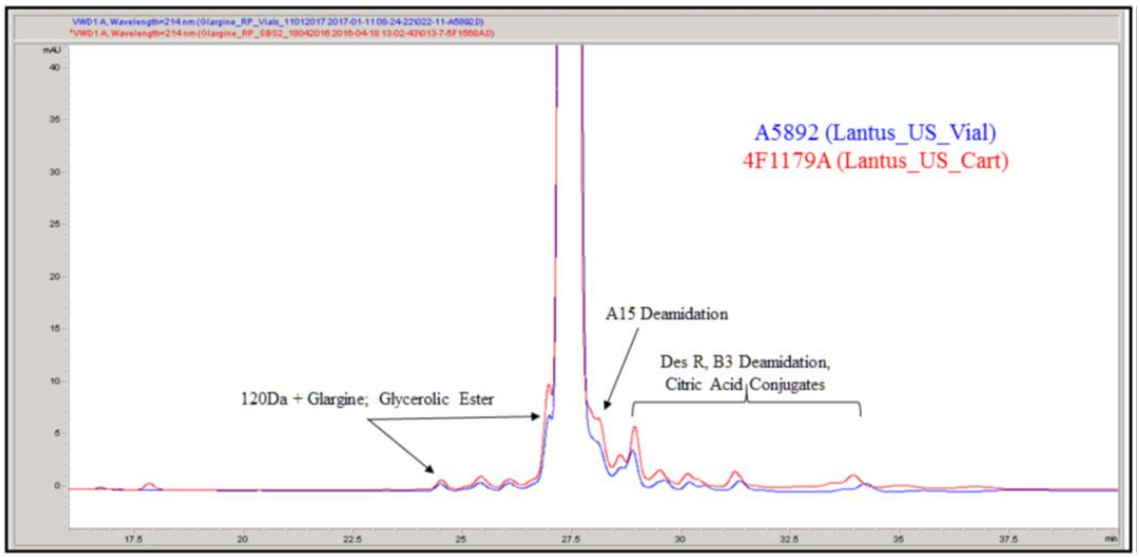
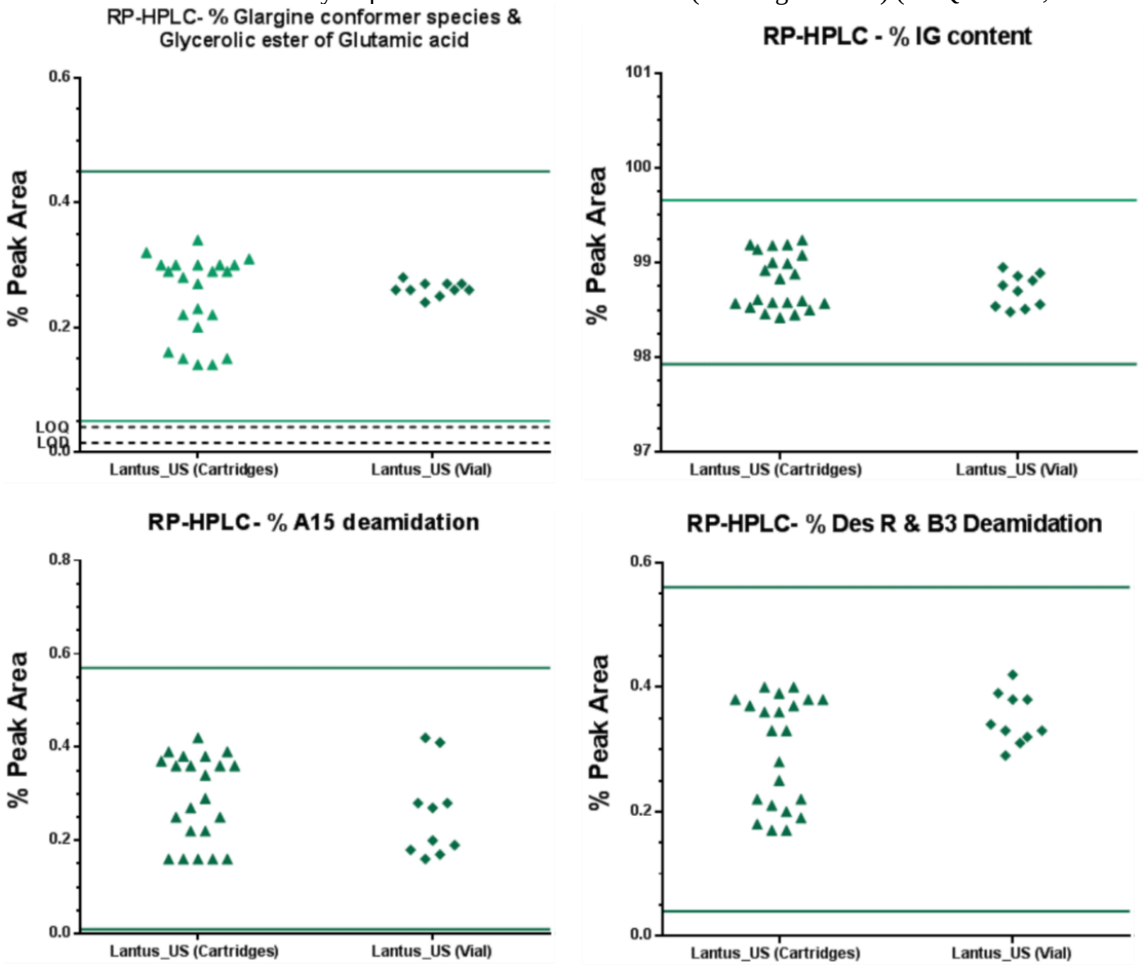


Figure 35: Scatter Plot distribution of hydrophobic variants of US-Lantus (Cartridge & Vial) (LOQ: 0.04%, LOD: 0.015%)

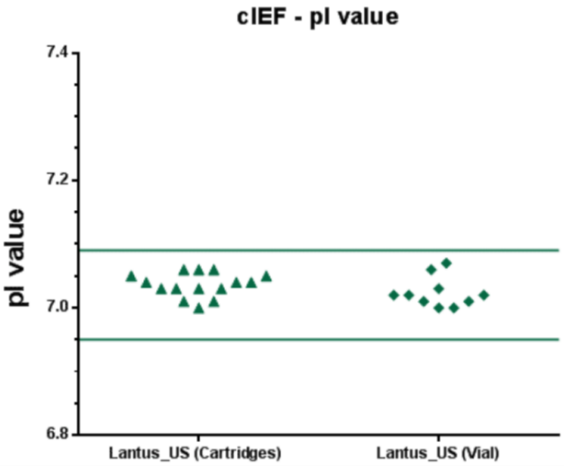


***Assessor's Comment**: The overlaid chromatograms in Figure 34 indicate the impurity profiles are similar between U.S.-licensed Lantus vial and cartridge presentation. Data distribution in Figure 35 show that product variants levels measured by RP-HPLC for U.S.-Lantus vials are 100% within the QR established for U.S.-Lantus cartridges. Levels of other product variants such as citrate conjugates or acetylated insulin glargine in both presentations are also very low and similar, as listed in Table 32 and 33 but not shown in scatter plots here. Overall, these data demonstrate that product variant profiles and levels are highly similar between U.S.-Lantus vial presentation and cartridge presentation.*

3.2.R.4.4.3.3 Capillary Isoelectric Focusing to Assess the Isoelectric Point (pI)

cIEF separates charge variants and provides information about the protein pI, which depends on the amino acid sequence of a protein. 10 lots of U.S.-Lantus in vial (age from 18 to 33 month at analysis) were compared to 15 lots of U.S.-Lantus in cartridge (age from 8 to 29 month at analysis). Representative overlaid cIEF profiles are provided in CAA report 2 but not shown here. The scatter plot distribution of pI values is provided in Figure 37 below.

Figure 37: Scatter plot distribution for pI value of US-approved Lantus® (Cartridge & Vial)



***Assessor's Comment:** The representative cIEF profiles for U.S.-Lantus vials are similar to that of U.S.-Lantus cartridges. The calculated pI values for the main peak of U.S.-Lantus vials are 100% within the QR observed for U.S.-Lantus cartridges, demonstrating a highly similar pI value between U.S.-Lantus vial presentation and cartridge presentation.*

Summary of Purity and Impurity Assays:

Results from multiple orthogonal analytic methods to assess size variants, product variants, and pI value demonstrate that the profiles and levels for size/product variants as well as pI values are highly similar between U.S.-Lantus vial presentation and cartridge presentation.

3.2.R.4.4.4 Primary, Secondary and Higher Order Structure

3.2.R.4.4.4.1 Primary Structure and Disulfide Linkage

The test methods used for assessing similarity of primary structure and disulfide linkage are presented in Table 63 below.

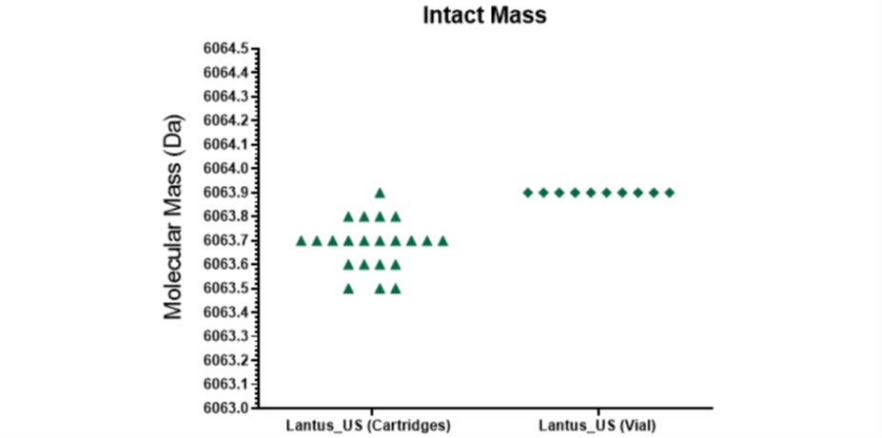
Table 63: Test Methods used for Primary Structure Similarity Assessment

Analytical Test	Description
Intact mass	Intact mass by ESI-MS Mass spectrometry
Reduced mass	Reduced by DTT to separate into two chains, Chain A and Chain B
Non-Reduced PMF	Peptide mass fingerprinting using GLU-C analysed using LC-MS and MS-MS
Reduced PMF	Peptide mass fingerprinting using GLU-C reduced with DTT analysed using LC-MS and MS-MS.

4.1a Intact Mass Analysis

The intact mass analysis not only confirms the identity of the molecule but also forms the first evidence of primary structure and hence primary sequence. 10 lots of U.S.-Lantus in vial (age from 17 to 32 month) and 22 lots of U.S.-Lantus in cartridge (age from 16 to 33 month) were analyzed for intact mass on a C18 column using RP-HPLC connected to an ESI-mass spectrometer.
Representative UV chromatograms and corresponding intact mass are provided in CAA report 2 but not shown here. Scatter plot representing the distribution of intact mass value is shown in Figure 39 below.

Figure 39: Scatter plot distribution for Intact Mass of US-approved Lantus® (Cartridge & Vial)

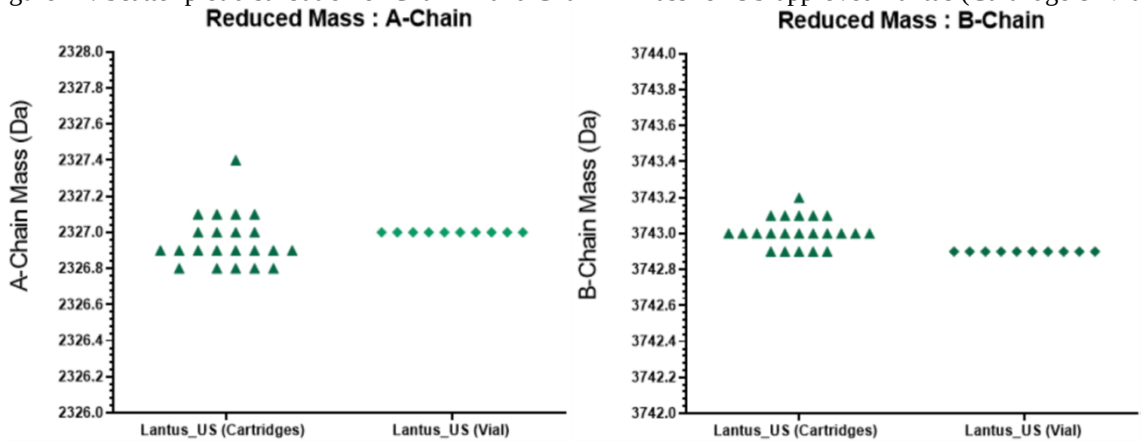


Assessor's Comment: *Representative intact mass UV profiles of U.S.-Lantus vials are similar to that of cartridges. The observed intact mass for U.S.-Lantus vials (mean: 6063.9) and cartridges (mean: 6063.7) are highly similar to each other and to the expected theoretical mass ([M+H] ± 1 Da) of 6063.9 Da. These results support a demonstration of highly similar primary sequence between U.S.-Lantus vial presentation and cartridge presentation.*

4.1b Reduced Mass analysis by RP-HPLC-ESI Mass Spectrometry

Reduced mass analysis with DTT not only confirms the characteristics of the two chains (Chain A and Chain B) but also confirms the identity of each individual chain at the level of the primary structure.
10 lots of U.S.-Lantus in vial (age from 17 to 32 month at analysis) were compared to 22 lots of U.S.-Lantus in cartridge (age from 16 to 33 month at analysis). Representative UV chromatograms of Chain-A and Chain-B are provided in CAA report 2 but not shown here. Scatter plots representing the distribution of mass values are provided in Figure 41 below.

Figure 41: Scatter plot distribution of Chain-A and Chain-B Mass for US-approved Lantus (Cartridge & Vial)



Assessor's Comment: *Representative UV profiles of Chain A and Chain B for U.S.-Lantus vials are similar to that of cartridges. The observed mass of Chain A and Chain B for U.S.-Lantus vials (mean: 2327.02 for A and 3742.9 for B) and cartridges (mean: 2327.0 for A and 3743.0 for B) are similar to each other and to the expected theoretical mass ([M+H] ± 1 Da) of 2327.6 Da (Chain A) and 3743.3 Da (Chain B). These results also support a demonstration of highly similar primary sequence between U.S.-Lantus vial presentation and cartridge presentation.*

4.1c Disulfide Linkage by Non-Reduced Peptide Mass Fingerprinting Analysis

In insulin glargine after enzyme cleavage, 4 glutamic acid residues (at positions A4, A17, B13 and B21) gives rise to 4 peptide fragments which could be analyzed by the LC-MS technique to generate mass fingerprint (PMF). Under non-reducing condition the disulfide bonds are still intact and hence PMF gives rise to A-B chain connected peptide providing the confirmation of disulfide linkages. The expected theoretical fragments on Glu C digestion of insulin glargine under non-reducing conditions along with their respective masses are tabulated in Table 70 below.

Table 70: List of Disulphide linked Peptide Fragments and Their Masses Monitored by Non-Reduced Glu-C Peptide Mass Fingerprinting

Fragment number	Fragment No. / Location	Amino acid Sequence	Theoretical mass $(M+H)^+ \pm 1Da$
4	A (1-4)	GIVE	417.2
3	B (22-32)	RGFFYTPKTRR	1428.8
2	A (18-21) & B (14-21)	(NYCG) & (ALYLVCGE)	1320.49
1	A(5-17) & B (1-13)	(QCCTSICSLYQLE) & (FVNQHLCGSHLVE)	2969.36

10 lots of U.S.-Lantus in vial (age from 18 to 32 month) and 22 lots of U.S.-Lantus in cartridge (age from 16 to 33 month) were subjected to proteolysis with Endoproteinase Glu C. Peptides were then detected on an ESI-mass spectrometer as they separate on a C18 column connected to RP-HPLC.
The non-reduced PMF analysis data are provided in Table 42 and Table 43 in CAA report 2 and are summarized in the table below (assessor generated). Representative overlaid UV-chromatograms are also provided but not shown here.

Peptide mass measured with non-reducing PMF	U.S.-Lantus (cartridge) Min – Max range	U.S.-Lantus (vial) Min – Max range
Fragment 4 (Da)	417.1 (mean: 417.1)	417.1 (mean: 417.1)
Fragment 3 (Da)	1428.7~1429.4 (mean: 1429.0)	1429.2~1429.6 (mean: 1429.3)
Fragment 2 (Da)	1320.5~1320.6 (mean: 1320.5)	1320.5~1320.7 (mean: 1320.6)
Fragment 1 (Da)	2969.1~2970.6 (mean: 2969.6)	2969.3~2970.4 (mean: 2970.1)

Assessor's Comment: *The representative UV chromatograms of 4 fragments for U.S.-Lantus vials are similar to that of cartridges. The observed peptide mass measured by non-reducing PMF for U.S.-licensed Lantus vials and cartridges are highly similar to each other and to the expected theoretical mass ([M+H] ± 1 Da) for fragment 1/2/3/4, supporting a demonstration of similar primary sequence and disulfide linkages between U.S.-Lantus vial presentation and cartridge presentation.*

4.1d Reducing Peptide Mass Fingerprinting Analysis

The difference between peptide mass fingerprinting (PMF) under reduced condition and non-reduced condition is that DTT is used to disrupt the disulfide bond under reduced condition. In the reducing PMF analysis of insulin glargine, the following six peptide fragments are expected (shown in Table 74 below) after digestion with Glu-C and are sequenced for confirmation.

Table 74: Expected theoretical fragments for Glu C digestion of Insulin Glargine under reduced conditions along with their respective masses

Fragment number	Fragment No. / Location	Amino Acid Sequence	Theoretical mass $(M+H)^+$ ±1Da
1	A(5-17)	QCCTSICSLYQLE	1490.6
2	B (14-21)	ALYLVCGE	867.4
3	B (1-13)	FVNQHLCGSHLVE	1482.7
4	B (22-32)	RGFFYTPKTRR	1428.8
5	A (1-4)	GIVE	417.2
6	A (18-21)	NYCG	456.1

10 lots of U.S.-Lantus in vial (age from 17 to 32 month) and 22 lots of U.S.-Lantus in cartridge (age from 16 to 33 month) were subjected to PMF analysis under reducing condition. Reducing PMF analysis data are provided in Table 45 and 46 in CAA report 2 and are summarized in the table below (assessor generated). Representative overlaid UV-chromatograms are also provided but not shown here.

Peptide mass measured with non-reducing PMF	U.S.-Lantus (cartridge) Min – Max range	U.S.-Lantus (vial) Min – Max range
Fragment 6 (Da)	456.0~456.1 (mean: 456.0, QR: 455.9~456.1)	456.1 (mean: 456.1)
Fragment 5 (Da)	417.1 (mean: 417.1, QR: 417.1~417.1)	417.1 (mean: 417.1)
Fragment 4 (Da)	1428.7~1429.2 (mean: 1428.8, QR: 1428.3~1429.2)	1428.7~1429.6 (mean: 1429.4)
Fragment 3 (Da)	1482.7~1482.8 (mean: 1482.7, QR: 1482.6~1482.8)	1482.7~1482.9 (mean: 1482.8)
Fragment 2 (Da)	867.3~867.4 (mean: 867.3, QR: 867.2~867.4)	867.4 (mean: 867.4)
Fragment 1 (Da)	1490.5~1490.7 (mean: 1490.6, QR: 1490.4~1490.7)	1490.6~1490.7 (mean: 1490.7)

Mylan stated that the amino acid sequence of each peptide was confirmed by tandem mass spectrometry (MS-MS). The peptide sequence coverage was 100% for Chain-A and Chain-B and indicates an identical primary sequence of U.S.-Lantus vials and cartridges. These results are not provided in CAA report 2.

Assessor's Comment: *Representative UV chromatograms of 6 fragments for U.S.-Lantus vials are similar to that of cartridges. The observed peptide mass measured by reducing PMF for U.S.-Lantus vials*

and cartridges are highly similar to each other and to the expected theoretical mass ([M+H] ± 1 Da) for fragment 1/2/3/4/5/6. These data, together with the data obtained from non-reduced PMF analysis in section 4.1c above, demonstrate the primary sequence and disulfide linkages are highly similar between U.S.-Lantus vial presentation and cartridge presentation. In order to pinpoint the position of disulfide linkages, NMR studies have been carried out on representative lot of U.S.-Lantus in vial and in cartridge. Refer to the following section 4.2c about 2D-NMR for more details.

3.2.R.4.4.4.2 Secondary and Tertiary Structure Confirmation

The test methods used for assessing similarity of secondary and tertiary structure are presented in Table 78 below.

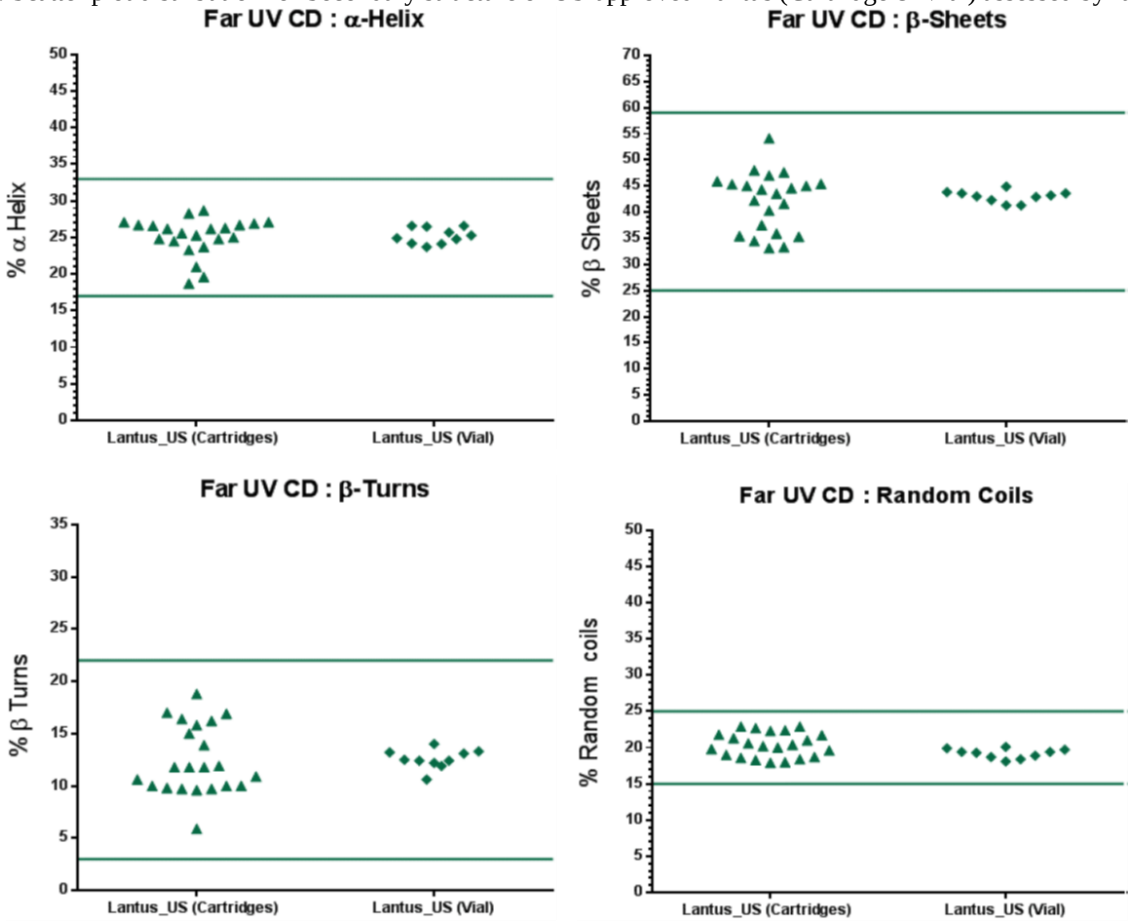
Table 78: Test Methods used for Higher order Structure Similarity Assessment

Analytical Test method	Description
Secondary Structure	Far-UV-CD Spectra
	Fourier Transform Infrared Spectroscopy
Higher Order Structure	Near-UV-CD Spectra
	Intrinsic Fluorescence
	Extrinsic Fluorescence
	Nuclear Magnetic Resonance (2D-NMR)
Thermal stability	Differential Scanning Calorimetry
Crystal structure	X-Ray Crystallography

4.2a Far UV CD Spectroscopic Analysis

Secondary structure of a protein can be determined by CD spectroscopy in the "far-UV" spectral region (190-260 nm). 10 lots of U.S.-Lantus in vial (age from 17 to 32 month at analysis) were compared to 22 lots of U.S.-Lantus in cartridge (age from 16 to 33 month at analysis). Representative overlaid far-UV CD profiles are provided in CAA report 2 but not shown here. Far-UV CD spectra were then deconvoluted by Yang's reference fit to estimate secondary structural components. Data distribution of secondary structures (α-helix, β-sheets, β-turns and random coil) are displayed as scatter plots in Figure 45 below.

Figure 45: Scatter plot distribution for Secondary structure of US-approved Lantus (Cartridge & Vial) assessed by far-UV CD.

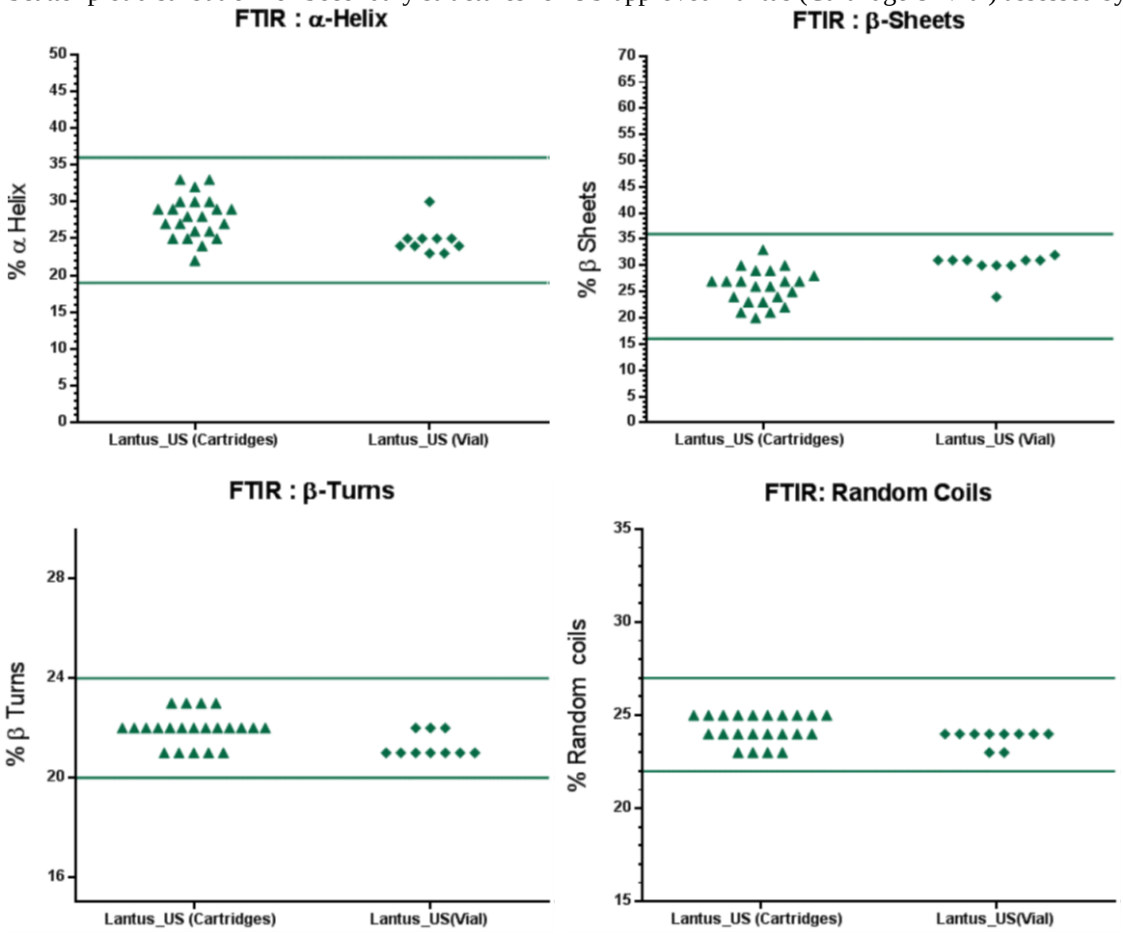


Assessor's Comment: *Representative Far-UV CD spectra profiles of U.S.-Lantus vials are similar to that of cartridges. The secondary structural contents (α-helix, β-sheets, β-turns and random coil) for U.S.-Lantus vials are 100% within the quality range established for U.S.-Lantus cartridges, supporting a demonstration of highly similar secondary structure between U.S.-Lantus vial presentation and cartridge presentation.*

4.2b Fourier Transform Infrared Spectroscopy (FTIR)

FTIR is used as an orthogonal tool to provide information about the secondary structure composition of proteins. 10 lots of U.S.-Lantus in vial (age from 19 to 34 month at analysis) were compared to 22 lots of U.S.-Lantus in cartridge (age from 14 to 33 month at analysis). Representative overlaid FTIR spectra are provided in CAA report 2 but not shown here. Data distribution for the secondary structures (α-helix, β-sheets, β-turns and random coil) are represented as scatter plots in Figure 47 below.

Figure 47: Scatter plot distribution for Secondary structures for US-approved Lantus (Cartridge & Vial) assessed by FTIR



Assessor's Comment: *The FTIR spectra profiles of U.S.-Lantus vials are similar to that of cartridges. The secondary structure (α-helix, β-sheets, β-turns, and random coil) estimations for U.S.-Lantus vials are 100% within the quality range of U.S.-Lantus cartridges, supporting a demonstration of highly similar secondary structure between U.S.-Lantus vial presentation and cartridge presentation.*
Overall, the assessment of secondary structure components by Far UV CD spectroscopy (section 4.2a above) and FTIR supports a demonstration of highly similar secondary structure between U.S.-Lantus vial presentation and cartridge presentation.

4.2c Disulfide Linkage Confirmation by Solution-State 2D NMR Spectroscopy

In Insulin Glargine, Chain A and Chain B are crosslinked by two disulfide bridges (A20–B19 and A7–B7). A third intra-chain disulfide linkage exists in the A-chain (A6–A11). As shown in the following Figure 48 and Figure 49, the presence of disulfide linkages in U.S.-Lantus cartridge (lot 4F1179A) and U.S.-Lantus vial (lot 5F193A) is confirmed by solution-state 2D NMR spectroscopy studies.

Figure 48: NMR spectra: a) 2D [^{1}H, ^{1}H] TOCSY and b) 2D [^{1}H, ^{1}H] NOESY of US-approved Lantus® (Cartridge; 4F1179A)

The vertical dotted lines indicate the spectral assignments for the Cysteines at positions A6, A7, A11, A20, B7 and B19. The horizontal dotted lines show one of the NOE connectivity's arising due to the disulphide linkage indicated as hyphenated residue numbers near the lines.

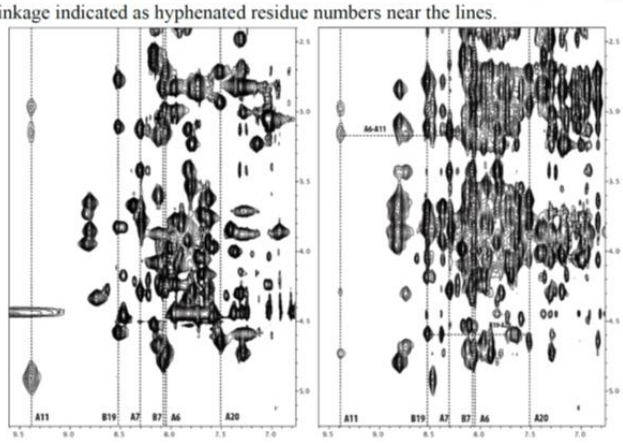
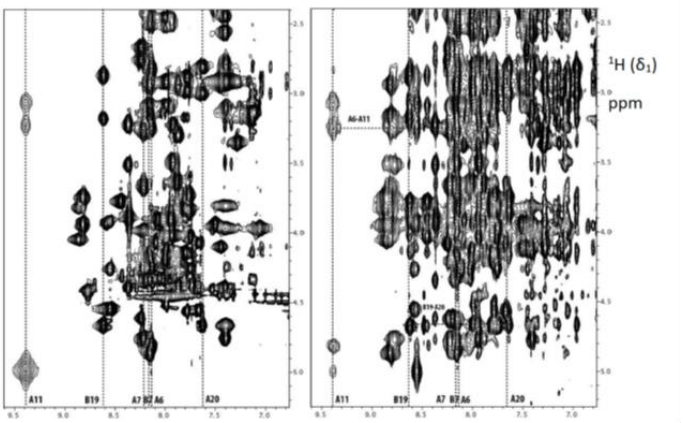


Figure 49: NMR spectra: a) 2D [^{1}H, ^{1}H] TOCSY and b) 2D [^{1}H, ^{1}H] NOESY of US-approved Lantus® (Vial; 5F193A)

The vertical dotted lines indicate the spectral assignments for the Cysteines at positions A6, A7, A11, A20, B7 and B19. The horizontal dotted lines show one of the NOE connectivity's arising due to the disulphide linkage indicated as hyphenated residue numbers near the lines.

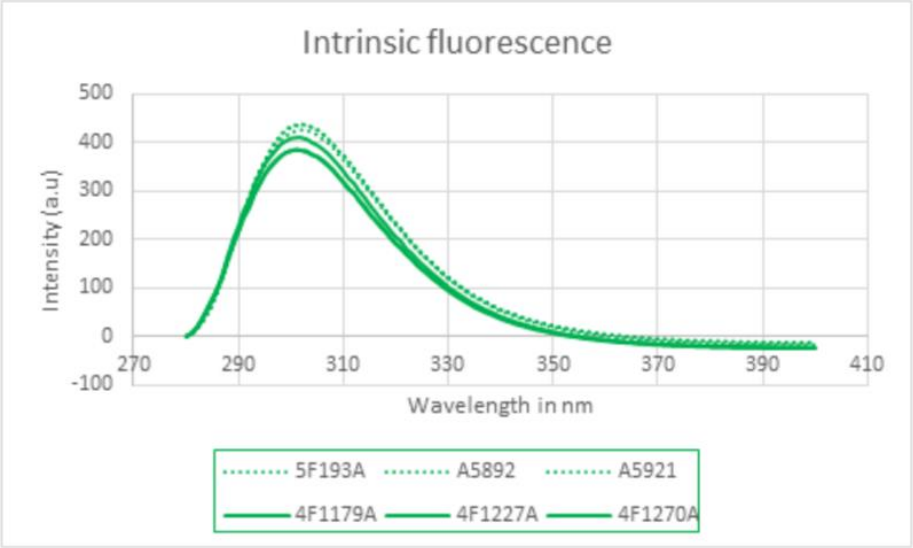


Assessor's Comment: *The 2D NMR spectra profile of U.S.-Lantus vial is similar to that of U.S.-Lantus cartridge. The minor changes in chemical shifts, peak splitting and extra peaks observed here could be due to differences in NMR buffer conditions. Since the peaks and connectivities that correspond to the disulfide linkages do not show any major change in the chemical shifts, the 2D NMR data support a demonstration of highly similar disulfide linkages between U.S.-licensed Lantus vial presentation and cartridge presentation.*

4.2d Intrinsic Fluorescence

Intrinsic fluorescence of a folded protein is used as a tool indicative of conformational state of a protein. The fluorescence emission depends on the type, number of aromatic residues, and their solvent exposure. The wavelength of the emitted light is an additional indicator of the fluorophore environment. 10 lots of U.S.-Lantus in vial (age from 19 to 34 month at analysis) and 10 lots of U.S.-Lantus in cartridge (age from 18 to 25 month at analysis) were analyzed to measure the peak maximum (λ_{max}). Representative overlaid intrinsic fluorescence spectra are provided in Figure 50 below.

Figure 50: Overlay of intrinsic fluorescence spectra of US-approved Lantus® (Cartridge & Vial)



The observed λ_{max} values for U.S.-Lantus cartridges and vials are provided in Table 52 and 53 in CAA report 2 and are summarized in the table below (assessor generated).

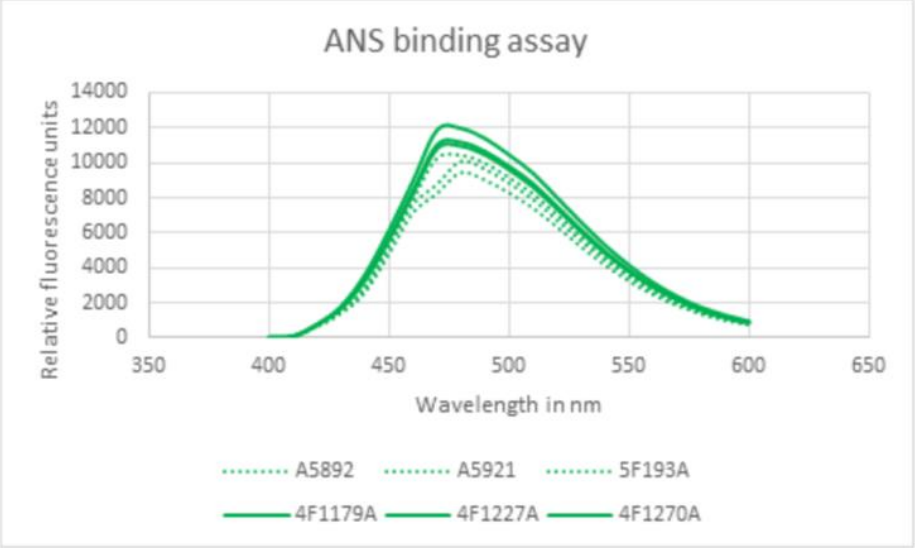
Intrinsic fluorescence	U.S.-Lantus (cartridge) Min – Max range	U.S.-Lantus (vial) Min – Max range
λ_{max} (nm)	300.93~302.03 (mean: 301.15, QR: 299.76~302.54)	301.07~302.00 (mean: 301.81)

Assessor's Comment: *The representative intrinsic fluorescence spectra of U.S.-Lantus vials are similar to that of U.S.-Lantus cartridges. The emitted peak maximum (λ_{max}) values for U.S.-Lantus vials are 100% within the quality range established for U.S.-Lantus cartridges. These data support a demonstration of highly similar protein conformation between U.S.-Lantus vial presentation and cartridge presentation.*

4.2e Extrinsic Fluorescence

Fluorescence spectroscopy techniques with non-covalent, extrinsic fluorescent dyes (such as ANS) are commonly used to monitor protein conformational variants, e.g. environmental stress or chemical induced protein change (oxidation or deamidation), or by protein aggregation. ANS binds with high affinity to the hydrophobic surfaces of proteins and the interaction is mediated by formation of ion pairs. The emission maximum of ANS undergoes a blue shift and fluorescence intensity increases significantly upon binding to the hydrophobic pockets in the protein molecule.
10 lots of U.S.-Lantus in vial (age from 19 to 34 month at analysis) and 22 lots of U.S.-Lantus in cartridge (age from 16 to 33 month at analysis) were analyzed using ANS binding assay. Representative overlaid extrinsic fluorescence spectra are provided in Figure 51 below.

Figure 51: Representative Overlay of extrinsic fluorescence spectra using ANS binding assay of US-approved Lantus® (Cartridge & Vial)



The observed λ_{max} value for U.S.-Lantus cartridges and vials are provided in Table 54 and 55 in CAA report 2 and are summarized in the table below (assessor generated).

Extrinsic fluorescence	U.S.-Lantus (cartridge) Min – Max range	U.S.-Lantus (vial) Min – Max range
λ_{max} (nm)	473~483 (mean: 477.8, QR: 468.3~487.3)	474~479 (mean: 476.7)

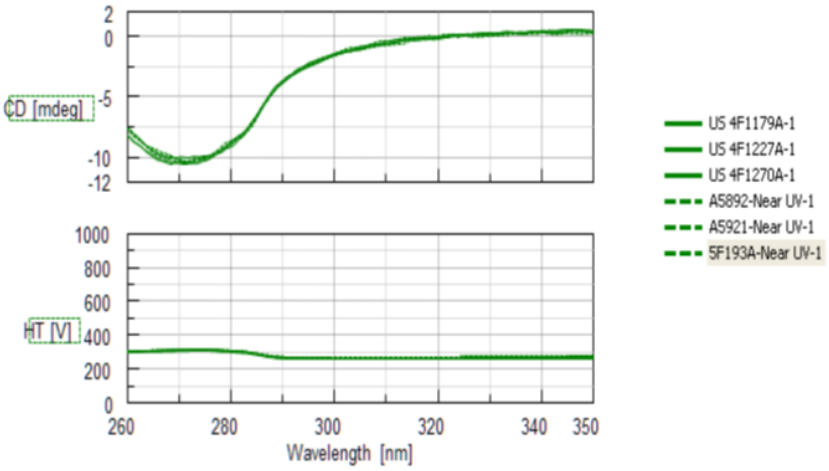
Assessor's Comment: *The representative extrinsic fluorescence spectra of U.S.-Lantus vials are similar to that of U.S.-Lantus cartridges. The emitted peak maximum (λ_{max}) values for U.S.-Lantus vials are 100% within the quality range established for cartridges. These data also support a demonstration of highly similar protein conformation between U.S.-Lantus vial presentation and cartridge presentation.*

4.2f Near UV CD Spectral Analysis

Wavelength scans, using a CD spectrometer, in the "near-UV" spectral region (260-360 nm) result in CD spectra that are characteristic of the tertiary structure of a protein. This near-UV CD spectral analysis can detect changes in the tertiary structure which includes environment around aromatic residues and disulfide linkages in the protein.

10 lots of U.S.-Lantus in vial and 10 lots of U.S.-Lantus in cartridge were subjected to near-UV CD spectral analysis. Representative overlaid near UV-CD spectra of 3 U.S.-Lantus vials (age from 17 to 20 month) and 3 cartridges (age from 21 to 25 month) are provided in Figure 52 below. The near-UV CD spectra profiles are compared visually for any conformational changes.

Figure 52: Representative Overlay of Near UV CD profile for tertiary structure of US-approved Lantus® (Cartridge & Vial)



Assessor's Comment: *The age information for U.S.-Lantus lots used in near UV CD spectral analysis was missing in the original submission. In response to the Agency's IR (OBP IR #2) sent on 02/09/2021, Mylan provided age information at analysis for all lots displayed in Figure 52 above on 02/16/2021. Mylan's response is acceptable.*

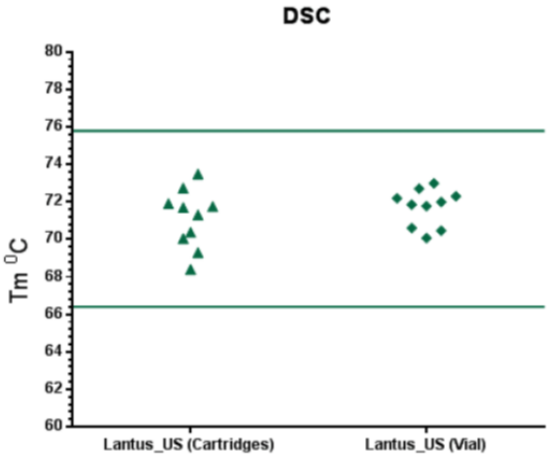
The near-UV CD spectra (260 – 350 nm) of representative U.S.-Lantus vials and cartridges all exhibit a similar pattern with a broad negative CD band around 270 nm and a shoulder at 300 – 310 nm, supporting a demonstration of highly similar tertiary structure between U.S.-Lantus vial presentation and cartridge presentation.

4.2g Thermal Stability by Differential Scanning Calorimetry (DSC)

DSC measures the heat capacity required to induce a change in the structure of a molecule. The temperature at which half of the protein molecules are unfolded is called the melting temperature (mid-point of DSC peak, Tm). This thermodynamic difference would indicate structural differences.

The thermal properties and structural-phase transitions of 10 lots of U.S.-Lantus in vial (age from 18 to 32 month) and 10 lots of U.S.-Lantus in cartridge (age from 20 to 28 month) were evaluated by DSC. Representative overlaid DSC profiles and observed Tm values are provided in CAA report 2 but not shown here. Scatter plot showing the distribution of data is presented in Figure 55 below.

Figure 55: Scatter plot distribution for Tm Values Using DSC for US-approved Lantus® (Cartridge & Vial)



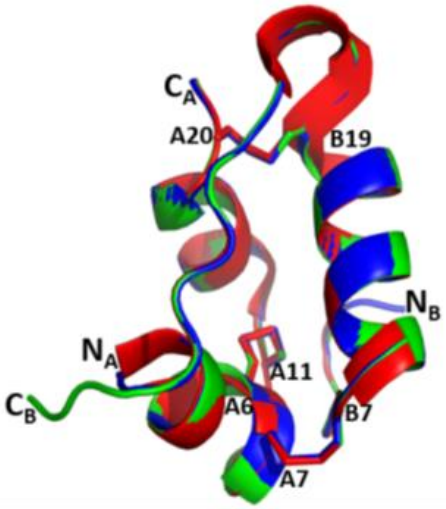
Assessor's Comment: *The representative DSC profile observed for U.S.-Lantus vial is similar to that of U.S.-Lantus cartridge. The measured melting temperature (Tm) values for U.S.-Lantus vials are 100% within the quality range established for U.S.-Lantus cartridges, support a demonstration of highly similar thermal stability and conformation between U.S.-Lantus vial presentation and cartridge presentation.*

4.2h X-Ray Crystallography

X-ray crystallography, which is an orthogonal method to near-UV CD, can provide more details about 3D structure of a protein. Two Insulin glargine extracted samples from U.S.-Lantus cartridge (lot 4F1179A) and U.S.-Lantus vial (lot 5F193A) were used for crystallization, X-ray diffraction experiments, structure determination and comparative structural analysis.

The structures were determined by molecular replacement using the human insulin polypeptide structure as the phasing model. The refined 3D structures of U.S.-Lantus vial and cartridge are compared to each other and compared to the previously determined 3D structures of insulin glargine (4IYD), as shown in the following Figure 3.

Figure 3: Superimposition of US-licensed Lantus® vial batch-5F193A (blue), US-licensed Lantus® cartridge batch-4F1179A (green) and published glargine structure-4IYD (red).



5F193A (blue): U.S.-Lantus in vial

4F1179A (green): U.S.-Lantus in cartridge

4IYD (red): Insulin glargine crystal structure 1 in PDB database

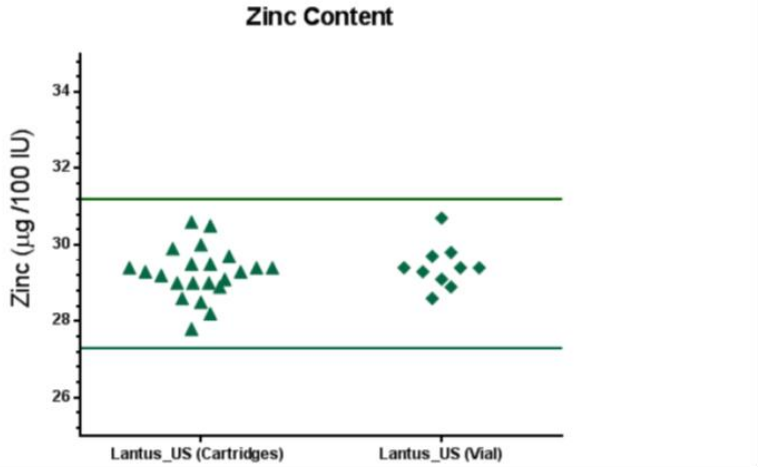
Assessor's Comment: *In Figure 56 of CAA report 2, the Applicant did not provide a superimposed structure with both U.S.-Lantus vial and cartridge but inadvertently included one lot of MYL-1501D in vial instead. An IR (OBP IR #2) was sent on 02/09/2021 regarding this issue. On 02/16/2021, the Applicant provided the above Figure 3 in their IR response to directly compare the 3D structure of U.S.-Lantus vial (lot 5F193A) and cartridge (lot 4F1179A). This IR response is acceptable.*
The 3D structures above show an overlay of the analyzed insulin glargine samples with the published structure of insulin glargine. The overlay closely resembles in terms of polypeptide fold, oligomeric organization and thermal parameters. All the molecules superpose well with an overall RMSD of 0.146 Å. Overall, the X-ray structure of U.S.-Lantus vial presentation and cartridge presentation is highly similar to each other and to the previously determined 3D structure of insulin glargine, supporting a demonstration of highly similar 3D structure between U.S.-Lantus vial presentation and cartridge presentation.

Summary of Primary, Secondary and Higher Order Structure:
Results obtained from multiple orthogonal analytic methods to assess the amino acid sequence, disulfide linkages, secondary and tertiary structure indicate that U.S.-Lantus vial presentation is highly similar to U.S.-Lantus cartridge presentation with respect to primary, secondary and higher order structure.

3.2.R.4.4.5 Zinc Content by Atomic Absorption Spectrometry (AAS)

The Zinc content for 10 lots of U.S.-Lantus in vial (age from 18 to 33 month) and 22 lots of U.S.-Lantus in cartridge (age from 15 to 30 month) were analyzed using Atomic Absorption Spectrometry (AAS). The scatter plot of Zinc content data is presented in Figure 57 below.

Figure 57: Scatter plot distribution of Zinc content in US-approved Lantus® (Cartridge & Vial)



Assessor's Comment: *Zinc content values for U.S.-Lantus vials are 100% within the quality range established for U.S.-Lantus cartridges, demonstrating a highly similar Zinc content between U.S.-licensed Lantus vial presentation and cartridge presentation.*

Summary of Overall Similarity between U.S.-licensed Lantus vial presentation and cartridge presentation:
Results from multiple orthogonal analytic studies demonstrate that the vial presentation of U.S.-licensed Lantus is highly similar to its cartridge presentation with respect to functional and biological activities, purity and impurities, primary, secondary as well as higher order structure. Due to the demonstrated similarity in functional activity by multiple orthogonal assays, the observed differences in IR-B binding

kinetics between the two presentations do not preclude a demonstration of similarity between U.S.-Lantus vial and cartridge presentation. Therefore, U.S.-licensed Lantus vial presentation is considered highly analytically similar to U.S.-licensed Lantus cartridge presentation.

3.2.R.4.5 Comparative Analytical Assessment between MYL-1501D (vial) and U.S.-Lantus (vial & cartridge)

The same as U.S.-Lantus vial presentation, MYL-1501D vial presentation has an additional excipient polysorbate 20 at a concentration of 20 µg/mL when compared to MYL-1501D cartridge presentation. An assessment has been conducted to demonstrate a similarity between the two presentations of U.S.-licensed Lantus in vial and in cartridge, as discussed in section 3.2.R.4.4 above. These CAA data in section 3.2.R.4.4, obtained from U.S.-Lantus vials and cartridges, are then combined for each assay to establish the QR for U.S.-Lantus (vial+ cartridge), and used for the similarity assessment between MYL-1501D vial presentation and U.S.-Lantus (vial+ cartridge).

Assessor's Comment: *The CAA results in section 3.2.R.4.4 as discussed above, demonstrate a similarity between the vial and the cartridge presentation of U.S.-Lantus therefore it's acceptable to combine data obtained from these two presentations to establish the U.S.-Lantus QR for the similarity assessment between MYL-1501D vial presentation and U.S.-Lantus. On 02/16/2021, Mylan provided information of reference standards used in each assay and results for bridging studies if different reference standards were used in an assay, in response to the Agency's IR (OBP IR #2) sent on 02/09/2021. The information provided by Mylan support the pooling of the data from various runs of the corresponding assays, as discussed in section 3.2.R.4.2 Quality Attributes/ Criticality Risk Ranking/ Reference Standards of this review memo previously therefore is acceptable.*

A summary of the analytical similarity results for MYL-1501D (vial) and U.S.-Lantus (vial+ cartridge) are provided in the following table (assessor generated based on CAA report CDL/TR/LR.19.0091/20/002, also referred as CAA report 2 in the following context, QR: quality range). For attributes that are evaluated using quality ranges, when at least 90% of MYL-1501D lots are within the U.S.-Lantus QR, the results support a demonstration of highly similar. In the following table, 'Yes' is indicated when similarity acceptance criteria are met or if the differences observed do not preclude a demonstration of highly similar.

Parameter	Quality Attribute	Test Method	Number of Lots U.S.-Lantus (vial + cartridge): MYL-1501D (vial)		U.S.-Lantus (vial+ cartridge) Min-Max Range (QR: Mean±3SD)	MYL-1501D (vial) Min-Max Range	Support a Demonstration of Highly Similar between MYL-1501D (vial) and U.S.-Lantus (vial + cartridge)
Protein content	Protein content/ Assay	RP-HPLC (% Assay: U/mL)	32:5		95.0~107.2 (QR: 90.1~110.2) (Cartridge 4F1270A is 107.2, resulted in wide QR)	99.1~102.0	Yes
Metabolic activity	IR-B binding kinetics	Surface Plasmon Resonance (SPR) k_a (1/Ms) k_d (1/s) K_D (nM)	13 :5	k_a	5.82E+05~7.55E+05 (QR: 4.85E+05 ~8.70E+05)	6.00E+05~ 6.87E+05	Yes)
				k_d	0.011~0.016 (QR: 0.008~0.019)	0.014~0.016	
				K_D	15.36~28.24 (QR: 8.25~32.08)	22.26~23.62	
	IR-B auto-phosphorylation	IR-B auto-phosphorylation assay (relative potency)	27:5		0.88~1.21 (QR: 0.85~1.28)	0.93~1.07	Yes

Parameter	Quality Attribute	Test Method	Number of Lots U.S.-Lantus (vial + cartridge): MYL-1501D (vial)		U.S.-Lantus (vial+ cartridge) Min-Max Range (QR: Mean±3SD)	MYL-1501D (vial) Min-Max Range	Support a Demonstration of Highly Similar between MYL-1501D (vial) and U.S.-Lantus (vial + cartridge)
	IR auto-phosphorylation	IR auto-phosphorylation assay using HepG2 cells (relative potency)	27:5		0.86~1.18 (QR: 0.81~1.25)	0.94~1.13	Yes
	Glucose uptake activity	Glucose uptake assay in 3T3-L1 cells (relative potency)	13:5		0.87~1.12 (QR: 0.82~1.23)	0.92~1.16	Yes
Mitogenic activity	IR-A binding kinetics	SPR k_a (1/Ms) k_d (1/s) K_D (nM)	13:5	k_a	1.15E+06~1.70E+06 (QR:8.07E+05~2.05E+06)	1.14E+06~ 1.36E+06	Yes
				k_d	0.022~0.036 (QR: 0.017~0.041)	0.024~0.030	
				K_D	17.62~23.20 (QR: 14.69~25.90)	21.07~24.07	
	IR-A auto-phosphorylation	IR-A auto-phosphorylation assay (relative potency)	27:5		0.97~1.17 (QR: 0.90~1.23)	0.92~1.12	Yes
	IGF-1 receptor binding kinetics	SPR k_a (1/Ms) k_d (1/s) K_D (nM)	27:5	k_a	1.47E+05~1.96E+05 (QR:1.40E+05~2.03E+05)	1.64E+05~ 1.73E+05	Yes
				k_d	0.04578~0.05421 (QR: 0.04420~0.05511)	0.04838~0.05023	
				K_D	0.26~0.34 (QR: 0.23~0.36)	0.29~0.31	
	Saos-2 cell proliferation	Cell proliferation assay in Saos-2 cells (relative potency)	13:5		0.92~1.19 (QR: 0.79~1.30)	0.92~1.08	Yes
Size variant	High Molecular Weight Protein (HMWP)/ Aggregates	SEC-HPLC (% HMWP)	32:5		LOD: 0.015%, LOQ: 0.050%		Yes
					BQL~0.08 (QR: 0.03~0.08)	BQL	
		SEC-MALS	20:5	Mass fraction%	100 (QR:100~100)	100	Yes
				Mw/Mn	1.000~1.006 (QR: 0.997~1.007)	1.000~1.002	
				Mz/Mn	1.000~1.012 (QR: 0.994~1.015)	1.000~1.004	
		AUC–sedimentation velocity	6:3	Monomer sedimentation coefficient (s)	1.60~1.64 (QR: 1.59~1.65)	1.61~1.65	Yes
				Total aggregate fraction (%)	0.0~3.2 (QR: 0~5.8)	0.2~3.2	
Product variant	Glyceridic ester of Glutamic acid	RP-HPLC (%) LOD: 0.015% LOQ: 0.040%	32:5	RRT: 0.96~0.98	0.14~0.34 (QR: 0.09~0.42)	0.13~0.25	Yes
	Insulin glargine			RRT: 1	98.42~99.24 (QR: 97.99~99.55)	99.30~99.55	
	A15 deamidation			RRT: 1.02~1.03	0.16~0.42 (QR: 0.00~0.56)	0.11~0.17	
	Des R & B3 deamidation			RRT: 1.04~1.08	0.17~0.40 (QR: 0.08~0.55)	0.06~0.32	
	Des TRR			RRT: 1.14~1.18	BDL~0.10 (QR: 0.00~0.11)	BQL~0.06	
	Citrate conjugate			RRT: 1.16~1.25	BDL~0.09 (QR: 0.03~0.10)	BQL	
	Acetylation			RRT: 1.24~1.34	BQL~0.06 (QR: 0.03~0.07)	Not determined	
Isoelectric point (pI)	Isoelectric point (pI)	Capillary Iso-Electric Focusing (cIEF)	25:5		7.00~7.07(QR: 6.97~7.10)	7.00~7.03	Yes
Primary structure & disulfide	Intact mass	ESI-MS Mass spectrometry (Da)	32:5		6063.5~6063.9	6063.9	Yes
				Chain A	2326.8~2327.4	2327.0	Yes

Parameter	Quality Attribute	Test Method	Number of Lots U.S.-Lantus (vial + cartridge): MYL-1501D (vial)		U.S.-Lantus (vial+ cartridge) Min-Max Range (QR: Mean±3SD)	MYL-1501D (vial) Min-Max Range	Support a Demonstration of Highly Similar between MYL-1501D (vial) and U.S.-Lantus (vial + cartridge)
confirmation	Intact mass of chain A and chain B	Reduced ESI-MS (DTT) to separate chain A and chain B (Da)	32:5	Chain B	3742.9~3743.2	3742.9	
	Disulfide confirmation	Non-reduced PMF using Glu-C analyzed with LC-MS and MS-MS (Da)	32:5	Fragment 4	417.1	417.1	Yes
				Fragment 3	1428.7~1429.6	1429.2~1429.7	
				Fragment 2	1320.5~1320.7	1320.6	
				Fragment 1	2969.1~2970.6	2970.1~2970.3	
		Reduced (DTT) PMF using Glu-C analyzed with LC-MS and MS-MS (Da)	32:5	Fragment 6	456.0~456.1	456.0~456.1	Yes
				Fragment 5	417.1	417.1	
				Fragment 4	1428.7~1429.6	1428.7~1429.5	
				Fragment 3	1482.7~1482.9	1482.8~1482.9	
				Fragment 2	867.3~867.4	867.4	
				Fragment 1	1490.5~1490.7	1490.7	
Secondary structure	Secondary structure (α-helix, β-sheets, β-turns and random coil)	Far UV-CD Spectra	32:5	α-helix %	18.7~28.7 (QR: 19~32)	20.2~29.0	Yes
				β-sheet %	33.1~54.1 (QR: 28~56)	43.6~48.4	
				β-turn %	5.9~18.8 (QR: 4~21)	9.1~11.2	
				Random coil %	17.9~22.9 (QR: 15~25)	18.3~22.1	
		Fourier Transform Infrared (FT-IR) Spectroscopy	32:5	α-helix %	22~33 (QR: 18~36)	23~25	Yes
				β-sheet %	20~33 (QR: 16~38)	30~32	
				β-turn %	21~23 (QR: 20~24)	21	
				Random coil %	23~25 (QR: 22~26)	23~24	
				Amide I (cm^{-1})	1646.91~1650.77 (QR: 1643.70~1654.10)	1646.91~1648.84	
				Amide II (cm^{-1})	1536.99~1540.85 (QR: 1536.1~1542.7)	1538.92	
Higher order structure	Higher order structure	Nuclear Magnetic Resonance (2D-NMR)	2:1		Similar 2D-NMR spectra were observed between MYL-1501D (vial) and U.S.-Lantus. Disulfide bonds between A6-A11, A7-B7 and A20-B19 were confirmed.		Yes
		Intrinsic Fluorescence (λ_{max}: nm)	20:5		300.93~302.03 (QR: 299.86~303.10)	302.00	Yes
		Extrinsic Fluorescence (λ_{max}: nm)	32:5		473~483 (QR: 469.1~485.9)	477~479	Yes
		Near UV-CD Spectra	32:5		Similar near UV-CD spectra were observed between MYL-1501D (vial) and U.S.-Lantus.		Yes
	Thermal stability	DSC (Tm: °C)	20:5		68.40~73.48 (QR: 67.47~75.32)	70.61~72.91	Yes
	Crystal structure	X-Ray Crystallography	2:1		The 3D-structures of U.S.-Lantus and MYL-1501D (vial) are similar to each other and to that of insulin glargine.		Yes
Excipient	Zinc content	Atomic Absorption Spectrometry (AAS) (µg/100U)	32:5		27.8~30.7(QR: 27.4~31.2)	28.4~30.2	Yes

Assessor's Comment: *Results for Des R and B3 levels do not meet the similarity acceptance criteria. However, the observed difference does not preclude a demonstration that MYL-1501D is highly similar to US-Lantus, as discussed in section 3.2.R.4.5.3.2 Product Variants by RP-HPLC of this memo.*

The lots used in the analytical similarity comparison in this section are listed in Table 61 below.

Table 61: List of MYL-1501D (vials), E.U.-Lantus (cartridges), U.S.-Lantus (cartridges and vials) lots used in CAA report 2. U.S.-Lantus vial lots are highlighted in green color.

Sl. No	EU-Approved (Cartridges) Lantus® Lots*		US-approved (Cartridges & Vials) Lantus® Lots*		MYL-1501D (Vial) Lots*	
	Lot Number	Expiry date	Lot Number	Expiry date	Lot Number	Manufacturing date
1	4F789A	Sep-17	4F1179A	Mar-17	BS16002122	Jun-16
2	5F035A	Dec-17	4F1227A	Aug-17	BS16002123	Jun-16
3	5F1325A	Jul-17	4F1270A	Jul-17	BS16002124	Jun-16
4	5F1446A	Jul-17	5F1296A	Aug-17	BS16002352	Jun-16
5	5F1709A	Oct-17	5F1357A	Aug-17	BS16002354	Jun-16
6	5F1895A	Dec-17	5F1492A	Apr-17		
7	5F2004A	Jan-18	5F1524A	Aug-17		
8	5F2014A	Jan-18	5F1568A	Mar-17		
9	5F2228A	Dec-17	5F1710A	Sep-17		
10	5F2251A	Feb-18	5F1739A	Oct-17		
11	4F209A	Apr-17	3F420A	May-16		
12	5F869B	Jan-18	3F393A	May-16		
13	5F1792A	Dec-17	3F425A	May-16		
14	5F1991A	Dec-17	4F924A	Jun-16		
15	5F1953A	May-17	4F723A	Sep-16		
16	5F1972A	Jan-18	3F417A	May-16		
17	5F1511A	Mar-17	3F072A	May-16		
18	3F105A	Mar-16	4F1023A	Apr-17		
19	3F124A	May-16	4F658A	Apr-17		
20	5F1324A	Jul-17	4F1050A	May-17		
21	5F038A	Dec-17	4F614A	May-17		
22	4F173A	Dec-16	4F655A	Jun-17		
23			1F759A	Jun-14		
24			1F767	Jun-14		
25			4F126A	Mar-17		
26			A4789	Jun-17		
27			A4803	Jul-17		
28			A4825	Aug-17		
29			4F148A	Sep-17		
30			4F169A	Oct-17		
31			5F412A	Feb-18		
32			A5892	Mar-18		
33			A5921	Jun-18		
34			5F193A	May-18		

U.S.-Lantus vial lots

* All MYL-1501D, EU-Approved Lantus® and US-approved lots were tested within their expiry

The detailed information for MYL-1501D vial lots used above is listed in the following table (assessor modified, Mfg: manufacturing).

MYL-1501D (vial) Lot #	DP Lot Size	DP Mfg Date & Site	Use of DP Lot	From DS Batch #	DS Batch Size	DS Mfg Process	DS Mfg Date & Site
BS16002122	(b) (4)	June 2016 Biocon, Malaysia (L2)	Process validation batch; Used in comparative PK/PD study (MYL-1501D-1004) for vial and cartridge presentation	BS15007170	(b) (4)	VI	January 2016 Biocon, Malaysia (L2)
BS16002123		June 2016 Biocon, Malaysia (L2)	Process validation batch; stability batch	BS15007370			February 2016 Biocon, Malaysia (L2)
BS16002124		June 2016 Biocon, Malaysia (L2)	Process validation batch; stability batch	BS15007370			February 2016 Biocon, Malaysia (L2)
				BS15006908			January 2016 Biocon, Malaysia (L2)
BS16002352		June 2016 Biocon, Malaysia (L2)	Representative commercial batch	BS15007488			February 2016 Biocon, Malaysia (L2)
BS16002354		June 2016 Biocon, Malaysia (L2)	Representative commercial batch	BS15007488			February 2016 Biocon, Malaysia (L2)
				BS15007049			January 2016 Biocon, Malaysia (L2)

Site L2: Biocon Sdn. Bhd. (930330-U), No.1, Jalan Bioteknologi 1, Kawasan Perindustrian SiLC, 79200 Iskandar Puteri, Johor, Malaysia. (FEI# 3011248248).

***Assessor's Comment**: The Applicant did not provide detailed information about MYL-1501D lots used in CAA studies in the original submission. Upon request (OBP IR #2 sent on 02/09/2021), on 02/16/2021, the Applicant provided the above table with detailed information (such as manufacturing scale, site, date, use of the lot, DS batch # and manufacturing information) about MYL-1501D lots used. The IR response provided by the Applicant is acceptable.*

The MYL-1501D vials used in the comparative analytical studies include process validation batches, clinical batch and representative commercial batches.

The DS lots used to produce MYL-1501D DP vial lots are all manufactured with Process VI. As indicated in the table above, DP lots BS16002124 and BS16002354 were manufactured using two DS batches each. Pooling of DS batches for DP manufacturing is a common practice in insulin manufacture and these pooled batches are representative of commercial MYL-1501D DP manufacturing process. Lots BS16002124 and BS16002354 each used a pool of a DS process validation batch and another representative commercial batch. DP lots manufactured using those DS PV lots separately were also included in the CAA. DS lots BS15006908, BS15007049, and BS15007170 are three DS process validation batches, and their batch release data indicate these batches are comparable in protein content, purity and impurity profiles, as well as size and product variants. Additionally, lots BS16002352 and BS16002123 manufactured using single DS lots BS15007488 and BS15007370 respectively did not show quality characteristics different from the pooled batches. Therefore, pooling of these DS PV batches together with another independent DS batch did not alter quality attributes of the DP batches manufactured by pooling DS batches and retains the independent nature of these DP lots. The lots of MYL-1501D vials used in the CAA are therefore acceptable.

Although at least 6 to 10 lots of the proposed product for comparative analytical assessment are recommended in the FDA Draft Guidance for Industry "Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations (May 2019)", Mylan used 5 lots of MYL-1501D vials for this CAA study. These lots are all commercial-scale vial lots they produced so far. This is acceptable for the following reasons: 10 lots of MYL-1501D in cartridge were used for the

similarity comparison between MYL-1501D and U.S.-Lantus cartridge presentation, and the results demonstrate a similarity between the cartridge presentation of both products. The only difference between the vial and cartridge presentation of MYL-1501D is the addition of polysorbate 20 in the vial presentation, the same as with U.S.-Lantus vial and cartridge presentation, which is not expected to significantly alter the quality attributes of MYL-1501D.
The lots of US-Lantus cartridges and vials used are within and span across 36 months of its shelf life. The age of lots at analysis allows for a meaningful comparison to support the demonstration of similarity. span the shelf life of US-Lantus.

3.2.R.4.5.1 Protein Content/ Assay

The concentration of insulin glargine (mg/mL) and assay in units (U) is determined using RP-HPLC method by comparing to standard solution each time. 5 lots of MYL-1501D in vial (8-month-old at analysis) were compared to 32 lots of U.S.-licensed Lantus (10 in vial and 22 in cartridge, age from 16 to 34 month). Representative overlaid chromatograms are provided in the following Figure 58. Scatter plot representing the distribution of protein content (mg/mL)/ Assay (IU/mL) for MYL-1501D and U.S.-Lantus is shown in Figure 59 and 60 below, respectively. Equivalence testing is conducted by Mylan but not discussed here.

Figure 58: Representative Overlay of the RP-HPLC Chromatograms for Protein content of MYL-1501D, US-approved Lantus® and EU-Approved Lantus®

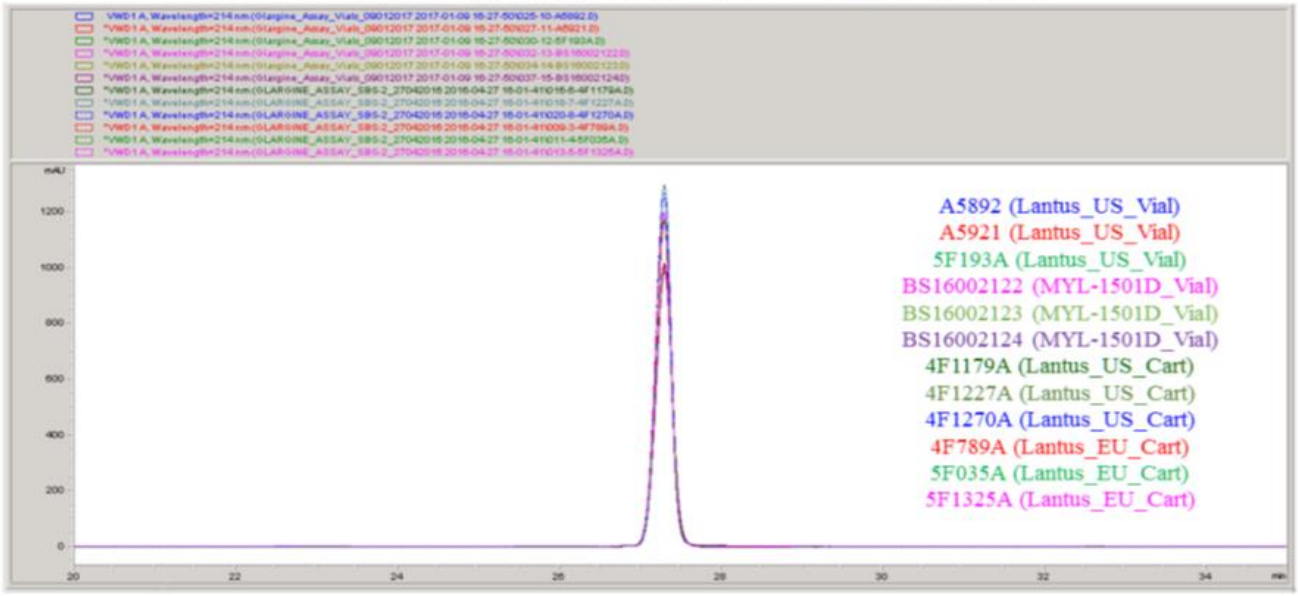


Figure 59: Scatter Plot Distribution for Content (mg/mL) of MYL-1501D, US-Lantus® and EU-approved Lantus®

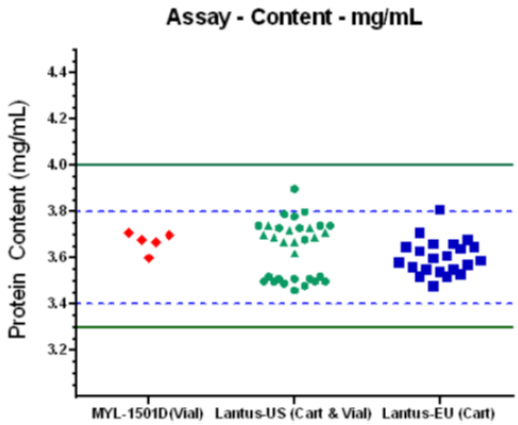
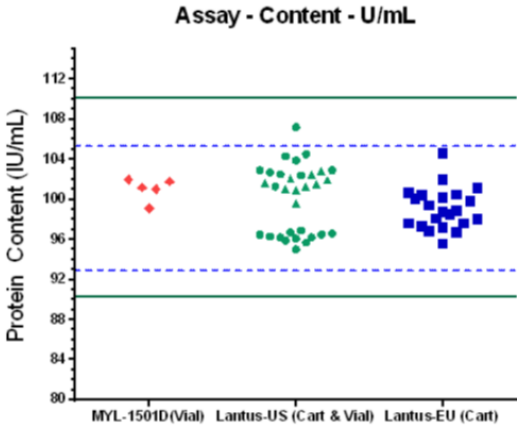


Figure 60: Scatter Plot Distribution for Assay (Units/mL) of MYL-1501D, US-Lantus® and EU-approved Lantus®



Data plots of MYL-1501D vial lots are displayed in red. The solid lines in Green represent the QR which has been set based on mean ± 3SD obtained from U.S.-Lantus lots (vials + cartridges). The dotted lines in Blue represent QR obtained from E.U.-Lantus cartridge lots. The same pattern and color code apply to all the following tables and figures unless otherwise stated.

***Assessor's Comment**: Mylan did not provide information about reference standard used in this assay in the original submission. Upon request (OBP IR #2, 02/09/2021), Mylan provided such information on 02/16/2021, indicating there were three RS* (b) (4) *used here for U.S.-Lantus and MYL-1501D lots. The Applicant provided a summary of bridging study which included three references standards* (b) (4) *used in protein content/Assay here which all performed very similarly to the common reference standard EPCRS LOT 1.0. These data indicated these RS performed very similarly to the common reference standard EPCRS LOT 1.0, supporting the pooling of data from various runs in this assay. Refer to section 3.2.R.4.2 Quality Attributes/ Criticality Risk Ranking/ Reference Standards of this review memo for detailed assessment.*
The representative RP-HPLC chromatograms of MYL-1501D vial lots are similar to that of U.S.-Lantus. The protein content/Assay values of MYL-1501D vials are 100% within the quality range established for U.S.-licensed Lantus, demonstrating the protein content/Assay is highly similar between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.

3.2.R.4.5.2 Functional and Biological Similarity Assessment

The biological and functional similarity assessment of MYL-1501D vial lots against U.S.-licensed Lantus cartridge and vial lots was carried out using multiple *in-vitro* assays to measure the biological activity. *In-vitro* bioassays performed include receptor auto-phosphorylation, receptor binding kinetics, metabolic and mitogenic activity. The *in-vivo* Rabbit Bioassay was not performed here. Adipogenesis assay and inhibition of stimulated lipolysis assay in 3T3-L1 cells were also not performed here.

***Assessor's Comment**: The Applicant used an appropriate panel of tests for assessing functional and biological similarity.*
Although the Adipogenesis assay and inhibition of stimulated lipolysis assay were performed for similarity assessment between MYL-1501D cartridge presentation and U.S.-Lantus cartridge presentation, these assays were not included in the comparative analytical assessment of the MYL-1501D vial presentation. These assays are orthogonal assays to the glucose uptake assays for assessment of insulin metabolic activity. Glucose uptake assay was included in the CAA for vials. The cell based assay for glucose uptake,

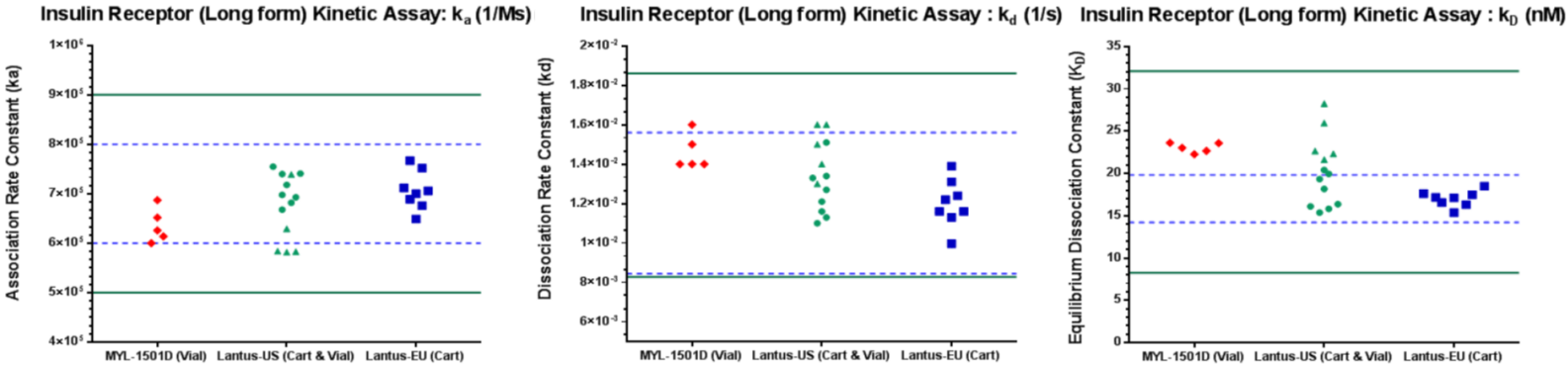
together with IR-B binding kinetics, and IR-B phosphorylation are acceptable for assessing the similarity of metabolic activity of MYL-1501D vials and U.S.-Lantus lots. Additionally, these assays have been used in the CAA of the MYL-1501D and US-Lantus cartridge lots, discussed earlier in this memo.
As previously stated in this memo, per current OBP recommendation, the rabbit bioassay is not recommended for demonstration of similarity of insulin products. The similarity of potency is assessed by other assays including protein content, metabolic assays and mitogenic assays. Overall, the chosen assays are sufficient for the assessment of functional and biological similarity.

3.2.R.4.5.2.1 Metabolic Activity

2.1a Insulin Receptor IR-B (long form) Binding Kinetics

Comparative IR-B receptor binding affinity has been studied by Surface Plasmon Resonance (SPR). 5 lots of MYL-1501D in vial (9-month-old at analysis) were compared to 13 lots of U.S.-licensed Lantus (5 in vial and 8 in cartridge, age from 17 to 28 month). Representative sensorgrams are provided in CAA report 2 but not shown here for brevity. Scatter plots distribution of the data for binding affinity to IR-B in terms of rate of association (ka), rate of dissociation (kd) and Dissociation Constant (KD) are provided in Figure 65 below.

Figure 65: Scatter Plot Distribution for Insulin receptor (Long form; IR-B) binding kinetic constants (k_a, k_d and K_D) of MYL-1501D, US-approved Lantus and EU-approved Lantus.

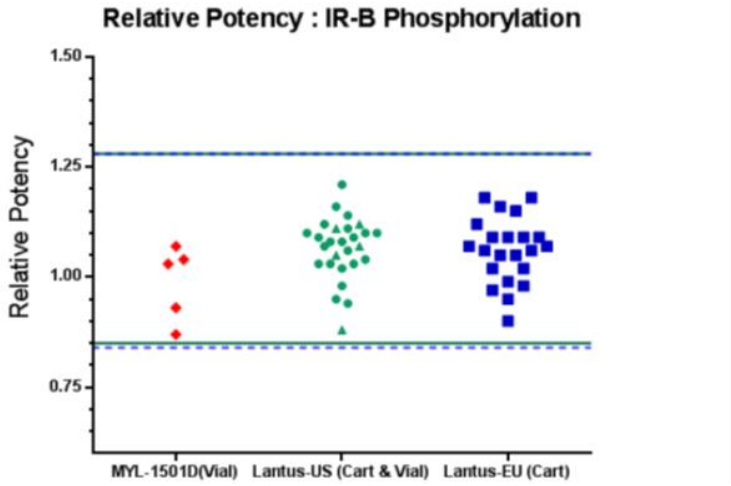


***Assessor's Comment**: The representative sensorgrams of IR-B binding kinetics for MYL-1501D vial lot are similar to that of U.S.-Lantus vial lot. The association rate constant (k_a), dissociation rate constant (k_d), and equilibrium dissociation constant (K_D) of MYL-1501D vials are 100% within the quality range of U.S.-licensed Lantus. These data demonstrate the IR-B binding kinetics are highly similar between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*
Of note, the QR of U.S.-licensed Lantus is based on combined data from vials and cartridges and therefore appears to be wide. The kinetics of MYL-1501D vials are closer to that of U.S.-Lantus vials rather than the cartridges. Based on the Assessor's independent calculation, the k_a, k_d, and K_D of MYL-1501D vials are also 100% within the quality range determined only from the 5 lots of U.S.-Lantus vial presentation. As discussed previously in section 3.2.R.4.4 of this review memo, the observed differences between U.S.-Lantus vial and cartridge presentation are small and have no impact on the metabolic activity, as also demonstrated by data obtained from glucose uptake assay in 3T3-L1 cells, discussed in section 2.1c below. Therefore, a demonstration of highly similar IR-B binding kinetics between MYL-1501D vial presentation and U.S.-licensed Lantus can be made here despite the differences observed within U.S.-Lantus group between its vial presentation and cartridge presentation.

2.1b Insulin Receptor IR-B (long form) Auto-phosphorylation Assay

This assay has been conducted to determine the phosphorylation of IR-B receptor once ligand (MYL-1501D or U.S.-licensed Lantus) binds to receptor.
5 lots of MYL-1501D in vial (8-month-old at analysis) were compared to 27 lots of U.S.-licensed Lantus (5 in vial and 22 in cartridge, age from 15 to 31 month). Representative dose response curves from each group are provided in CAA report 2 but not shown here. The Insulin receptor-B phosphorylation activity data along with descriptive statistics are also provided in the report. The scatter plot representing the distribution of data is shown in the following Figure 69. Equivalence testing was conducted by Mylan but not discussed here.

Figure 69: Scatter Plot Distribution for Relative potency (IR-B phosphorylation activity) of MYL-1501D, US-approved Lantus® and EU-approved Lantus®

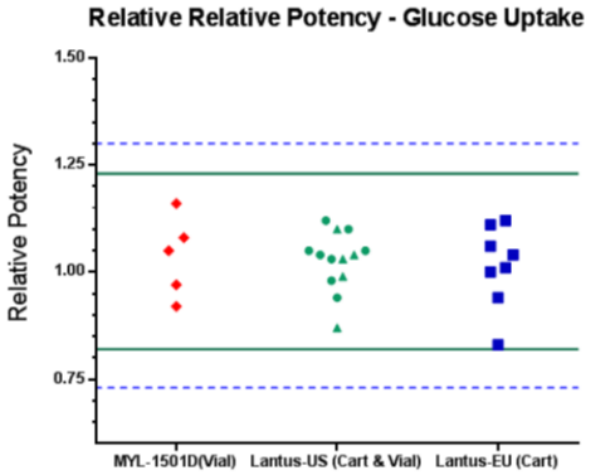


***Assessor's Comment**: The relative values of IR-B phosphorylation activity for MYL-1501D vial lots are 100% within the quality range of U.S.-licensed Lantus, demonstrating a highly similar IR-B phosphorylation activity between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

2.1c Glucose Uptake Assay in 3T3-L1 Cells

The assay measured glucose uptake in differentiated mouse 3T3-L1 adipocyte cells using the glucose oxidase/peroxidase (GOPOD) assay, which measures residual glucose left in the medium using a colorimetric method.
5 lots of MYL-1501D in vial (8-month-old at analysis) were compared to 13 lots of U.S.-licensed Lantus (5 in vial and 8 in cartridge, age from 17 to 27 month). Representative dose response curves (PLA) are provided in CAA report 2 but not shown here. The scatter plot representing the distribution of data is shown in Figure 74 below.

Figure 74: Scatter Plot Distribution for Relative potency (Glucose Uptake) of MYL-1501D, US-approved Lantus® and EU-Approved Lantus®



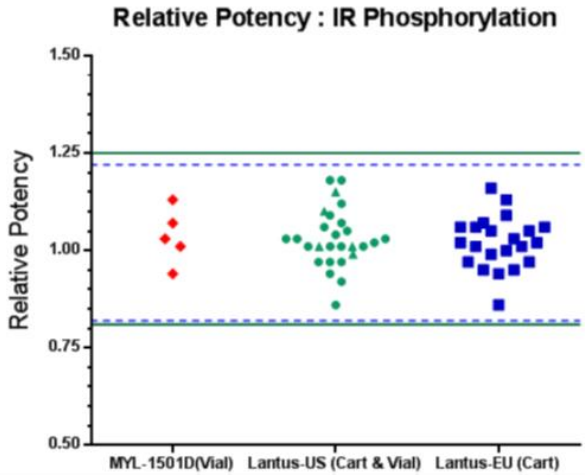
***Assessor's Comment**: The relative values of 3T3-L1 cell glucose uptake activity for MYL-1501D vial lots are 100% within the quality range of U.S.-licensed Lantus, demonstrating a highly similar activity in stimulating 3T3-L1 cell glucose uptake between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

2.1d Insulin Receptor Phosphorylation Assay Using HepG2 Cell Lysates

The AlphaScreen SureFire INSR p-Tyr1150/1151 assay is used to measure the auto-phosphorylation of endogenous IR in cellular lysates of HepG2 cells which are prior stimulated with different doses of insulin glargine.

5 lots of MYL-1501D in vial (8-month-old at analysis) were compared to 27 lots of U.S.-licensed Lantus (5 in vial and 22 in cartridge, age from 15 to 31 month). Representative dose response curves are provided in CAA report 2 but not shown here. The scatter plot demonstrating distribution of the relative potency data is shown in Figure 78 below. Equivalence testing was conducted but not discussed here.

Figure 78: Scatter Plot Distribution for relative potency (IR phosphorylation) of MYL-1501D, US-approved Lantus® and EU-approved Lantus®



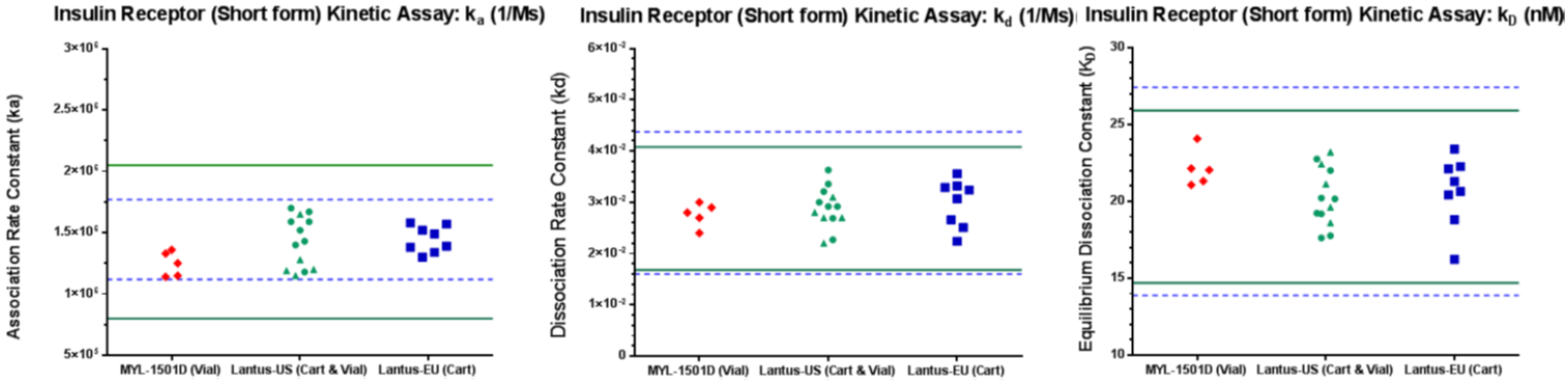
***Assessor's Comment**: The relative values of IR phosphorylation activity for MYL-1501D vial lots are 100% within the quality range of U.S.-licensed Lantus, demonstrating a highly similar IR phosphorylation activity between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

3.2.R.4.5.2.2 Mitogenic Activity

2.2a Insulin Receptor IR-A (short form) Binding Kinetics

Comparative binding affinity to IR-A (short form) has been studied using Surface Plasmon Resonance (SPR). 5 lots of MYL-1501D in vial (9-month-old at analysis) were compared to 13 lots of U.S.-licensed Lantus (5 in vial and 8 in cartridge, age from 17 to 28 month). Representative sensorgrams of IR-A binding kinetics are provided in CAA report 2 but not shown here. The IR-A binding affinity data in terms of rate of association (k_a), rate of dissociation (k_d) and Dissociation Constant (K_D) are shown in scatter plots in Figure 99 below.

Figure 99: Scatter plot distribution of Insulin receptor (short form; IR-A) binding kinetic constants of MYL-1501D, US-approved Lantus and EU-approved Lantus

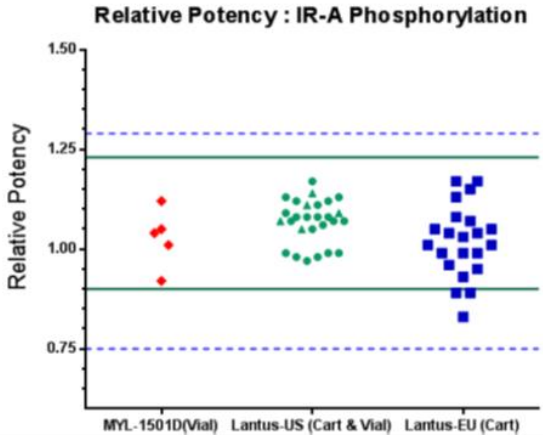


***Assessor's Comment**: The representative sensorgrams of IR-A binding kinetics for MYL-1501D vial lot are similar to that of U.S.-Lantus vial lot. The association rate constant (k_a), dissociation rate constant (k_d), and equilibrium dissociation constant (K_D) of MYL-1501D vials are all 100% within the quality range of U.S.-licensed Lantus, demonstrating the highly similar IR-A binding kinetics between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

2.2b Insulin Receptor IR-A Phosphorylation Assay

The auto-phosphorylation of IR-A when ligand (MYL-1501D or U.S.-licensed Lantus) binds with IR-A receptor has also been compared with 5 lots of MYL-1501D in vial (8-month-old at analysis) and 27 lots of U.S.-licensed Lantus (5 in vial and 22 in cartridge, age from 15 to 31 month). Representative dose response curves for each group are provided in CAA report 2 but not shown here. The scatter plot representing the distribution of the data is shown in Figure 90. Equivalence testing was conducted by Mylan but not discussed here.

Figure 90: Scatter Plot Distribution for Relative potency (IR-A phosphorylation) of MYL-1501D, US-approved Lantus® and EU-Approved Lantus®



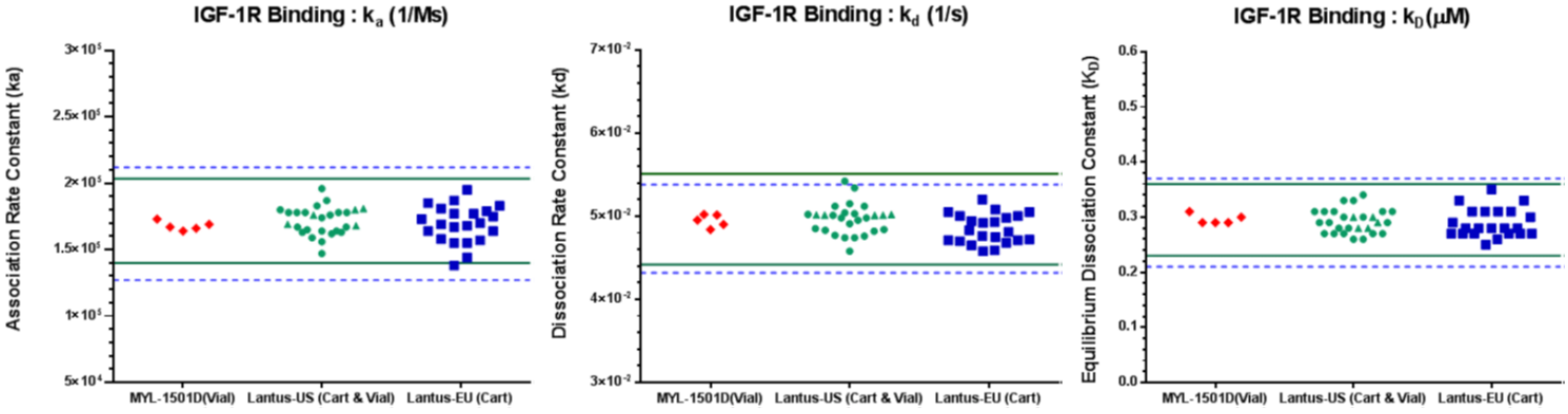
***Assessor's Comment**: The relative values of IR-A phosphorylation activity for MYL-1501D vial lots are 100% within the quality range of U.S.-licensed Lantus, demonstrating a highly similar IR-A phosphorylation activity between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

2.2c Insulin Growth Factor-1 Receptor (IGF-1R) Binding Kinetics

Surface Plasmon Resonance (SPR) based assay is used to evaluate the binding of ligand (MYL-1501D or U.S.-licensed Lantus) to purified recombinant human IGF-1 receptor, using BIAcore. The binding affinity is determined in terms of rate of association (k_a), rate of dissociation (k_d) and Dissociation Constant (K_D) which are used to compare MYL-1501D and U.S.-licensed Lantus.

5 lots of MYL-1501D in vial (7-month-old at analysis) were compared to 27 lots of U.S.-licensed Lantus (5 in vial and 22 in cartridge, age from 17 to 31 month). Representative sensorgrams are provided in CAA report 2 but now shown here. Scatter plots demonstrating the distribution of the data are shown in Figure 83 below. Equivalence testing was conducted based on obtained data but not discussed here.

Figure 83: Scatter Plot Distribution for IGF-1R binding kinetic constants of MYL-1501D, US-approved Lantus and EU-approved Lantus.



***Assessor's Comment**: The representative sensorgrams of IGF-1R binding kinetics for MYL-1501D vial lot are similar to that of U.S.-Lantus vial lot. The IGF-1R association rate constant (k_a), dissociation rate constant (k_d), and equilibrium dissociation constant (K_D) of MYL-1501D vials are all 100% within the*

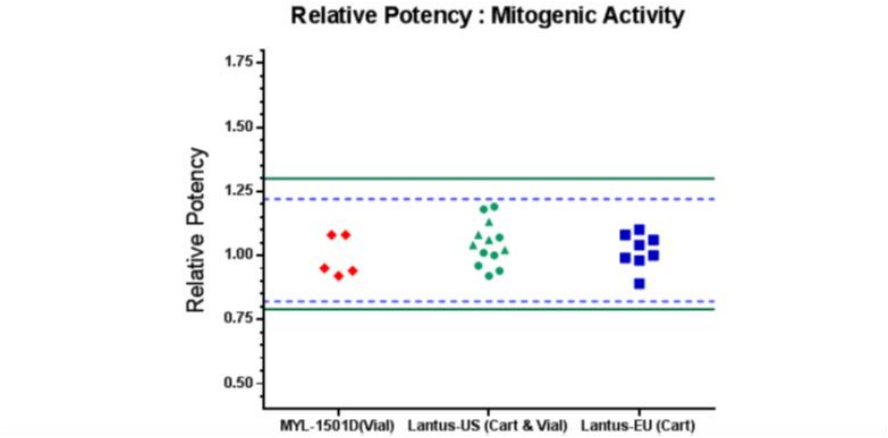
quality range of U.S.-licensed Lantus, demonstrating the highly similar IGF-1R binding kinetics between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.

2.2d Mitogenic Activity Using Saos-2 Cell-Based Assay

The proliferation of Saos-2 cells exposed to different lots of MYL-1501D or U.S.-Lantus was measured calorimetrically using the redox indicator dye Alamar Blue. The relative fluorescence unit (RFU) obtained is directly proportional to the increase in cell number. Mitogenic activity is measured in terms of Relative Potency using Parallel Line Assay software by Stegmann Systems.

5 lots of MYL-1501D in vial (8-month-old at analysis) were compared to 13 lots of U.S.-licensed Lantus (5 in vial and 8 in cartridge, age from 17 to 27 month). Representative dose response curves (PLA) for each group are provided in CAA report 2. The scatter plot representing the distribution of data is shown in the following Figure 95.

Figure 95: Scatter Plot Distribution of Relative Potency (Mitogenic Assay) of MYL-1501D, US-approved Lantus® and EU-approved Lantus®



***Assessor's Comment**: The relative values of mitogenic activity in Saos-2 cells for MYL-1501D vial lots are 100% within the quality range of U.S.-licensed Lantus, demonstrating a highly similar mitogenic activity between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

Summary of Functional and Biological Assays:

Results obtained from multiple orthogonal analytic methods to assess metabolic activity and mitogenic activity demonstrate that the overall functional and biological activities are highly similar between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.

3.2.R.4.5.3 Purity and Impurity

3.2.R.4.5.3.1 Size Variant- High Molecular Weight Protein (HMWP)/Aggregates

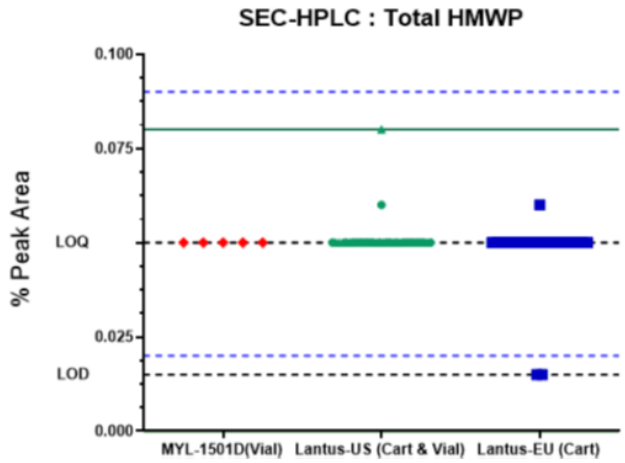
Size variants such as high molecular weight impurity (HMWP) species including aggregates, formed due to association of two or more molecules of the monomer or fragments, are primarily estimated by SEC-HPLC. Orthogonal methods such as SEC-MALS and AUC have also been used to assess size-based variants. Results for each assay are discussed below.

3.1a HMWP Assessment Using SEC-HPLC

5 lots of MYL-1501D in vial (7-month-old at analysis) were compared to 32 lots of U.S.-licensed Lantus (10 in vial and 22 in cartridge, age from 13 to 33 month). Representative overlaid SEC-HPLC chromatograms for size-based quality attributes are provided in CAA report 2 but not shown here. The

scatter plot representing the distribution of data is provided in Figure 101 below (LOD=0.015%, LOQ=0.050%).

Figure 101: Scatter Plot distribution of HMWP in MYL-1501D, US-approved Lantus® and EU-approved Lantus®

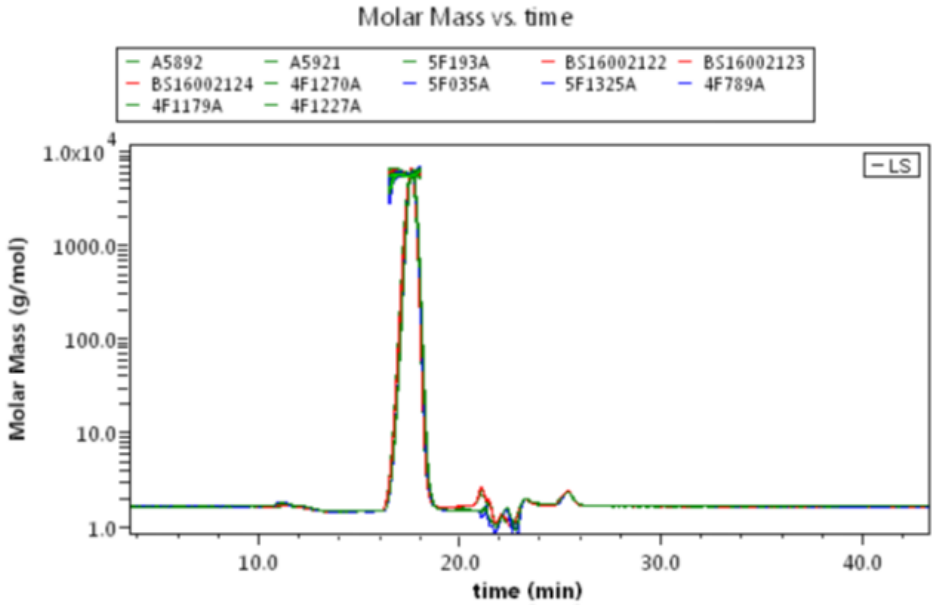


***Assessor's Comment**: The representative SEC-HPLC UV chromatograms of MYL-1501D vial lots are similar to that of U.S.-Lantus. The total HMWP content for most lots of MYL-1501D in vial presentation and U.S.-licensed Lantus were below the quantification limit (LOQ: 0.05%) by SEC-HPLC analysis. The HMWP content levels of MYL-1501D vials are 100% within the QR established for U.S.-licensed Lantus, demonstrating a highly similar HWMP profile and levels between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

3.1b HMWP Assessment Using SEC-MALS

SEC-MALS is an orthogonal tool to assess and characterize the size variants. 5 lots of MYL-1501D in vial (6-month-old at analysis) were compared to 20 lots of U.S.-licensed Lantus (10 in vial and 10 in cartridge, age from 17 to 32 month). Representative overlaid molar mass (g/mol) vs time plots of MYL-1501D and U.S.-Lantus lots are shown in Figure 102 below.

Figure 102: Representative Overlaid Molar mass chromatogram by SEC-MALS for MYL-1501D, US-approved Lantus® and EU-approved Lantus®



The SEC-MALS analysis data are tabulated in Table 101 and 103 but not shown in a scatter plot in CAA report 2. The following table contains summarized data from Table 101 and 103 (assessor generated).

Molar mass measured with SEC-MALS	U.S.-Lantus (10 vial + 10 cartridge) Min – Max range	MYL-1501D (5 vial) Min – Max range
Mass fractions (%)	100 (mean: 100, QR: 100~100)	100 (mean: 100)
Mw/Mn	1.000~1.006 (mean: 1.002, QR: 0.997~1.007)	1.000~1.002 (mean: 1.000)
Mz/Mn	1.000~1.012 (mean: 1.004, QR: 0.994~1.015)	1.000~1.004 (mean: 1.001)

***Assessor's Comment**: SEC-MALS analysis data of MYL-1501D vial and U.S.-Lantus lots indicate that a similar size range is obtained for the monomer across both products. A single predominant peak of monomer is observed in both groups with a similar distribution of molar mass. The content of multimers or aggregate is low in both products to provide a measurement of molar mass. These data support the demonstration of a highly similar HMWP profile obtained from SEC-HPLC analysis in section 3.1a above between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

3.1c HMWP Assessment Using AUC– Sedimentation Velocity

Sedimentation velocity measured by the AUC, provides information on the protein heterogeneity and state of association or aggregation. Aggregates can be detected based on their different sedimentation coefficients.

3 lots of MYL-1501D in vial (8-month-old at analysis) were compared to 6 lots of U.S.-licensed Lantus (3 in vial and 3 in cartridge, age from 19 to 25 month). Representative normalized sedimentation coefficient distribution graphs are presented in Figure 103, 104, and 106 below.

Figure 103: Representative Normalized sedimentation coefficient distribution for US-approved Lantus® (Cartridge)

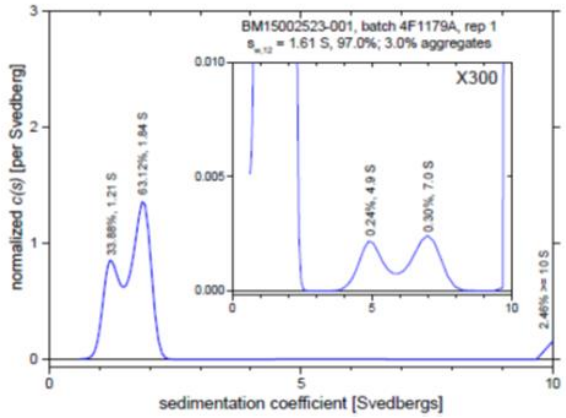


Figure 104: Representative Normalized sedimentation coefficient distribution for US-approved Lantus® (Vial)

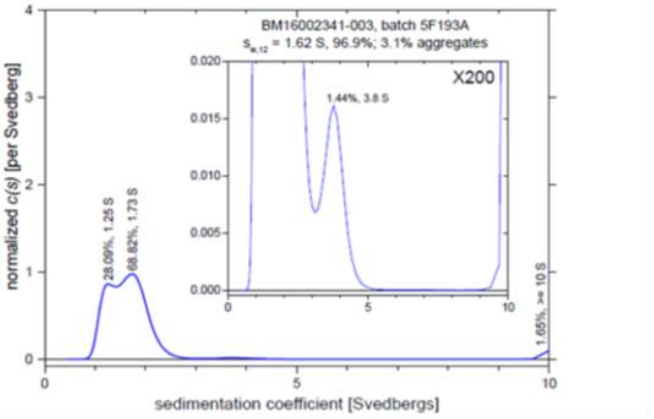
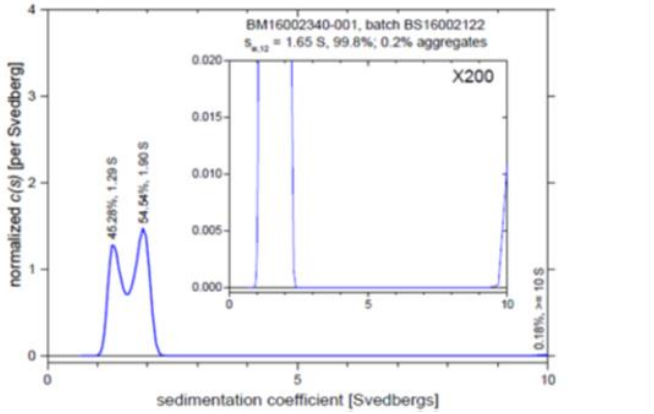


Figure 106: Representative Normalized sedimentation coefficient distribution for MYL-1501D (Vial)



The AUC analysis data are tabulated in Table 104 to 106 but not shown in a scatter plot in CAA report 2. The following table contains summarized data obtained from Table 104 and 106 (assessor generated).

Size variant measured using AUC	U.S.-Lantus (3 vial + 3 cartridge) Min – Max	MYL-1501D (3 vial) Min – Max
Monomer sedimentation coefficient (S)	1.60~1.64 (mean: 1.62, QR: 1.59~1.65)	1.61~1.65 (mean: 1.63)
Total aggregate fraction (%)	0.0~3.2 (mean: 1.9, QR: 0~5.8)	0.2~3.2 (mean: 1.5)

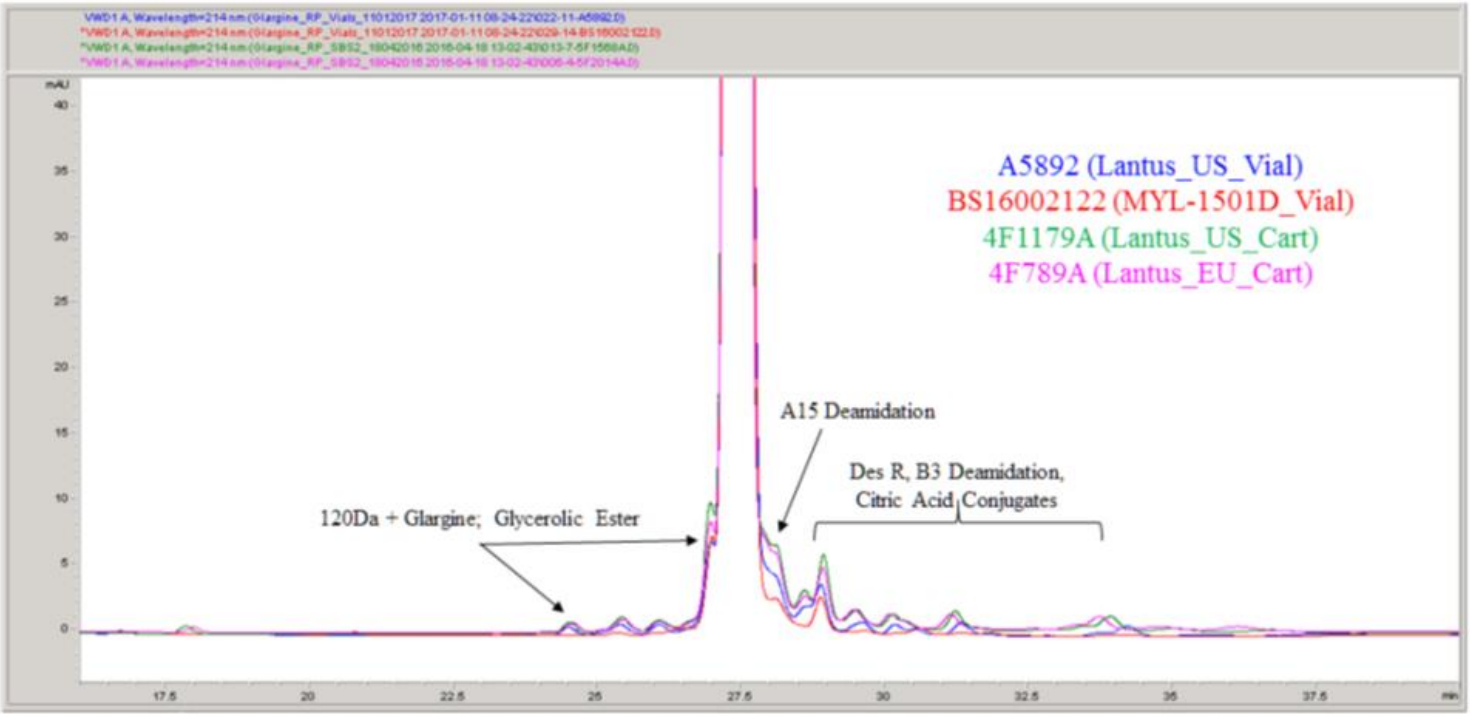
***Assessor's Comment**: The Applicant proposed assessment of AUC results by profile comparison/overlay and data table. Since an orthogonal method of evaluation of HMWP by SEC-HPLC using quality range statistical approach was also applied (discussed in section 3.1a HMWP Assessment Using SEC-HPLC above), the evaluation of AUC by profile comparison is acceptable. Additionally, the Applicant's AUC method seems to have high variability, making it not amenable for meaningful quantitative analyses. The AUC profiles of MYL-1501D and U.S.-Lantus lots are comparable, and data tables show comparable monomer sedimentation coefficients and aggregate fractions, which together support a demonstration of highly similar HMWP profile between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

3.2.R.4.5.3.2 Product Variants by RP-HPLC

The product related variants generated by deamidation/ clipping of the B-chain C-terminal amino acids, mis-cleavage of precursor by trypsin are monitored by RP-HPLC.

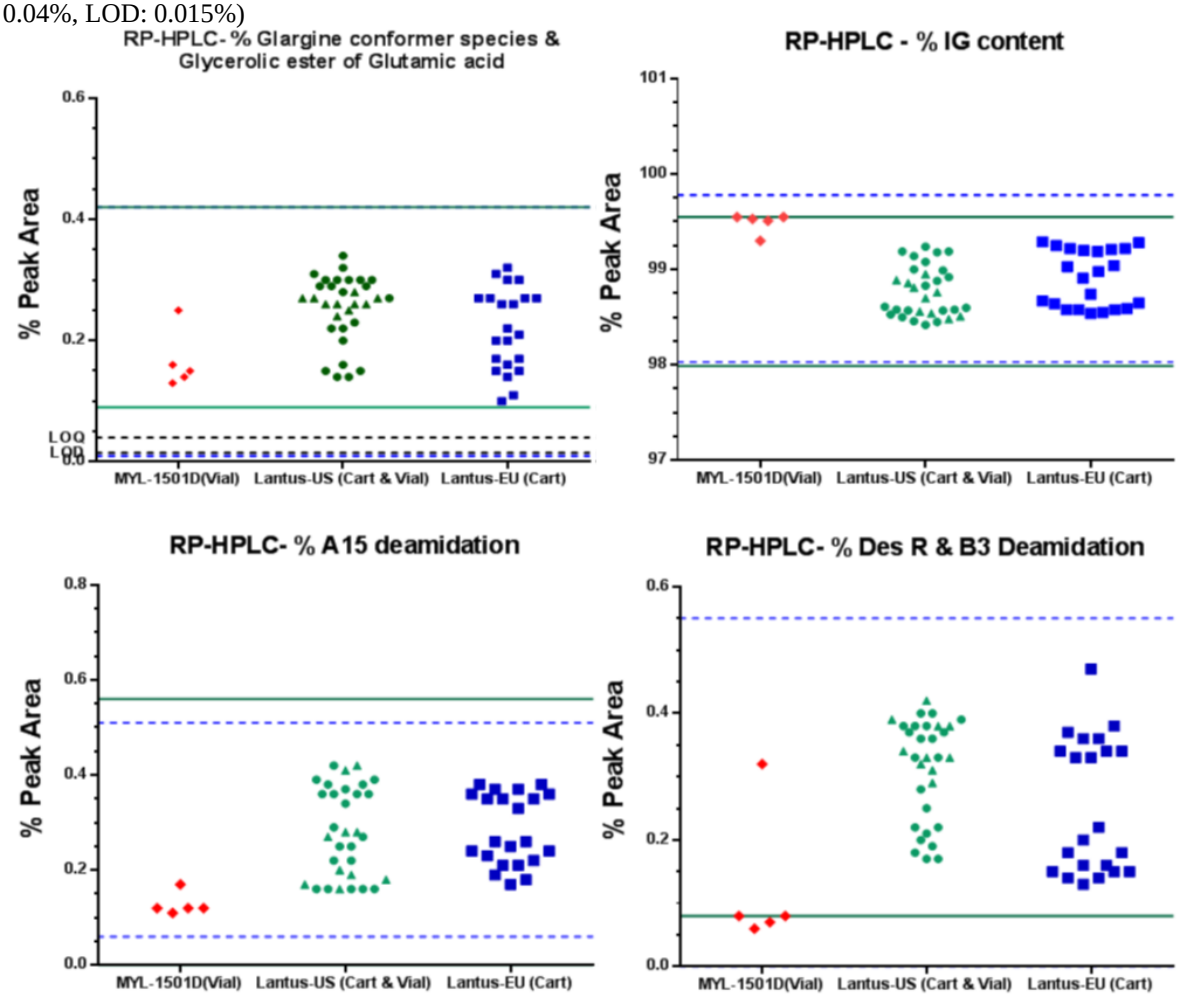
5 lots of MYL-1501D in vial (8-month-old at analysis) were compared to 32 lots of U.S.-Lantus (10 in vial and 22 in cartridge, age from 13 to 34 month). Representative overlaid RP-HPLC chromatograms are shown in Figure 107 below.

Figure 107: Representative overlaid RP-HPLC Chromatogram of MYL-1501D, EU-approved Lantus® and US-approved Lantus®



RP-HPLC data for product variants are tabulated in Table 107 to 109 in CAA report 2 but not shown here. Scatter plots distribution of the data for individual product variants are provided in Figure 108 below.

Figure 108: Scatter Plot distribution of Hydrophobic variants of MYL-1501D, US-approved Lantus and EU-Approved Lantus (LOQ: 0.04%, LOD: 0.015%)



***Assessor's Comment**: The overlaid chromatograms in Figure 107 indicate product variant profiles and levels are overall similar between MYL-1501D vials and U.S.-Lantus. Data in Figure 108 show that product variants, except Des R and B3 deamidation, measured by RP-HPLC for MYL-1501D vials are 100% within the QR established for U.S.-Lantus.*

Des R is a clipped insulin glargine variant that lacks the B32 arginine, while B3 desamido results from deamidation at the B3 asparagine. The Des R and B3 desamido levels of two out of five lots of MYL-1501D (0.06% and 0.07%) are marginally lower than the quality range of U.S.-licensed Lantus (0.08% - 0.55%). The lower levels in MYL-1501D lots suggests comparable or slightly improved purity compared to U.S.-Licensed Lantus. The observed lower level of Des R and B3 deamidation in MYL-1501D vial lots might be partially attributed to younger age of MYL-1501D lots used here since U.S.-Lantus lots also display an age-related increasing pattern. No impact of this difference is seen on the biological activity of MYL-1501D in comparison to U.S.-licensed Lantus. Due to the low levels of the Des R and B3 desamido variants in both MYL1501D and U.S.-licensed Lantus, the observed marginal difference in levels, and comparable biological activity of MYL-1501D and U.S.-licensed Lantus, the observed difference in Des R and B3 deamidation levels does not preclude a determination of highly similar between MYL-1501D and U.S.-licensed Lantus.

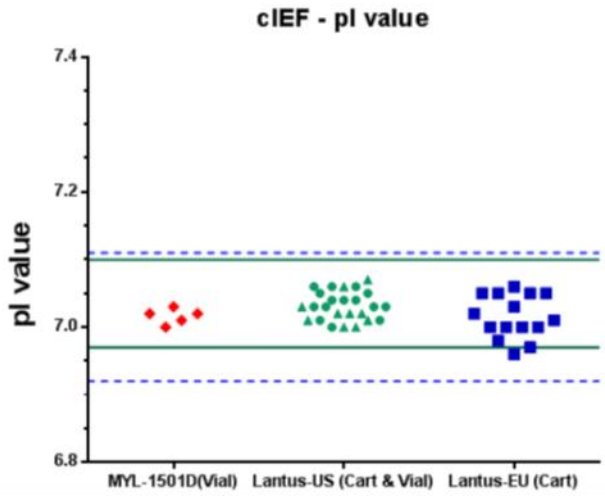
Levels of other product variants such as citrate conjugates, acetylated insulin glargine and iso-glargine in both products are very low and at similar levels but not shown as scatter plots here.

Overall, the data presented here do not preclude a determination of similarity between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.

3.2.R.4.5.3.3 Capillary Isoelectric Focusing to Assess the Isoelectric Point (pI)

cIEF separates charge variants and provides information about the protein pI, which depends on the amino acid sequence of a protein. 5 lots of MYL-1501D in vial (8-month-old at analysis) were compared to 25 lots of U.S.-licensed Lantus (10 in vial and 15 in cartridge, age from 8 to 33 month). Representative overlaid cIEF profiles are provided in CAA report 2 but not shown here. The scatter plot distribution of pI values is provided in Figure 110 below.

Figure 110: Scatter plot distribution for pI value for MYL-1501D, US-approved Lantus® and EU-approved Lantus®



Assessor's Comment: *Representative cIEF profiles for MYL-1501D vial lots are similar to that of U.S.-licensed Lantus. The calculated pI values of the main peak in MYL-1501D lots are 100% within the QR observed for U.S.-licensed Lantus, demonstrating a highly similar pI value between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

Summary of Purity and Impurity Assays:

Results from multiple orthogonal analytic methods to assess the size variants, product variants, and pI value support a demonstration of highly similar between MYL-1501D vial presentation and U.S.-licensed Lantus.

3.2.R.4.5.4 Primary, Secondary and Higher Order Structure

3.2.R.4.5.4.1 Primary Structure and Disulfide Linkage

The test methods used for assessing similarity of primary structure and disulfide linkage are presented in Table 63 below.

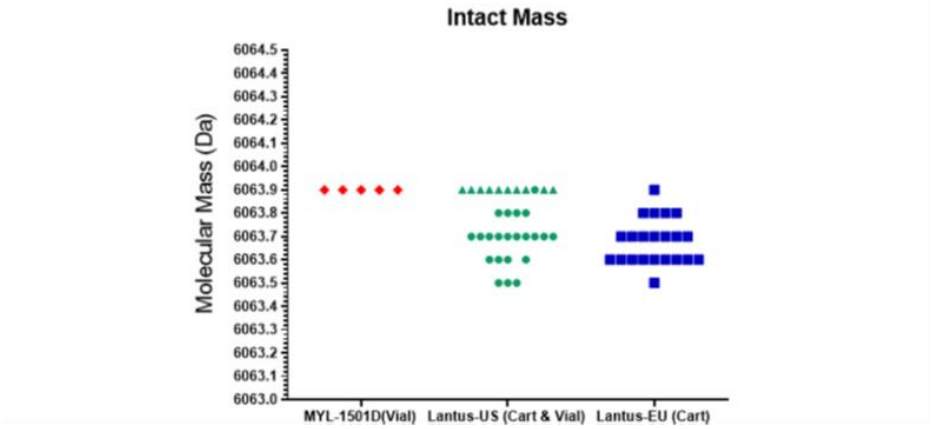
Table 63: Test Methods used for Primary Structure Similarity Assessment

Analytical Test	Description
Intact mass	Intact mass by ESI-MS Mass spectrometry
Reduced mass	Reduced by DTT to separate into two chains, Chain A and Chain B
Non-Reduced PMF	Peptide mass fingerprinting using GLU-C analysed using LC-MS and MS-MS
Reduced PMF	Peptide mass fingerprinting using GLU-C reduced with DTT analysed using LC-MS and MS-MS.

4.1a Intact Mass Analysis

The intact mass analysis not only confirms the identity of the molecule but also forms the first evidence of primary structure and hence primary sequence. 5 lots of MYL-1501D in vial (6-month-old at analysis) and 32 lots of U.S.-licensed Lantus (10 in vial and 22 in cartridge, age from 16 to 33 month) were analyzed for intact mass on a C18 column using RP-HPLC connected to an ESI-mass spectrometer.
Representative UV chromatograms and corresponding intact mass for MYL-1501D and U.S.-Lantus are provided in CAA report 2. Scatter plot representing the distribution of intact mass values is shown in Figure 112 below.

Figure 112: Scatter plot distribution for Intact Mass of MYL-1501D, US-approved Lantus® and EU-approved Lantus®

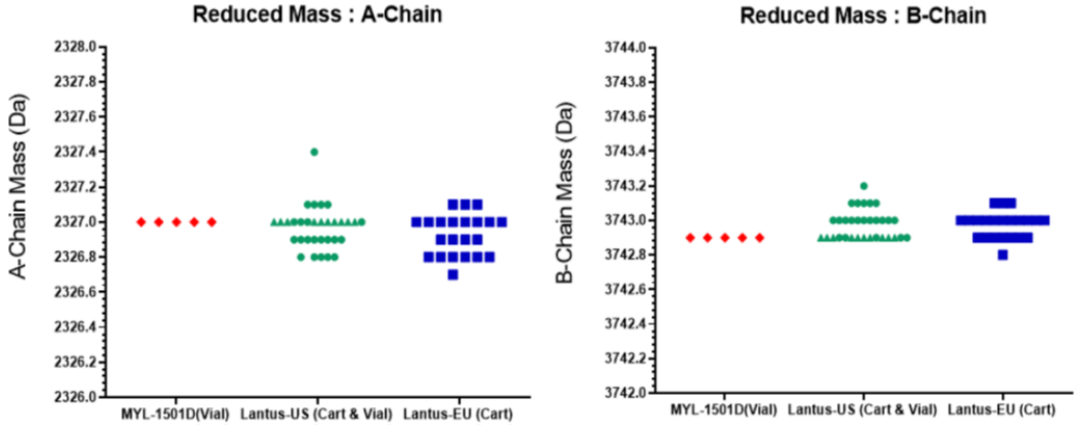


Assessor's Comment: *The representative intact mass UV chromatograms of MYL-1501D vial lots are similar to that of U.S.-licensed Lantus. The observed intact mass for MYL-1501D vial presentation (mean: 6063.9) and U.S.-licensed Lantus (mean: 6063.8) are highly similar to the expected theoretical mass ([M+H] ± 1 Da) of 6063.9 Da. These results support a demonstration of highly similar primary sequence between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

4.1b Reduced Mass analysis by RP-HPLC-ESI Mass Spectrometry

Reduced mass analysis with DTT not only confirms the characteristics of the two chains (Chain A and Chain B) but also confirms the identity of each individual chain at the level of the primary structure.
5 lots of MYL-1501D in vial (6-month-old at analysis) were compared to 32 lots of U.S.-licensed Lantus (10 in vial and 22 in cartridge, age from 16 to 33 month). Representative UV chromatograms of Chain-A and Chain-B are provided in CAA report 2 but not shown here. Scatter plots representing the distribution of mass values are provided in Figure 114 below.

Figure 114: Scatter plot distribution of Chain-A and Chain-B Mass for MYL-1501D, US-approved Lantus and EU-approved Lantus



Assessor's Comment: *The representative UV chromatograms of Chain A and Chain B for MYL-1501D vial lots are similar to that of U.S.-licensed Lantus. The observed mass of Chain A and Chain B for MYL-1501D vial presentation (mean: 2327.0 for A and 3742.9 for B) and U.S.-licensed Lantus (mean: 2327.0 for A and 3743.0 for B) are highly similar to the expected theoretical mass ([M+H] ± 1 Da) of 2327.6 Da for Chain A and 3743.3 Da for Chain B. These results also support a demonstration of highly similar primary sequence between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

4.1c Disulfide Linkage by Non-Reduced Peptide Mass Fingerprinting Analysis

For insulin glargine after enzyme cleavage, 4 glutamic acid residues (at positions A4, A17, B13 and B21) gives rise to 4 peptide fragments which could be analyzed by the LC-MS technique to generate mass fingerprint (PMF). Under non-reducing condition the disulfide bonds are still intact and hence PMF gives rise to A-B chain connected peptide providing the confirmation of disulfide linkages. The expected theoretical fragments on Glu C digestion of insulin glargine under non-reducing conditions along with their respective masses are tabulated in Table 70 below.

Table 70: List of Disulphide linked Peptide Fragments and Their Masses Monitored by Non-Reduced Glu-C Peptide Mass Fingerprinting

Fragment number	Fragment No. / Location	Amino acid Sequence	Theoretical mass $(M+H)^+ \pm 1Da$
4	A (1-4)	GIVE	417.2
3	B (22-32)	RGFFYTPKTRR	1428.8
2	A (18-21) & B (14-21)	(NYCG) & (ALYLVCGE)	1320.49
1	A(5-17) & B (1-13)	(QCCTSICSLYQLE) & (FVNQHLCGSHLVE)	2969.36

5 lots of MYL-1501D in vial (6-month-old at analysis) and 32 lots of U.S.-licensed Lantus (10 in vial and 22 in cartridge, age from 16 to 33 month) were analyzed by PMF method under non-reduced condition. The non-reduced PMF data for U.S.-Lantus and MYL-1501D are provided in Table 121 and 123 in CAA report 2 and are summarized in the table below (assessor generated). Representative overlaid UV-chromatograms are also provided but not shown here.

Peptide mass measured with non-reducing PMF	U.S.-Lantus (vial + cartridge) Min – Max range	MYL-1501D (vial) Min – Max range
Fragment 4 (Da)	417.1 (mean: 417.1)	417.1 (mean: 417.1)
Fragment 3 (Da)	1428.7~1429.6 (mean: 1429.1)	1429.2~1429.7 (mean: 1429.4)
Fragment 2 (Da)	1320.5~1320.7 (mean: 1320.5)	1320.6 (mean: 1320.6)
Fragment 1 (Da)	2969.1~2970.6 (mean: 2969.7)	2970.1~2970.3 (mean: 2970.2)

Assessor's Comment: *The representative UV chromatograms of 4 fragments for MYL-1501D vial lots are similar to that of U.S.-licensed Lantus. The measured peptide mass values for MYL-1501D vials and U.S.-Lantus lots are all highly similar to the expected theoretical mass ([M+H] ± 1 Da) for fragment ½/3/4 as shown in Table 70 and the assessor generated table above, supporting a demonstration of similar primary sequence and disulfide linkages between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

4.1d Reducing Peptide Mass Fingerprinting Analysis

The difference between peptide mass fingerprinting (PMF) under reduced condition and non-reduced condition is that DTT is used to disrupt the disulfide bond under reduced condition. In the reducing PMF analysis of insulin glargine, the following six peptide fragments are expected (shown in Table 74 below) after digestion with Glu-C.

Table 74: Expected theoretical fragments for Glu C digestion of Insulin Glargine under reduced conditions along with their respective masses

Fragment number	Fragment No. / Location	Amino Acid Sequence	Theoretical mass $(M+H)^+$ ±1Da
1	A(5-17)	QCCTSICSLYQLE	1490.6
2	B (14-21)	ALYLVCGE	867.4
3	B (1-13)	FVNQHLCGSHLVE	1482.7
4	B (22-32)	RGFFYTPKTRR	1428.8
5	A (1-4)	GIVE	417.2
6	A (18-21)	NYCG	456.1

5 lots of MYL-1501D in vial (6-month-old at analysis) and 32 lots of U.S.-licensed Lantus (10 in vial and 22 in cartridge, age from 16 to 33 month) were subjected to PMF analysis under reducing condition. The reducing PMF data are provided in Table 125 and 127 in CAA report 2 and are summarized in the table below (assessor generated). Representative overlaid UV-chromatograms are also provided but not shown here.

Peptide mass measured with non-reducing PMF	U.S.-Lantus (vial + cartridge) Min – Max range	MYL-1501D (vial) Min – Max range
Fragment 6 (Da)	456.0~456.1 (mean: 456.0)	456.1 (mean: 456.1)
Fragment 5 (Da)	417.1 (mean: 417.1)	417.1 (mean: 417.1)
Fragment 4 (Da)	1428.7~1429.6 (mean: 1429.0)	1428.7~1429.5 (mean: 1429.2)
Fragment 3 (Da)	1482.7~1482.9 (mean: 1482.7)	1482.8~1482.9 (mean: 1482.8)
Fragment 2 (Da)	867.3~867.4 (mean: 867.3)	867.4 (mean: 867.4)
Fragment 1 (Da)	1490.5~1490.7 (mean: 1490.6)	1490.7 (mean: 1490.7)

Mylan stated that the amino acid sequence of each peptide was confirmed by tandem mass spectrometry (MS-MS). The peptide sequence coverage was 100% for Chain-A and Chain-B and indicates an identical primary sequence of MYL-1501D vials and U.S.-Lantus. These results are not provided in CAA report 2.

Assessor's Comment: *Representative UV chromatograms of 6 fragments for MYL-1501D vial lots are similar to that of U.S.-licensed Lantus. The measured peptide mass values for MYL-1501D vials and U.S.-Lantus lots are highly similar to the expected theoretical mass ([M+H] ± 1 Da) for fragment ½/3/4/5/6 as shown in Table 74 and the assessor generated table above. These data, together with the data obtained from non-reduced PMF analysis in section 4.1c above, support a demonstration of similar primary sequence and disulfide linkages between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*
In order to pinpoint the position of disulfide bonds, NMR studies were carried out on representative lot of U.S.-Lantus and MYL-1501D. Refer to section 4.2c below about 2D-NMR for more details.

3.2.R.4.5.4.2 Secondary and Tertiary Structure Confirmation

Test methods used for assessing secondary and tertiary structure similarity are shown in Table 78 below.

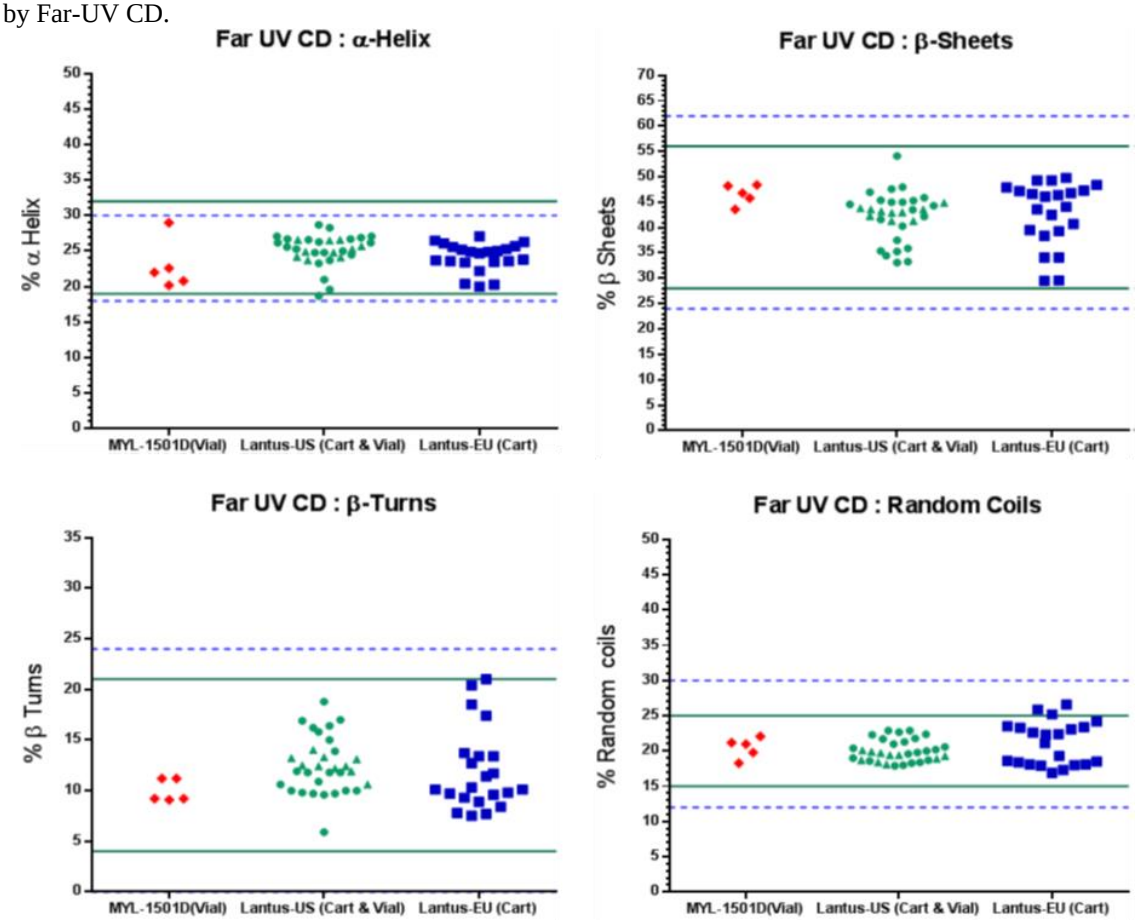
Table 78: Test Methods used for Higher order Structure Similarity Assessment

Analytical Test method	Description
Secondary Structure	Far-UV-CD Spectra
	Fourier Transform Infrared Spectroscopy
Higher Order Structure	Near-UV-CD Spectra
	Intrinsic Fluorescence
	Extrinsic Fluorescence
	Nuclear Magnetic Resonance (2D-NMR)
Thermal stability	Differential Scanning Calorimetry
Crystal structure	X-Ray Crystallography

4.2a Far UV CD Spectroscopic Analysis

CD spectroscopy in the "far-UV" spectral region (190-260 nm) can provide information about the secondary structure of a protein. 5 lots of MYL-1501D in vial (6-month-old at analysis) were compared to 32 lots of U.S.-licensed Lantus (10 in vial and 22 in cartridge, age from 16 to 33 month). Representative overlaid far-UV CD profiles of both products are provided in CAA report 2 but not shown here. The far-UV CD spectra were then deconvoluted by Yang's reference fit to estimate the secondary structural components such as α-helix, β-sheets, β-turns and random coil. Data distribution of the secondary structures are shown in scatter plots in Figure 118 below.

Figure 118: Scatter plot distribution for secondary structure of MYL-1501D, US-approved Lantus and EU-approved Lantus assessed by Far-UV CD.

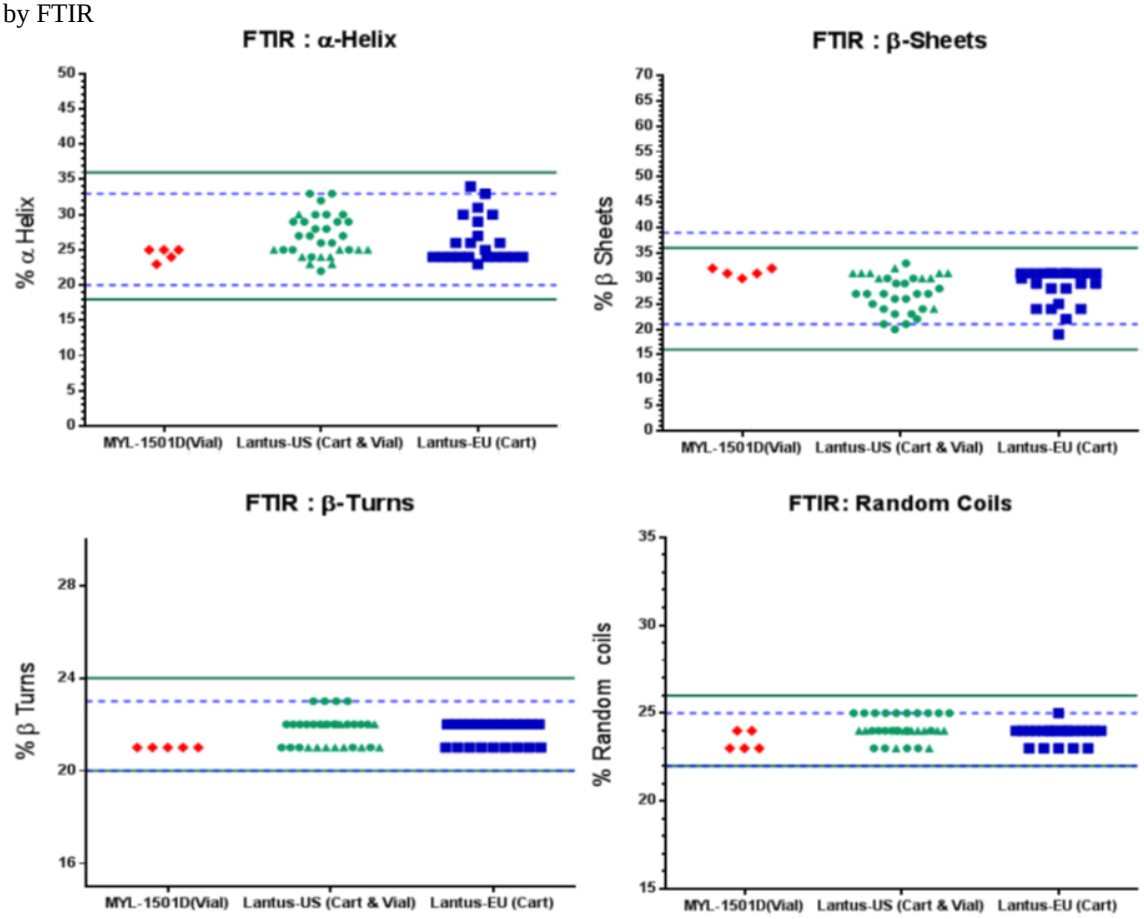


Assessor's Comment: *The representative Far-UV CD spectra for MYL-1501D vial lots are similar to that of U.S.-licensed Lantus. Estimations of secondary structural contents (α-helix, β-sheets, β-turns and random coil) for MYL-1501D vial lots are 100% within the quality range established for U.S.-Lantus, supporting a demonstration of highly similar secondary structure between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

4.2b Fourier Transform Infrared Spectroscopy (FTIR)

FTIR is used as an orthogonal tool to provide information about the secondary structure composition of proteins. 5 lots of MYL-1501D in vial (8-month-old at analysis) were compared to 32 lots of U.S.-licensed Lantus (10 in vial and 22 in cartridge, age from 16 to 34 month). Representative overlaid FTIR spectra are provided in CAA report 2 but not shown here. Data distribution for the secondary structures (α-helix, β-sheets, β-turns and random coil) are represented as scatter plots in Figure 120 below.

Figure 120: Scatter plot distribution for Secondary structures for MYL-1501D, US-approved Lantus and EU-approved Lantus assessed by FTIR



Assessor's Comment: *The representative FTIR spectra for MYL-1501D vial lots are similar to that of U.S.-licensed Lantus cartridge and vial lots. The secondary structure (α-helix, β-sheets, β-turns and random coil) estimations for all MYL-1501D vial lots are 100% within the quality range established for U.S.-Lantus, supporting a demonstration of highly similar secondary structure between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*
Overall, the assessment of secondary structure components by Far UV spectroscopy (section 4.2a above) and FTIR supports a demonstration of highly similar secondary structure between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.

4.2c Disulfide Linkage Confirmation by Solution-State 2D NMR Spectroscopy

In Insulin Glargine, Chain A and Chain B are crosslinked by two disulfide bridges (A20–B19 and A7–B7). A third intra-chain disulfide linkage exists in the Chain A (A6–A11). As shown in the following Figure 121 to Figure 123, the presence and position of disulfide linkages in MYL-1501D vial (lot BS BS16002122), U.S.-Lantus vial (lot 5F193A) and cartridge (lot 4F1179A) are confirmed by solution-state 2D NMR spectroscopy studies.

Figure 121: NMR spectra: a) 2D [^{1}H, ^{1}H] TOCSY and b) 2D [^{1}H, ^{1}H] NOESY of MYL-1501D (Vial; BS16002122)

The vertical dotted lines indicate the spectral assignments for the Cysteines at positions A6, A7, A11, A20, B7 and B19. The horizontal dotted lines show one of the NOE connectivity's arising due to the disulphide linkage indicated as hyphenated residue numbers near the lines

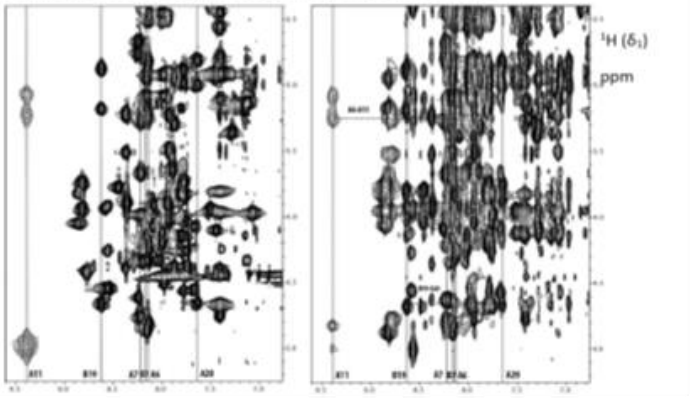


Figure 122: NMR spectra: a) 2D [^{1}H, ^{1}H] TOCSY and b) 2D [^{1}H, ^{1}H] NOESY of US-approved Lantus® (Vial; 5F193A)

The vertical dotted lines indicate the spectral assignments for the Cysteines at positions A6, A7, A11, A20, B7 and B19. The horizontal dotted lines show one of the NOE connectivity's arising due to the disulphide linkage indicated as hyphenated residue numbers near the lines

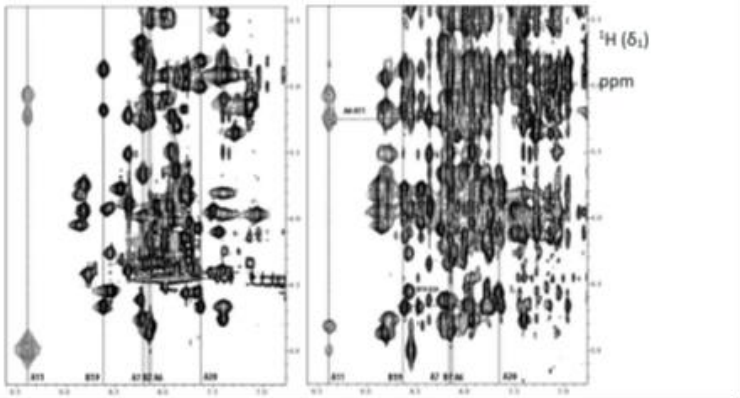
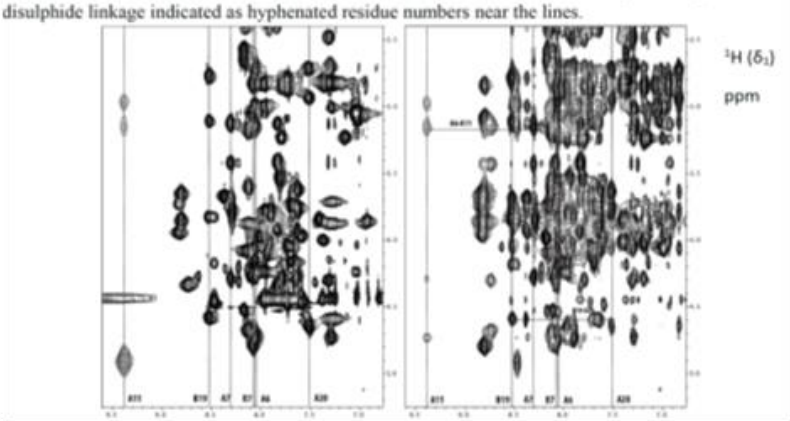


Figure 123: NMR spectra: a) 2D [^{1}H, ^{1}H] TOCSY and b) 2D [^{1}H, ^{1}H] NOESY of US-approved Lantus® (Cartridge; 4F1179A)

The vertical dotted lines indicate the spectral assignments for the Cysteines at positions A6, A7, A11, A20, B7 and B19. The horizontal dotted lines show one of the NOE connectivity's arising due to the disulphide linkage indicated as hyphenated residue numbers near the lines.



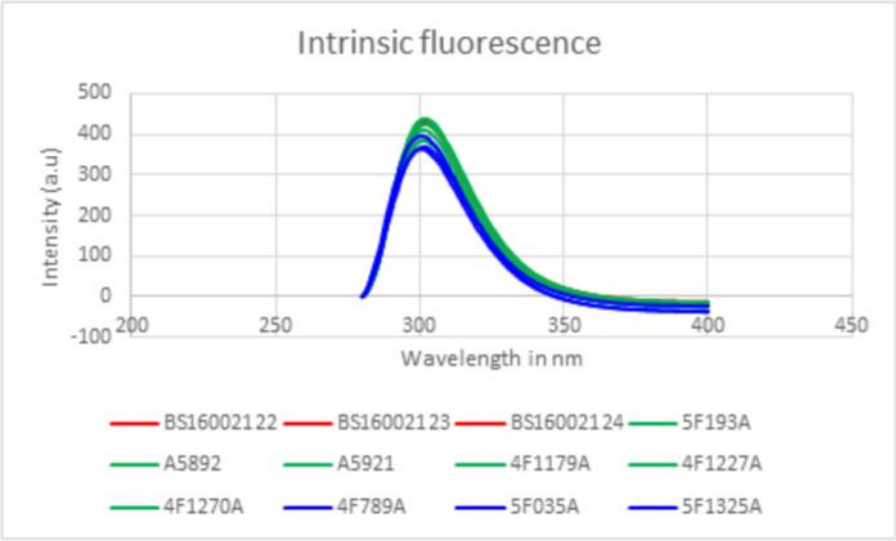
Assessor's Comment: *The 2D NMR spectra profiles of MYL-1501D vial lot is similar to that of U.S.-licensed Lantus cartridge and vial lots. The minor changes in chemical shifts, peak splitting and extra peaks observed here could be due to differences in NMR buffer conditions. Since the peaks and connectivities that correspond to the disulfide linkages do not show any major change in the chemical shifts, the 2D NMR data here support a demonstration of highly similar disulfide linkages between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

4.2d Intrinsic Fluorescence

Intrinsic fluorescence of a folded protein is used as a tool indicative of conformational state of a protein. The fluorescence emission depends on the type, number of aromatic residues and solvent exposure. The wavelength of the emitted light is an additional indicator of the fluorophore environment.

5 lots of MYL-1501D in vial (8-month-old at analysis) and 20 lots of U.S.-licensed Lantus (10 in vial and 10 in cartridge, age from 18 to 34 month) were analyzed to measure the peak maximum (λ_{max}). Representative overlaid intrinsic fluorescence spectra are provided in Figure 125 below.

Figure 125: Overlay of intrinsic fluorescence spectra of MYL-1501D, US-approved Lantus® and EU-approved Lantus®



The observed λ_{max} values for U.S.-Lantus and MYL-1501D are provided in Table 135 and 137 in CAA report 2 and are summarized in the table below (assessor generated).

Intrinsic fluorescence	U.S.-Lantus (vial + cartridge) Min – Max range	MYL-1501D (vial) Min – Max range
λ_{max} (nm)	300.93~302.03 (mean: 301.48) (QR: 299.86~303.10)	302.00 (mean: 302.00)

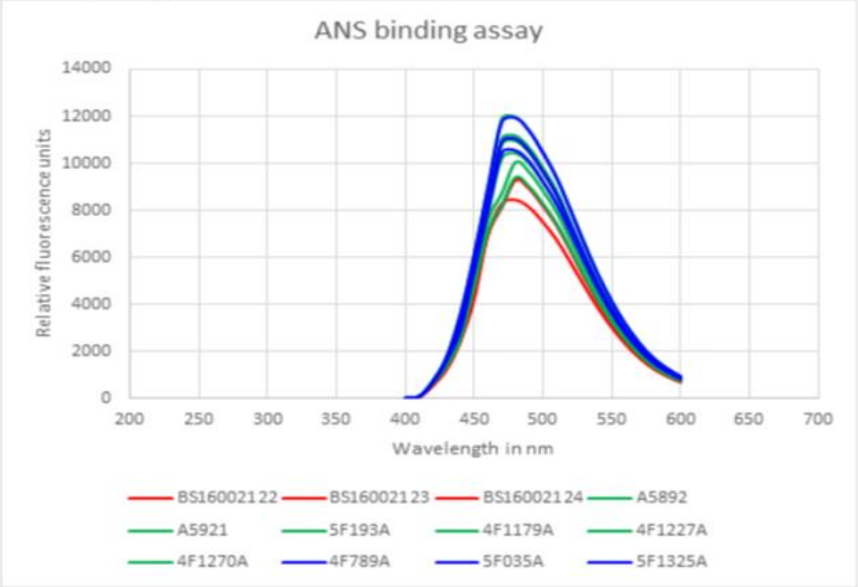
Assessor's Comment: *Of note, red lines (MYL-1501D vial lots) are behind green lines (U.S.-Lantus) and blue lines (E.U.-Lantus) but still can be seen if Figure 125 is enlarged. Representative intrinsic fluorescence spectra for MYL-1501D vial lots are similar to that of U.S.-licensed Lantus cartridge and vial lots. Additionally, the emitted peak maximum (λ_{max}) values for MYL-1501D lots are within the min-max range of U.S.-Lantus cartridge and vial lots. These data support a demonstration of highly similar conformation between MYL-1501D vial presentation and U.S.-Lantus vial and cartridge presentations.*

4.2e Extrinsic Fluorescence

Fluorescence spectroscopy with non-covalent, extrinsic fluorescent dyes (such as ANS) can be used to monitor protein conformational variants. ANS binds with high affinity to the hydrophobic surfaces of proteins. Upon binding the hydrophobic pockets in the protein molecule, the emission maximum of ANS undergoes a blue shift and fluorescence intensity increases significantly.

5 lots of MYL-1501D in vial (8-month-old at analysis) and 32 lots of U.S.-licensed Lantus (10 in vial and 22 in cartridge, age from 16 to 34 month) were analyzed using ANS binding assay. The fluorescence spectra for both products were acquired in formulation buffer, with the excitation at 388 nm and the emission scanned from 400 to 660 nm. Representative overlaid extrinsic fluorescence spectra are provided in Figure 126 below.

Figure 126: Representative Overlay of extrinsic fluorescence spectra using ANS binding assay of MYL-1501D, US-approved Lantus® and EU-approved Lantus®



The observed λ_{max} values for U.S.-Lantus and MYL-1501D are provided in Table 138 and 140 in CAA report 2 and are summarized in the table below (assessor generated).

Extrinsic fluorescence	U.S.-Lantus (vial + cartridge) Min – Max range	MYL-1501D (vial) Min – Max range
λ_{max} (nm)	473~483 (mean: 477.5) (QR: 469.1~485.9)	477~479 (mean: 478.2)

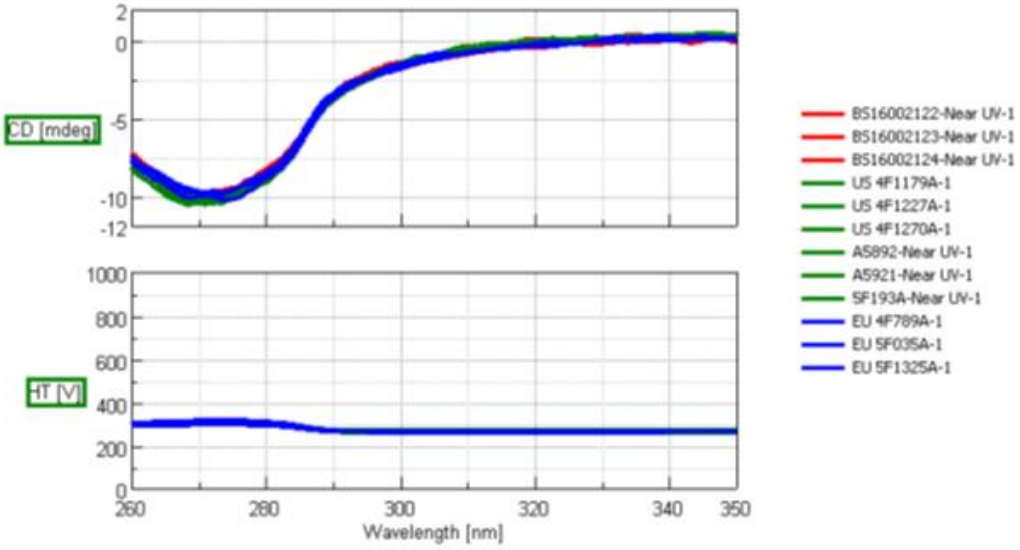
Assessor's Comment: *Representative extrinsic fluorescence spectra of MYL-1501D vial lots are similar to that of U.S.-licensed Lantus with minor differences in relative fluorescence units. Additionally, the emitted peak maximum (λ_{max}) values for MYL-1501D vial lots are within the quality range established for U.S.-Lantus. These data also support a demonstration of highly similar conformation between MYL-1501D vial presentation and U.S.-Lantus vial and cartridge presentations.*

4.2f Near UV CD Spectral Analysis

Wavelength scans, using a CD spectrometer, in the "near-UV" spectral region (260-360 nm) result in CD spectra that are characteristic of the tertiary structure of a protein. This near-UV CD spectral analysis can detect changes in the tertiary structure which includes environment around aromatic residues and disulfide linkages in the protein.

32 lots of U.S.-Lantus and 5 lots of MYL-1501D in vial were subjected to near-UV CD spectral analysis. Representative overlaid near UV-CD spectra of 3 MYL-1501D vial lots (age of 6-month) and 6 U.S.-licensed Lantus lots (age from 17 to 25 month) are provided in Figure 127 below. The near UV CD spectra profiles are compared visually for any conformational changes.

Figure 127: Representative Overlay of Near UV CD profile for tertiary structure of MYL-1501D US-approved Lantus® and EU-approved Lantus®

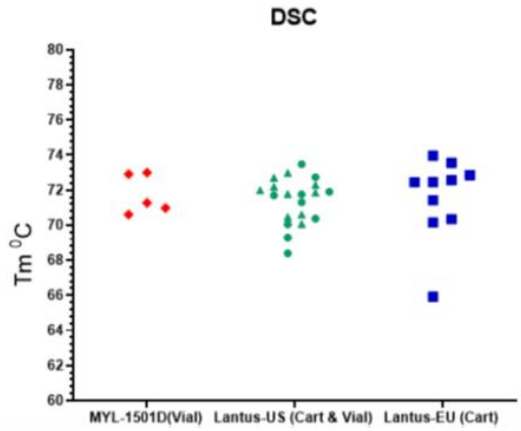


Assessor's Comment: *The age information for MYL-1501D and U.S.-Lantus lots used in near UV CD spectral analysis was missing in the original submission. In response to the Agency's IR (OBP IR #2) sent on 02/09/2021, Mylan provided age information at analysis for all lots displayed in Figure 127 above on 02/16/2021. Mylan's response is acceptable.*
The representative near-UV CD spectra (260 – 350 nm) of MYL-1501D and U.S.-Lantus lots all exhibit a similar pattern with a broad negative CD band around 270 nm and a shoulder at 300 – 310 nm, supporting a demonstration of highly similar tertiary structure between MYL-1501D vial presentation and U.S.-Lantus vial and cartridge presentations.

4.2g Thermal Stability by Differential Scanning Calorimetry (DSC)

DSC measures the heat capacity required to induce a change in the structure of a molecule. The temperature at which half of the protein molecules are unfolded is called the melting temperature (mid-point of DSC peak, Tm). This thermodynamic difference would indicate structural differences.
The thermal properties and structural-phase transitions of 5 MYL-1501D lots in vial (7-month-old at analysis) and 20 U.S.-Lantus lots (10 in vial and 10 in cartridge, age from 18 to 32 month) were evaluated by DSC. The conformational changes can be visualized by profile comparison in addition to the Tm values. Representative overlaid DSC profiles and observed Tm values for both products are provided in CAA report 2 but not shown here. Scatter plot representing the distribution of data is presented in Figure 132 below with the QR and/or minimum to maximum value for each group listed by the right side.

Figure 132: Scatter plot distribution for Tm Values Using DSC for MYL-1501D, US-approved Lantus® and EU-approved Lantus®



MYL-1501D Tm (°C):
Min-Max: 70.61~72.91
Mean: 71.75

U.S.-Lantus Tm (°C):
Min-Max: 68.40~73.48
Mean: 71.40
QR: 67.47~75.32

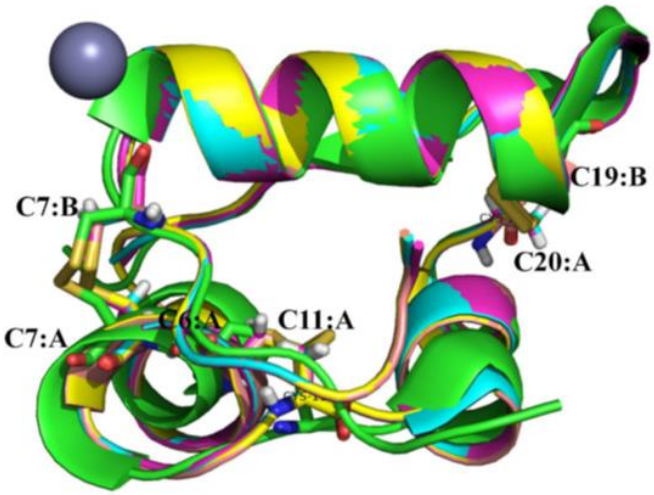
Assessor's Comment: *The representative DSC profiles for MYL-1501D vial lots are similar to that of U.S.-licensed Lantus. The measured values of melting temperature (Tm) for MYL-1501D lots are 100% within the quality range established for U.S.-Lantus. These data support a demonstration of highly similar thermal stability and conformation between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

4.2h X-Ray Crystallography

X-ray crystallography, an orthogonal method to near UV CD, can provide more details about the 3D structure of a protein. Insulin glargine samples extracted from U.S.-Lantus (cartridge lot 4F1179A and vial lot 5F193A) and MYL-1501D (vial lot BS16002122) were used for crystallization, X-ray diffraction experiments, structure determination and comparative structural analysis.

The structures were determined by molecular replacement using the human insulin polypeptide structure as the phasing model. The refined 3D structure of MYL-1501D (vial) and U.S.-licensed Lantus are compared to each other and to the previously determined 3D structures of insulin glargine and human insulin, are shown in Figure 133 and 134 in CAA report 2. For briefly, only Figure 134 is shown below with superposition of the structural models for MYL-1501D vial (lot BS16002122), U.S.-Lantus vial (lot 5F193A), insulin glargine, and human insulin.

Figure 134: Superposition of the structural models of MYL-1501D (Vial) (Salmon), US-approved Lantus® (Yellow) with the previously reported Insulin Glargine structures 4IYD (Cyan) and 4IYF (Purple) and human insulin 3W7Y (Green).



MYL-1501D vial (lot BS16002122) (Salmon)

U.S.-Lantus vial (lot 5F193A) (Yellow)

4IYD (Cyan): Insulin glargine crystal structure 1 in PDB database

4IYF (purple): Insulin glargine crystal structure 2 in PDB database

3W7Y (Green): 0.92A structure of human insulin at 100K in PDB database

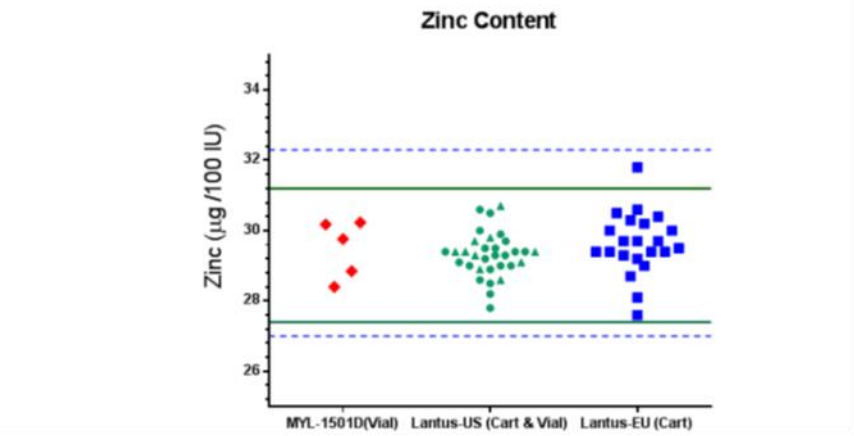
Assessor's Comment: *On 02/16/2021, Mylan provided response to the Agency's IR (OBP IR #2 sent on 02/09/2021) to update the missing legend information in the above Figure 134 in CAA report 2. The new Figure 2 in their IR response is the same as Figure 134 here except with updated legend which is shown on the right side of Figure 134 above. This IR response is acceptable.*
The 3D structures above show an overlay of the analyzed insulin glargine samples with the published structure of human insulin and insulin glargine. The overlay closely resembles in terms of polypeptide fold, oligomeric organization and thermal parameters. All the molecules superpose well with an overall RMSD of 0.146 Å. Overall, the X-ray structures of MYL-1501D vial and U.S.-Lantus vial lots are highly similar to each other and to the previously determined 3D structures of insulin glargine, supporting a demonstration of highly similar 3D structure between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.

Summary of Primary, Secondary and Higher Order Structure:
Results obtained from multiple orthogonal analytic methods to assess the amino acid sequence, disulfide linkages, secondary and tertiary structure demonstrate that MYL-1501D vial presentation is highly similar to U.S.-licensed Lantus vial and cartridge presentations with respect to primary, secondary and higher order structure.

3.2.R.4.5.5 Zinc Content by Atomic Absorption Spectrometry (AAS)

The Zinc content for 5 lots of MYL-1501D in vial (age at 7 month) and 32 U.S.-Lantus lots (10 in vial and 22 in cartridge, age from 15 to 33 month) were analyzed using Atomic Absorption Spectrometry (AAS). Scatter plot of Zinc content data is presented in Figure 135 below.

Figure 135: Scatter plot distribution of Zinc content in MYL-1501D, US-approved Lantus® and EU-approved Lantus®



Assessor's Comment: *The measured values of Zinc content for MYL-1501D vial lots are 100% within the quality range established for U.S.-Lantus, demonstrating a highly similar Zinc level between MYL-1501D vial presentation and U.S.-licensed Lantus vial and cartridge presentations.*

3.2.R.4.5.6 Comparative Forced Degradation Study for MYL-1501D (vial) and U.S.-Lantus (vial)

A comparative forced-degradation (FD) study was performed to establish the similarity of degradation profiles of MYL-1501D vial presentation to that of U.S-Lantus vial presentation. Protocols and results for this FD study can be found in eCTD Section 3.2.P.8 Stability (vial) in the application.

The details of MYL-1501D lots and U.S-Lantus lot used in this study are provided in the table below (assessor modified based on Table 3.2.P.8.1/10 in eCTD Section 3.2.P.8.1 Stability Summary and Conclusion).

Sample	Lot Number	Product Age at Start of FD Study	Expiry or Manufacturing Date	Used in Other CAA Studies
U.S.-Lantus vial	6F501A	10 months	Unknown	No
MYL-1501D vial (Process VI DS)	BS16002124	8 months	June 2016	Yes
MYL-1501D cartridge (Process VI DS)	BS15009375	10 months	March 2016	Yes

In this FD study, all samples were placed under identical degradation conditions to compare the product degradation rate, mechanisms and impurity profiles. These multiple degradation conditions, including elevated temperature, variable pH (acidic and alkaline), photo exposure, mechanical stress (agitation), and oxidation were implemented on all products. The testing conditions and protocols are detailed in Table 3.2.P.8.1/11 below. The analytical methods are the same as those presented in eCTD Section 3.2.P.5.2 Analytical Procedures (vial).

Table 3.2.P.8.1/11: Testing Protocol –Comparative Forced Degradation Study

Degradation Factor	Condition	Time-points	% HMWP by SE-HPLC	Related Compounds	Assay by RP-HPLC
pH stress	pH 2	0, 1, 3, 8 days	All	All	All
	pH 10	0, 1, 3 and 6 hours	All	All	All
Chemical Treatment	Oxidation	0, 1, 6 and 12 hours	All	All	All
Photo Treatment	Photo exposure	0, 0.6, 1.2 Million lux hours	All	All	All
Mechanical Stress	Agitation at 250 RPM at 25±3°C	0, 1, 3, 7,15 days	All	All	All
Temp. Stress	60°C	0, 1, 3, 7,15 days	All	All	All
	2-8°C (Control)	0, 1, 3, 7,15 days	All	All	All

Assessor's Comment: *All tested forced degradation conditions, testing frequency and duration are the same as those in the comparative forced degradation study for MYL-1501D cartridge presentation and U.S.-Lantus cartridge presentation.*

Results for this FD study under various stress conditions are presented in eCTD Section 3.2.P.8.3 Stability Data (vial) and are summarized in the table below (assessor generated). Only data obtained from the initial time-point and the end time-point of MYL-1501D vial/cartridge (all from Process VI DS) and U.S-Lantus vial are shown here.

Summary results of initial/end time point under various stress conditions for MYL-1501D and U.S.-Lantus

Forced degradation factors	Condition	Initial/ End time point	% HMWP by SE-HPLC			% Total impurities by RP-HPLC			% Any individual impurity by RP-HPLC			% Assay by RP-HPLC		
			MYL-VI (vial)	US-Lantus (vial)	MYL-VI (cart)	MYL-VI (vial)	US-Lantus (vial)	MYL-VI (cart)	MYL-VI (vial)	US-Lantus (vial)	MYL-VI (cart)	MYL-VI (vial)	US-Lantus (vial)	MYL-VI (cart)
Initial time point (control)		**Time 0**	**0.03**	**0.03**	**BQL**	**0.34**	**0.70**	**0.40**	**0.15**	**0.21**	**0.18**	**101.4**	**101.2**	**102.2**
Temperature stress	2-8°C (control)	15 days	0.04	0.04	0.03	0.39	0.80	0.40	0.16	0.22	0.18	101.3	101.2	101.8
	60°C	15 days	16.44	63.66	2.54	20.74	24.34	24.53	10.86	5.99	13.24	61.7	17.3	72.9
Photo stress	Photo exposure	1.2M lux hrs	16.62	27.74	16.0	6.67	14.62	5.02	1.25	1.59	1.23	77.9	61.1	83.0
Oxidative stress	3% H_2O_2	12 hours	1.71	1.02	1.70	11.01	7.25	11.25	6.60	3.85	6.37	73.9	74.6	73.9
pH stress	pH 2	8 days	0.05	0.05	0.03	1.27	1.77	1.64	0.44	0.51	0.55	98.2	97.5	99.3
	pH 10	6 hours	0.06	0.06	0.05	0.76	1.03	0.59	0.29	0.23	0.23	100.4	98.9	102.6
Mechanical stress	Agitation at 250rpm & 25°C	15 days	0.05	0.04	0.03	0.62	1.01	0.71	0.27	0.30	0.30	101.8	99.4	101.9

MYL-VI (vial): MYL-1501D vial manufactured with Process VI DS (lot #: BS16002124, 8-month old at FD study)
US-Lantus (vial): U.S.-licensed Lantus vial (lot #: 6F501A, 10-month old at FD study)
MYL-VI (cart): MYL-1501D cartridge manufactured with Process VI DS (lot #: BS15009375, 10-month old at FD study)

Assessor's Comment: *Mylan did not provide information about impurities species and levels in all FD studies in the original submission for the Agency to compare the degradation pathways between different products. An IR (OBP IR #2) was sent on 02/09/2021 regarding this issue. Mylan provided response on 02/19/2021 with tabulated results for each impurity species under all tested stress conditions in eCTD Section 1.11.1 Quality Information Amendment - Response to Information Request Dated February 9, 2021 - Comment 7a. Their IR response is acceptable. These results, together with the forced degradation data presented in eCTD Section 3.2.P.8.3 Stability Data (vial), are discussed in the following section a/b/c/d/e.*

a. Temperature Stress

Assessor's Comment: *All products under the control temperature condition of 2°C~8°C remained stable, showing no meaningful change during the whole testing period with very low levels of all individual impurity species.*

Under the stressed temperature condition of 60°C, increases in HMWP, total impurity, and any individual impurity were observed in both MYL-1501D lots and U.S.-Lantus lot and similar levels were seen during the whole testing period of 15 days, except the level of HMWP, which was significantly higher in U.S.-Lantus than that in MYL-1501D. This difference might suggest a slightly enhanced stability of MYL-1501D vial lots than U.S.-Lantus vial lots. When comparing individual impurity species and levels, the major degradation species seen in both MYL-1501D vial and US-Lantus vial lot are Des R & B3 deamidation, A15 deamidation, and Des TRR. While there are some small differences in levels of individual impurities, these differences are not considered significant. Overall, the data presented here do not preclude the demonstration that the degradation pathways are similar between MYL-1501D vial and U.S.-Lantus vial under 60°C.

Of note, the results showing here are inconsistent with the results obtained from the comparative forced degradation study under the same condition (60°C) with the cartridge presentation of MYL-1501D and U.S.-Lantus, which only show a slight increase in HMWP (up to 0.86%) and a moderate increase in total impurity (up to 13.80%) and in any individual impurity (up to 7.12%), compared to the degradation seen in the vial lots presented here. Additionally, the MYL-1501D cartridge lot evaluated in this study showed higher degradation than that seen in the comparative forced degradation study for MYL-1501D cartridge and U.S.-Lantus cartridge. Refer to section 3.2.R.4.3.6 "Comparative Forced Degradation Study for MYL-1501D (cartridge) and U.S.-Lantus (cartridge)" in this memo for more details. An IR (OBP IR #2) was sent on 02/09/2021 regarding this data inconsistency. Mylan provided response to this question on 02/16/2021 and their response is summarized as below.

Mylan described that these are two independent forced degradation studies performed at different times for the two presentations with different batches of different age.

The Applicant attributed the difference in degradation between cartridge and vial lots primarily to the additional head space and polysorbate 20 contained in the vial but not in the cartridge presentation. Polysorbate is reported to have dual effects on protein stability. While it prevents aggregation at lower temperature (2-8°C), at elevated temperatures it has reported to induce aggregation.

The differences in the rate of degradation between the MYL-1501D cartridge batches evaluated in the two studies is attributed to the difference in the age of the batches, as well as inconsistent degradation under extreme condition of 60°C.

Assessor's Comment: *Mylan's explanation is acceptable. The different rates of degradation seen in the two forced degradation studies in this BLA could be attributed to polysorbate 20 in the vial presentation, different age of cartridge lots used in the two studies, and the inconsistency of degradation under the extreme thermal stress condition of 60°C.*

b. Photo Exposure

Assessor's Comment: *With 1.2 million lux hours of photo exposure, MYL-1501D vial lot showed lower levels of HMWP, total impurity, and any individual impurity, as well as higher level of protein content by Assay than that of U.S.-Lantus vial lot. These results might indicate a slightly enhanced stability of the MYL-1501D DP compared to U.S.-Lantus under photo stress or may be attributed to the younger age (8 months) of MYL-1501D vial used in this study, when compared to U.S-Lantus vial (10 month). When comparing individual impurity species and levels, the major degradation species are Des R & B3 deamidation, citrate conjugate, with some other minor species like glargine conformer species. There are minor differences in the level of each individual impurity species, but these individual differences are not significant, indicating the degradation pathways are similar between MYL-1501D vial and U.S.-Lantus vial. Overall, the photo stress study results do not preclude a demonstration that the degradation pathways of MYL-1501D vial are similar to US-Lantus vial under photo exposure conditions.*

c. Oxidative Stress

Assessor's Comment: *MYL-1501D and US-Lantus vial lots show degradation under oxidative stress in terms of changes in levels of HMWP, total impurities, any individual impurity and protein content by Assay. The major degradation species is glargine + 120 Da (RRT 0.85– 0.89, or RRT 0.90- 0.94) in all products. The study indicates that MYL-1501D and US-Lantus vial have a similar degradation pathway and profile under oxidative stress. Minor differences are observed in terms of rates of degradation under oxidative stress between MYL-1501D and US-Lantus vial. However, oxidative stress is not expected to be a stress that insulin glargine product is typically subjected to under conditions of use; therefore, the observed differences under oxidative stress do not preclude a demonstration of highly similar between MYL-1501D and U.S.-Lantus vial presentations.*

d. pH Stress

Assessor's Comment: *All tested samples showed low level of degradation with very low levels of all individual impurity species under the testing conditions at pH 2 for up to 8 days or at pH 10 for up to 6 hours, supporting a demonstration of highly similar stability under tested pH stress conditions between MYL-1501D and U.S.-Lantus vial presentation.*

e. Mechanical Stress

Assessor's Comment: *On 02/16/2021, in a response to our IR (OBP IR #2), Mylan clarified that the mechanical stress condition is agitation at 250 rpm at 25°C ± 3°C (not 230 rpm as indicated before) and updated Table 3.2.P.8.3/30 in eCTD Section 3.2.P.3 Stability Data (vial).*
All tested samples showed low level of degradation under the testing condition for up to 15 days with very low levels of all individual impurity species, supporting a demonstration of highly similar stability under tested mechanical stress condition between MYL-1501D and U.S.-Lantus vial presentation.

Summary of Comparative Forced Degradation Study:
As discussed above, results from multiple methods to assess impurities (HMWP, total impurities, and any individual impurity) and insulin glargine Assay under various forced degradation conditions do not preclude a demonstration of highly similar between MYL-1501D vial presentation and U.S-Lantus vial presentation. The stability of MYL-1501D vial presentation and U.S.-Lantus vial presentation are also similar under accelerated condition (25°C ± 2°C/60% ± 5% RH), refer to the aforementioned NDA-210605 Review 1 (dated 4/5/2018) and NDA-210605 Review 2 (dated 8/22/2019) for detailed assessment about comparative accelerated stability study.

Summary of Overall Similarity between MYL-1501D (vial) and U.S.-licensed Lantus (vial + cartridge):

Overall, results from multiple orthogonal analytic studies indicate that MYL-1501D vial presentation is highly similar to the vial and cartridge presentation of U.S.-licensed Lantus with respect to functional and biological activities, purity and impurities, primary, secondary, and higher order structure.

Overall Conclusion for Comparative Analytical Assessment:

In summary, the analytical comparisons support the demonstration that MYL-1501D cartridge (pen) presentation is highly similar to U.S.-licensed Lantus cartridge (pen) presentation, and MYL-1501D vial presentation is highly similar to both the vial and the cartridge presentation of U.S.-licensed Lantus.

5.3.1.4 Immunogenicity Assays

The information provided in this BLA-761201 for MYL-1501D immunogenicity assays and immunogenicity data is identical to that in the NDA-/deemed BLA-210605. This information includes:

- Validation of Radio-Immuno-Precipitation Assay (RIPA) for detection of anti-drug antibodies (ADA): This RIPA method has been validated for minimum required dilution, cut points, sensitivity, selectivity, specificity, cross reactivity, interference (hemoglobin and lipids), stability and drug interference.

- Validation of an ECL method for detection of anti-*Pichia* Host Cell Protein (HCP) antibodies: This ECL method has been validated for positive controls, minimum required dilution, selectivity (matrix effect), screening or confirmatory cut point, precision, specificity, robustness, stability, cross reactivity, sensitivity and titer.

- Analysis of clinical immunogenicity results: These immunogenicity data were obtained from clinical Study MYL-GAI-3001 (conducted in a Type 1 diabetes population), Study MYL-GAI-3002 (conducted in a Type 2 diabetes population), Study MYL-GAI-3004 (conducted in a Type 1 diabetes population), and MYL-GAI-3003 (conducted in a Type 1 diabetes population).

Assessor's Comment: *Clinical studies evaluating immunogenicity (as described above) are the same as those previously submitted to NDA/deemed BLA 210605. There is no new information provided in this BLA-761201 regarding MYL-1501D immunogenicity assays and immunogenicity data, compared to that already presented in the NDA-/deemed BLA-210605. All immunogenicity information presented in the NDA-/deemed BLA-210605 has been previously assessed by OBP assessor. The Assessor concurs with the previous OBP assessor that both the RIPA method and ECL method have been appropriately validated for the detection of ADA and anti-Pichia HCP antibodies, respectively. Refer to these two immunogenicity review memos NDA-210605 ImmReview4 and NDA-210605 ImmReview9 documented by the previous OBP assessor for detailed assessment about MYL-1501D immunogenicity assays and immunogenicity analysis.*

Qiong Fu

Digitally signed by Qiong Fu
Date: 3/22/2021 03:00:03PM
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Anjali Shukla

Digitally signed by Anjali Shukla
Date: 3/22/2021 03:04:15PM
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OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	12/8/2020		
To:	Anika Lalmansingh, Senior Regulatory Health Project Manager		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	RBPMB2
From	David Wolloscheck, PhD, Chemist OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Rumi Young, Assistant Director OPEQ/OHT3/DHT3C		
Subject	BLA 761201 , Semglee (MYL-1501D) ICC2000698 00026066		
Recommendation	**Filing Recommendation Date: 8/24/2020** ☐ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☑ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 12/11/2020 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☑ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 2/11/2021 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761201
Sponsor	Mylan Pharmaceuticals Inc.
Drug/Biologic	Semglee (MYL-1501D)
Indications for Use	To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus
Device Constituent	Pen-Injector
Related Files	NDA 210605 (March 19, 2018), PIND 140431 (October 11, 2018- July 3, 2020)

Review Team		
Lead Device Reviewer	*David Wolloscheck, PhD, Chemist*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
N/A		

Important Dates	
Discipline-Specific Review Memos Due	03/22/2021
Final Lead Device Review Memo Due	05/25/2021
Interim Due Dates	**Meeting/Due Date**
Filing	09/07/2020
74-Day Letter	10/05/2020
Mid-Cycle	12/08/2020
Primary Review	03/22/2021

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			3.2.P.2, 3.2.P.7
Labeling	X			1.1.4
Design Controls	X			3.2.P.5.1 (specification for activation force and injection time not provided. Extended needle length not provided in original application.). **Update:** Additional information was provided as responses to information requests. Information is acceptable.
Risk Analysis			X	Risk analysis for device was provided in original biosimilar application.
Design Verification			X	Verfication testing was provided in original biosimilar application.
Consultant Discipline Reviews			X	None required
Clinical Validation	X			5.3.5.1, device used in clinical study
Human Factors Validation			X	Deferred to DMEPA
Facilities & Quality Systems	X			3.2.P.3, no mention of 820 requirements just cGMP. **Update:** Additional information was provided as responses to information requests. Information is acceptable.

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

TABLE OF CONTENTS

3. PURPOSE/BACKGROUND

3.1. Scope

Mylan Pharmaceuticals Inc. is requesting approval of Semglee (MYL-1501D). The device constituent of the combination product is a Pen-Injector.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

Requesting a review of the device. A separate consult will be submitted for the facility.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Mylan submitted this BLA in order to seek interchangeability to the US-licensed Lantus (NDA deemed BLA 021081). In Seq. 001 Section 2.2, the Applicant provided a general overview of the application and stated that the majority of the device development data is cross-referenced to BLA 210605 which is the identical product that is subject of this submission. BLA 210605 was reviewed by CDRH under ICCR2017-01604 / ICC1700398 by Dr. Rong Guo. On March 19, 2018 (See attachment A), Dr. Guo recommended that the device constituent parts of this submission are approvable for the intended use. Since the majority of the data provided with this submission is references/leveraged from the approved BLA 210605, the device development data will not be reviewed again under this submission. The scope of this review memo is the additional information provided by Mylan to support a finding of interchangeability to US-licensed Lantus and information regarding the facilities for device considerations (e.g., design controls, CAPA, etc.) used to manufacture the product.

This review will not cover the following review areas:

Acceptability of biosimilar (established in original review of ICC1700398 on March 19, 2018) Human Factors evaluation

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

NDA 210605 (March 19, 2018), PIND 140431 (October 11, 2018- July 3, 2020)

3.3. Indications for Use

Combination Product	Indications for Use
Semglee (MYL-1501D)	To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus
Pen-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0001	Module 2 and 3

4. DEVICE DESCRIPTION

4.1. Device Description

(b) (4)

The MYL-1501D PFP is designed to deliver a maximum of 80 U per injection and the total deliverable content of the MYL-1501D cartridge is 300 U, consistent with the reference product. Prior to injection, the pen cap is removed and a new pen needle is attached to the front end of the cartridge holder. In its initial position, the DSK (located at the rear end of the device) is flush with the body and "0" is displayed in the dose. The dose is pre-selected by rotating the DSK and the number of insulin glargine units (U) is displayed in the dose window. The dialling mechanism allows dosage increments of 1 U. The injection is then performed by pushing the dose button. As the user pushes the dose button the DSK rotates, clicking down through each unit administered. Once the injection is complete, the dose button will have returned to its original position and "0" is displayed in the dose window. The display of "0" assures the user that the injection is complete.

(b) (4)

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(b) (4)

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The sponsor has provided all of the necessary information in the device description for filling.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

CDRH performed Filing Review	☑
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist				
Description		**Present**		
		Yes	**No**	**N/A**
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor			X (specification for activation force and injection time not provided. Extended needle length not provided in original application.)	
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X		
	Reliability			X
	Biocompatibility	X		
	Sterility	X		
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors	X		
	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation	X		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)		X	
	CAPA Procedure		X	
	Control Strategy provided for EPRs		X	

Reviewer Comment

The application is complete for filing. The majority of the provided documents are cross-referenced from the previously approved BLA 210605.

5.2. Facilities Information

Firm Name:	Biocon Sdn. Bhd.
Address:	No.1, Jalan Bioteknologi 1, Kawasan Perindustrian SiLC, 79200 Iskandar Puteri, Johor, Malaysia
FEI:	3011248248
Responsibilities:	The activities related to manufacturing, filling, primary packaging, quality control testing [Chemical/Physical, Microbiological (sterility and non-sterility) testing] of the 3 mL cartridges and pre-filled pen assembly (secondary packaging), quality control testing [Chemical/Physical] of the pre-filled pens and secondary packaging in\ carton box.

Inspectional History

An analysis of the firm's inspection history over the past 2 years:

☑ Inspection was conducted 2/10/2020 to 2/21/2020. The inspection covered both drug CGMPs and medical device QS and was classified VAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:

☐ A pre-approval inspection is required because:

The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,

A recent medical device inspection of the firm has not been performed.

☑ An inspection is not required because A recent medical device inspection of the firm was acceptable.

Firm Name:	Biocon Biologics India Limited
Address:	Special Economic Zone Plot No: 2, 3, 4 & 5, Phase – IV Bommasandra-Jigani Link Road Bommasandra Post Bengaluru Karnataka, 560099 India
FEI:	3003981475

Responsibilities:	Pre-filled Pen Assembly (Secondary Packaging), Quality Control Testing (Chemical/Physical) and Secondary Packaging in Carton Box. Analytical similarity assessment: Compilation (data from outsourced tests), analysis and assessment of analytical similarity.

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted 8/22/2019 to 8/30/2019. The inspection covered drug CGMP and was classified VAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☐ A pre-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm has not been performed.

☑ An inspection is not required because This facility was removed from the application. Please see IR#3 for details.

5.3. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☑ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☑ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☑ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☑ Yes ☐ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☑ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☑ Yes ☐ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☑ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☑ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment
No new cGMP information was submitted. The cross-referenced GMP information previously provided under BLA 210605 was previously reviewed by CDRH and found acceptable. Please refer to Attachment B for the CDRH compliance memo of BLA 210605.

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION
Acceptable for Filing: ☑ Yes ☐ No (Convert to a RTF Memo) ☐ N/A
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☑ No Inspection ☐ N/A **Site(s) needing inspection: N/A**
Reviewer Comments The Biocon India facility has not received a recent medical device inspection and a PAI is recommended. The Malaysia manufacturing site received a QSIT level 2 inspection on June 24th, 2019. The inspection was indicated as OAI, in part, due to an insufficient CAPA system, a non-validated pen-injector assembly process, and environmental monitoring concerns. A follow-up inspection was carried out on February 10, 2020 and was classified as VAI. Based on the inspection report, observations related on injector assembly and CAPA were resolved. Hence, another PAI for this submission is not necessary. UPDATE 11/11/2020: The Sponsor stated that the India facility will be removed from the application. Hence, a PAI of this facility is no longer needed. The memo was updated to reflect this. Please see IR#3 for details.
Refuse to File Deficiencies: ☐ Yes ☑ No ☐ N/A **74-Day Letter Deficiencies:** ☑ Yes ☐ No ☐ N/A

	Date Sent: **8/21/2020**	**Date/Sequence Received:** **11/2/2020**
Information Request #1	You have provided a comparative analysis of the Semglee prefilled pen and Lantus solostar. However, you have not addressed the comparison of performance. Provide a comparison of the dose accuracy, injection time, and activation force. Provide a comparison table that compares the performance of both device that you wish to interchangeable.	
Sponsor Response	Reviewed in Risk Analysis Section	

	Date Sent: **8/21/2020**	**Date/Sequence Received:** **11/2/2020**

Information Request #2	You have indicated that you are implementing a drug based CGMP streamlined approach. Please provide the following information related to the medical device Quality System for the device: a. Provide a summary of your management structure with executive responsibility for those who manage, perform, and assess work affecting quality of the product and related controls to ensure that your quality policies are appropriately implemented and followed, and the product appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements met, per 21 CFR 820.20. b. Provide a summary of your design control system under 21 CFR 820.30 for the device constituent part and combination product. The design control information should include initial design, planning and development, design input, design output, design review, design transfer, design verification, design validation that meets the proposed intended use of the final combination product, design changes, and design history file. For changes made to the device constituent part of the combination product, the impact of the design changes on the overall combination product performance should be considered and documented. All the design control activities must be documented in the Design History File (DHF) and subjected for design reviews. In addition, identify the facility containing the DHF so that the Agency inspection planning activities are appropriately determined. c. Provide a summary of your purchasing control system per 21 CFR 820.50 to demonstrate controls and documentation for components, products, or services (e.g., sterilization) received at your facility for use in the manufacture of the combination product. The summary should include your evaluation process of your suppliers that meet the manufacturing acceptance criteria of the combination product specifications. Notification of changes made by the suppliers should be considered in your Purchasing/Supplier agreement as changes to incoming specification that can impact the safety and effectiveness of the final combination product. d. Provide a summary of your corrective and preventive actions (CAPA) system per 21 CFR 820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of nonconformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions must be documented under your CAPA System as described in 21 CFR 820.100.
Sponsor Response	Reviewed in Quality Systems/Manufacturing Controls Section

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	X		
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments

The labeling contains all required elements (e.g., RX statement, indications for use, name of the drug, etc.) and the instructions for use are appropriate. Please note that a human factors evaluation and a detailed review of the step by step instructions for use of the devices is deferred to DMEPA.

6.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The provided labeling is appropriate for the device type. A usability review of the instructions and device design is deferred to DMEPA.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Reviewer Comments

The Sponsor indicated in Section 2.2 of the submission that no new documents regarding the design control process were submitted by the Sponsor. All documents that are included in this submission are cross-referenced from BLA 210605. A review of this information was conducted by Dr. Rong Guo. Please see her memo in Appendix B.

8. RISK ANALYSIS

8.1. Risk Management Plan

Reviewer Comments

No new risk management documents were submitted with this application. Please see Dr. Rong Guo's review of the cross-referenced data in Appendix B.

8.2. Device Interchangeability

Mylan has submitted this BLA submission to claim interchangeability between the US-licensed Lantus and the EU-approved Lantus. In order to support the interchangeability, a comparative analysis between Semglee and the comparator product was submitted in Sequence 0001 Section 3.2.P.2. The provided analysis included a physical comparison of the subject and the comparator device constituent and summarizes a human factors study that was done with the product. Analysis and interpretation of the conducted human factors study is deferred to DMEPA.

It is to note that the Sponsor has not provided a comparison of the two devices in terms of device performance. While both devices comply with ISO 11608-1 regarding dose accuracy, it is unclear how other performance attributes compare. The most critical performance attribute that should be assessed by the Sponsor is the injection force (i.e., the force required to operate the device). The injection force could pose a significant difference between the two devices in terms of usability. An IR will be issued to the Sponsor requesting a comparison of performance attributes of the devices.

Please see IR#1.

8.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☑ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A

Reviewer Comments

No additional risk analysis/management documentation was provided in this submission. The Sponsor is cross-referencing a previously submitted application for this information which was reviewed and found approvable by the device reviewer Dr. Rong Guo.

CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No

	Date Sent: **8/21/2020**	**Date/Sequence Received:** **11/2/2020**
Information Request #1	You have provided a comparative analysis of the Semglee prefilled pen and Lantus solostar. However, you have not addressed the comparison of performance. Provide a comparison of the dose accuracy, injection time, and activation force. Provide a comparison table that compares the performance of both device that you wish to interchangeable.	
Sponsor Response	A Device Comparative Analysis Report was provided, as requested by the Agency in the Meeting Request – Written Responses dated July 03, 2020, in Section 3.2.P.2.4 of the 351(k) BLA 761201, submitted on July 29, 2020 (Sequence Number 0001). This Comparative Analysis (also referred to as a Threshold Analysis) presented Mylan's comparison of the functional performance attributes of the device constituents within three Threshold Analyses [TAs] - a comparative task analysis, a labeling comparison and a physical comparison between the US-licensed Lantus® SoloSTAR® and Mylan's proposed interchangeable product, MYL- 1501D). The Semglee (MYL-1501D) Pre-filled Pen (PFP) was developed with the same user requirements, technical operating principles, dosing increments, sequence of operation and labeling as the Reference Product (RP), US-licensed Lantus SoloSTAR, including confirmation through a comprehensive performance verification program that the PFP met all Food and Drug Administration (FDA) and International Organization for Standardization (ISO) requirements for a PFP delivery system, inclusive of: • Guidance for Industry – Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (FDA, June 2013) • ISO 11608-1:2014 Needle-based Injection Systems for Medical Use – Requirements and Test Methods - Part 1: Needle-based Injection Systems • ISO 11608-2:2012 Needle-based Injection Systems for Medical Use – Requirements and Test Methods – Part 2: Needles • ISO 11608-3:2012 Needle-based Injection Systems for Medical Use – Requirements and Test Methods - Part 3: Finished containers • EN ISO 62366-1:2015 – Medical Devices. Application of Usability Engineering to Medical Devices The device development program confirmed the safe and effective use of the PFP by the intended user population in simulated use environments through the Human Factors Validation program as presented in BLA 210605 and BLA 761201. In	

	addition to the demonstration of safe and effective use of the Semglee PFP, the development program also considered the Semglee PFP in comparison with Lantus SoloSTAR and its Instructions for Use (IFU). The three TAs were undertaken to identify any differences in device and labelling between the Semglee PFP and the Lantus SoloSTAR PFP. If differences were identified through these TAs the acceptability of the difference was assessed, based on the assessment of risk profile of the two products, in support of the proposal of Semglee as the interchangeable product with the RP. This was with the full expectation that Semglee will produce the same clinical effect and safety profile as Lantus SoloSTAR under the conditions specified in the labelling and therefore be interchangeable with Lantus SoloSTAR without the intervention of a health care provider and/or without additional training prior to use of the Semglee PFP. The Comparative Task Analysis (CTA) TA compared the task sequence associated with use of the Semglee PFP to the task sequence associated with use of the Lantus SoloSTAR PFP. No differences were identified that had an impact on user safety or the interchangeability of the Semglee PFP with the Lantus SoloSTAR PFP. The CTA then went a step further by using a Perception, Cognition and Action (PCA) model to assess cognitive decisions and actions taken at each individual task in the use of the PFPs thus confirming that the user would have no cognitive impediment to the actions required in order to use either PFP to deliver a dose based on knowledge of the other PFP. The Human Factors Validation studies, presented in Sections 3.2.P.2.4.2.6.1 and 3.2.P.2.4.2.6.2 of BLA 761201, in addition, included patients currently prescribed Lantus SoloSTAR in both the adult and pediatric usability assessments (46 Lantus SoloSTAR patients in total - 30 adult and 16 pediatric). It was found that for those 46 Lantus SoloSTAR patients 11 use errors were recorded that related to the functional performance attributes, namely that the users did not hold the purple button down for 10 seconds. These use errors and one close call (that did not result in use error) are presented in Table 1 for ease of reference. (For a comprehensive overview of all use errors, close calls and use difficulties, including those reproduced here, please refer to Section 1.11.1 of the Information Request Response provided on September 9, 2020 [SEMGLEE™ {insulin glargine} Solution for Subcutaneous Injection, 100 Units/mL, BLA 761201, Sequence Number 0004 {Response to Information Request dated August 28, 2020}] in which updates were made to Module 3 in alignment with the response to deficiencies and Information Requests for BLA 210605, as requested by the Agency. As part of the Module 3 updates the comprehensive overview was provided in Annexure 8, included in Section 3.2.P.2.4.2.6.1 Human Factors Validation Studies [of Section 3.2.P.2.4 Container Closure System – Design and Development] of BLA 761201. Usability Tasks assessed through the Human Factors Validation studies (that utilised the proposed commercial pen configuration) which would highlight any use errors related to the functional performance attributes of the PFP are: • User removes the pen cap (UC2) – cap removal force

	• User correctly attaches the needle to the pen (UC4) • User selects the correct dose (UC8) • User administers full dose (UC12) – includes activation force • User holds purple button down for 10 seconds (UC13) • User replaces the cap over the cartridge (UC16) One current Lantus SoloSTAR user recorded a close call against UC4 on one occasion where they did not secure the needle onto the pen (they twisted it in the wrong direction): this user could not identify a root cause for their action. 11 use errors were recorded against UC13 from the cohort of current Lantus SoloSTAR users. 11 users did not hold the pen button down for the required hold time of 10 seconds; of these: 6 users associated the error with their current practice with Lantus SoloSTAR, 2 users counted to 10 but in an actual time of less than 10 seconds, 2 users could not identify a root cause, and 1 error was recorded as a study artefact. No use errors, difficulties or close calls were recorded for current Lantus SoloSTAR users for any of the other tasks related to the functional performance attributes. No usability issues were attributed to the device constituent drug delivery performance attributes (including activation force and cap removal force) when switching between Lantus SoloSTAR PFP use and that of Semglee PFP. The Semglee PFP meets the requirements of the FDA guidance and ISO standards referenced above, providing additional confirmation of performance supporting both usability and interchangeability. The comprehensive device development program of the Semglee PFP, inclusive of Human Factors Validation, Comparative Analysis and Design Verification Testing, confirmed through objective evidence that intended users (including patients currently using Lantus SoloSTAR) are able to safely and effectively administer a dose from the Semglee (MYL-1501D) PFP and hence supports the demonstration of interchangeability of MYL-1501D with US-licensed Lantus.
Reviewer Comments	The Sponsor relies on a comparative analysis of the physical aspects of the device, the labeling, and a human factors study. The physical comparison of the two products is limited to the appearance of the individual parts of the device (e.g., size of the pen, size of the viewing window, design of the dose dial, etc.). However, it does not specifically address

	device performance attributes such as injection force. While the injection force specification was validated for a similar/the same patient population during the original review, a demonstration of interchangeability should include a comparison of performance attributes of the device to support adequate use. Hence, this response is not acceptable. A follow-on IR is recommended.
Response Adequate:	☐ **Yes** ☑ **No, See IR # Sent on 12/21/2020**

Follow-On Deficiency	Date Sent: 12/21/2020	Date/Sequence Received: 1/8/2021 Sequence 13
Information Request #4	In your response to Comment 2 of the 74 Day comment letter, you referred to your comparative analysis report and the three conducted threshold analyses (physical comparison, labeling, and comparative task analysis). However, you have not provided a comparison of the functional performance attributes of the two devices. Please note that differences in device performance can impact the usability and efficacy of your product. In order to establish interchangeability, provide a comparison of the essential performance requirements (i.e., dose accuracy and injection force) of the proposed product and the reference product.	
Sponsor Response	The Semglee (MYL-1501D) Pre-filled Pen (PFP) was developed with the same user requirements, technical operating principles, dosing increments, sequence of operation and labeling as the Reference Product (RP), US-licensed Lantus® SoloSTAR®, including confirmation through a comprehensive performance verification program that the PFP met all Food and Drug Administration (FDA) and International Organization for Standardization (ISO) requirements for a PFP delivery system, inclusive of ISO 11608-1:2014 Needle-based Injection Systems for Medical Use – Requirements and Test Methods - Part 1: Needle-based Injection Systems. Both the Semglee (MYL-1501D) and Lantus SoloSTAR® PFPs met the dose accuracy requirements of ISO 11608-1:2014 as shown in Table 33 and Table 34.	

Table 33: Dose Accuracy Performance of MYL-1501D PFP at Standard In Use Conditions (23 (± 5)°C, 50 (± 25)% RH)

Test Requirement	Sample Size	The pen must maintain volumetric accuracy in accordance with ISO 11608-1:2014 under the operating conditions 23°C ± 5°C/50% ± 25% RH				Met Requirements
Dose Accuracy (Needle BD Ultra-Fine 31G x 5 mm)	n = 60 pens (MYL-1501D cartridge) (Initial commercial pen configuration) (b) (4) Assembly Line, Biocon, Bangalore	Requirement (b) (4)	Results (mL)			
			Dose	V_{min} (0.01 mL)	V_{mid} (0.40 mL)	V_{max} (0.80 mL)	Yes
			Mean	0.01	0.40	0.80	
			SD*	0.001	0.003	0.006	
			LTI	0.01	0.39	0.79	
			UTI	0.01	0.41	0.82	
			k_{actual}	9.547	5.572	6.252	
	n = 60 pens (MYL-1501D cartridge) (Refined commercial pen configuration) (b) (4) Assembly Line, Biocon, Bangalore		Results (mL)				
			Dose	V_{min} (0.01 mL)	V_{mid} (0.40 mL)	V_{max} (0.80 mL)	Yes
			Mean	0.01	0.40	0.80	
			SD*	0.001	0.003	0.006	
			LTI	0.01	0.40	0.79	
			UTI	0.01	0.41	0.82	
			k_{actual}	7.946	5.510	5.975	
	n = 60 pens (MYL-1501D cartridge) (Refined commercial pen configuration) (b) (4) Assembly Line, Biocon, Malaysia		Results (mL)				
			Dose	V_{min} (0.01 mL)	V_{mid} (0.40 mL)	V_{max} (0.80 mL)	Yes
			Mean	0.01	0.40	0.81	
			SD*	0.002	0.004	0.007	
			LTI	0.01	0.39	0.79	
			UTI	0.02	0.41	0.82	
			k_{actual}	5.664	4.258	4.903	

Table 34: Dose Accuracy Performance of Lantus SoloSTAR® PFP at Standard In-Use Conditions (23 (± 5)°C, 50 (± 25)% RH)

Test Requirement	Sample Size	The pen must maintain volumetric accuracy in accordance with ISO 11608-1:2014 under the operating conditions 23°C ± 5°C/50% ± 25% RH			
		Requirement	Results (mL)		
		(b) (4)	Dose	V_{min} (0.01 mL)	V_{mid} (0.40 mL)	V_{max} (0.80 mL)
Dose Accuracy (Needle BD Ultra-Fine 31G x 5 mm)	n = 60 pens Lantus SoloSTAR® Pre-filled Pen (PFP)		Mean	0.01	0.40	0.81
			SD*	0.002	0.004	0.006
			LTI	0.01	0.39	0.78
			UTI	0.02	0.41	0.81
			k_{actual}	2.796	4.534	5.808

The device development program confirmed the safe and effective use of the PFP by the intended user population (inclusive of Lantus SoloSTAR® users) in simulated use environments through the Human Factors Validation program, in accordance with EN ISO 62366-1:2015 – Medical Devices. Application of Usability Engineering to Medical Devices, as presented in BLA 210605 and BLA 761201. In addition to the demonstration of safe and effective use of the Semglee PFP, the development program also considered the Semglee PFP in comparison with Lantus SoloSTAR® and its Instructions for Use (IFU). Injection force data for the proposed MYL-1501D product and the reference product, Lantus SoloSTAR®, are presented in Table 35 and Table 36. This comparable injection force data supports the outcome of the Human Factors Validation that the intended users (including patients currently using Lantus SoloSTAR)® are able to safely and effectively administer a dose from the Semglee (MYL-1501D) PFP and hence supports the demonstration of interchangeability of MYL-1501D with US-licensed Lantus.

Table 35: Injection Force of MYL-1501D Pre-filled Pen (PFP) at 23 (± 5)°C, 50 (± 25)% RH

Device Requirement		Injection Force (with Cartridge and Needle)			Met Requirements
		Test Requirement	Results (N)		
Injection Force (with Cartridge and Needle - BD Ultra-Fine 31G x 5 mm) for 80-unit dose (Vmax)	Sample Size n = 30 PFPs (MYL-1501D cartridge) (Refined commercial pen configuration)	(b) (4)	Injection Force Mean	9	Yes

Table 36: Injection Force of Lantus SoloSTAR® Pre-filled Pen (PFP) at 23 (± 5)°C, 50 (± 25)% RH

Device Requirement		Injection Force (with Cartridge and Needle)		
		Test Requirement	Results (N)	
Injection Force (with Cartridge and Needle - BD Ultra-Fine 31G x 5 mm) for 80-unit dose (Vmax)	Sample Size n = 60 PFPs (Lantus SoloSTAR®)	(b) (4)	Injection Force Mean	11

Reviewer Comments	Mylan provided summary test results of the RLD pen injector and the subject device. However, only summary data was provided for injection forces (i.e., only averages were reported). Additional information is necessary to evaluate this performance attribute (e.g., min, max, sd, etc.). Hence, a follow-on deficiency is recommended.
Response Adequate:	☐ **Yes** ☑ **No, See IR #5 Sent on 1/22/2021**

Follow-On Deficiency	**Date Sent: 1/22/2021**	**Date/Sequence Received: 1/29/2021 Seq 15**
Information Request #5	In your response to Comment 13 of the information requested dated 21DEC2020, you provided a comparison of results of dose accuracy and injection forces of the Lantus SoloSTAR and the MYL-1501D Pre-filled Pen. However, you only provided the mean injection forces for each injector. More detail is needed to evaluate the provided response. Provide complete test results (i.e., data for each injector tested and a statistical analysis of the test results) for your injection force testing.	
Sponsor Response	In accordance with the Agency's request, Mylan have provided in Table 1 and Table 2 the complete test results for injection force for each sample of the MYL-1501D Pre-filled Pen (PFP) (for data originally presented in Section 2.4 Container Closure System – Design and Development of the BLA) and the Lantus® SoloSTAR® PFP (for data provided in response to the Agency communication dated December 21, 2020). A statistical analysis including the mean and standard deviation for each data set has also been provided for your evaluation. Table 1: Injection Force of MYL-1501D PFP at 23 (± 5)°C, 50 (± 25)% RH	

Device Requirement		Injection Force (with Cartridge and Needle)		
		Test Requirement	Sample Replicate	Results (N)
Injection Force (with Cartridge and Needle - BD Ultra-Fine™ 31G x 5 mm) for 80-unit dose (Vmax)	**Sample Size** n = 30 PFPs; (3 replicates per PFP) (MYL-1501D drug filled cartridge) (Refined commercial pen configuration)	(b) (4)	1	9
			2	9
			3	10
			4	10
			5	10
			6	9
			7	9
			8	9
			9	9
			10	10
			11	9
			12	9
			13	10
			14	9
			15	9
			16	9
			17	9
			18	9
			19	10
			20	9
			21	9
			22	9
			23	8
			24	8
			25	9
			26	8
			27	9
			28	9
			29	9
			30	8
			31	9
			32	9

Device Requirement	Injection Force (with Cartridge and Needle)

				Test Requirement	Sample Replicate	Results (N)
					33	9
					34	11
					35	10
					36	10
					37	10
					38	9
					39	9
					40	9
					41	9
					42	8
					43	10
					44	9
					45	9
					46	10
					47	9
					48	9
					49	10
					50	9
					51	10
					52	9
					53	9
					54	8
					55	9
					56	9
					57	9
					58	9
					59	10
					60	9
					61	10
					62	9
					63	9
					64	10
					65	9
					66	9
					67	11
					68	10

				69	9
				70	10
				71	9
				72	10
				73	10
				74	8
				75	9
				76	9
				77	9
				78	8
				79	9
				80	9
				81	9
				82	9
				83	10
				84	9
				85	9
				86	9

Device Requirement		**Injection Force (with Cartridge and Needle)**		
		Test Requirement	**Sample Replicate**	**Results (N)**
			87	9
			88	9
			89	9
			90	8
Minimum (N)			8	
Maximum (N)			11	
Mean (N)			9	
Standard Deviation (SD)			0.55	

Table 2: Injection Force of Lantus SoloSTAR PFP at 23 (± 5)°C, 50 (± 25)% RH

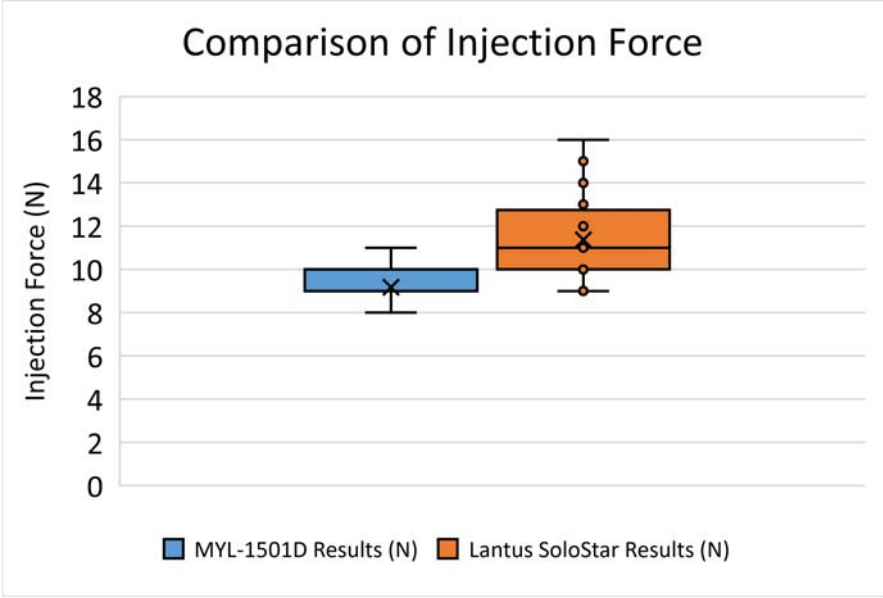
Device Requirement	**Injection Force (with Cartridge and Needle)**

				Test Requirement	Sample Replicate	Results (N)
		Injection Force (with Cartridge and Needle - BD Ultra-Fine 31G x 5 mm) for 80-unit dose **(Vmax)**	**Sample Size** n = 60 PFPs (Lantus SoloSTAR)	(b) (4)	1	13
					2	14
					3	15
					4	12
					5	10
					6	12
					7	16
					8	14
					9	10
					10	13
					11	12
					12	10
					13	11
					14	12
					15	11
					16	11
					17	10
					18	12
					19	13
					20	12
					21	13
					22	10
					23	12
					24	11
					25	11
					26	10
					27	13
					28	10
					29	10
					30	10
					31	11
					32	11
					33	12
					34	9
					35	15

			36	10
			37	9
			38	11
			39	10

Device Requirement		Injection Force (with Cartridge and Needle)		
		Test Requirement	Sample Replicate	Results (N)
			40	13
			41	9
			42	13
			43	11
			44	10
			45	13
			46	11
			47	10
			48	11
			49	12
			50	10
			51	11
			52	10
			53	10
			54	11
			55	10
			56	13
			57	13
			58	9
			59	11
			60	10
Minimum (N)			9	
Maximum (N)			16	
Mean (N)			11	
Standard Deviation (SD)			1.60	

This data is in addition to the totality of the evidence provided in our application that the MYL-1501D PFP met all the FDA and ISO requirements for a PFP delivery system, inclusive of ISO 11608-1:2014- Needle-based Injection Systems for Medical Use –

	Requirements and Test Methods – Part 1: Needle-based Injections Systems. The totality of the data related to the stand alone performance characteristics of the MYL-1501D PFP, as well as the current approval of this PFP as a 351(a) biologic, support the safe and effective use of our proposed product including with respect to injection force. This performance data, along with our user data showing Reference Product users can safely and effectively use the MYL-1501D PFP (without training or the intervention of a health care professional), support our demonstration of interchangeability consistent with section 351(k) of the PHSA and FDA guidance.
Reviewer Comments	Mylan provided the raw data for the injection force comparison study. The data indicates that the average injection force of the RLD (Lantus SoloStar) is slightly higher (2 N) compared to the MYL-1501D injector. The data was analyzed and showed that the difference between the two data sets is statistically significant ($p = 1.9*10^{-15}$). However, there is overlap in the reported data (i.e., the max of the MYL is 11 whereas the min of the Lantus is 9 N). Furthermore, the difference of 2 N does appear to be minor. The following provides a graphical representation of the provided data: 

	In addition to this comparison study, the Sponsor has provided a Usability comparison study of the two devices. Based on the provided injection force data, the usability comparison may provide more insight regarding the appropriateness of interchangeability of the two devices. A review of this study is deferred to DMEPA. The provided response is acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

9. DESIGN VERIFICATION REVIEW

No additional design verification documents have been submitted. The Applicant is asked to provide a comparison of device performance (please see IR#1 and #4).

9.1. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Please see Dr. Rong Guo's review in Attachment A for a review of the design verification data. The Sponsor is asked to provide a performance comparison of the subject device and the comparator. Please see IR#1, IR#4, and IR#5 for details.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

9.2. Discipline Specific Sub-Consulted Review Summary

☑ No Additional Discipline Specific Sub-Consults were requested
☐ The following additional Discipline Specific Sub-Consults were requested:

10.CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

☑ There is no device related clinical studies for review
☐ There are clinical studies for review

Reviewer Comments

Please see Dr. Guo's review in Attachment A for a review of the design validation data.

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☑

Reviewer Comments

The Sponsor submitted a comparative task analysis of the subject device and the reference product. An evaluation of this information is deferred to DMEPA.

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	☑

Reviewer Comments

The Agency issued a comment to Mylan on September 29, 2020 that an inspection of the Biocon India site will be required prior to approval of the application and that this inspection may delay the approval process for the product. In response, the Applicant stated that the Biocon India facility may be removed from the application to accelerate the review process of the product. However, once this facility is removed, any data from devices assembled at this facility (i.e., batch records etc.) will also need to be removed. As a result, an information request is recommended. **Please see IR#3 for additional information.**

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☐
CDRH Quality Systems Documentation Review was not conducted	☑

Reviewer Comments

The Sponsor has initially not provided any information regarding compliance with the relevant sections of the Quality Systems regulations. An IR was issued (IR#2) that asked the Applicant to provide information regarding management controls, purchasing controls, design controls, and CAPA. In response the Sponsor stated that the missing information was originally provided in response to an Information Request under BLA 210605 and that Module 3 was updated with the missing information. The response submitted under BLA 210605 (Sequence 0004, Section 1.11.1; DocuBridge files are under NDA 210605), was compared to the newly provided document under Sequence 0004, 3.2.P.2.4 of this submission. No substantial differences were identified between the information. Small edits were made by the Sponsor as this document is no longer provided as a response to an information request and certain Section were updated to state that activities, such as development of a design history file at Biocon, were completed.

The provided information was previously reviewed under BLA 210605 by CDRH. The compliance reviewer, Habacuc Barrera, found all information sufficient and recommended approval. Please see his memo in Attachment B. Hence, no additional desk review of the Quality Systems documentation is needed.

12.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Dose Accuracy	(b) (4)	Y
Injection Force		Y

Reviewer Comments

No changes are made to the product control strategy compared to the approved BLA 210605.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☑ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: 8/21/2020	Date/Sequence Received: 11/2/2020
Information Request #2	(b) (4). Please provide the following information related to the medical device Quality System for the device: a. Provide a summary of your management structure with executive responsibility for those who manage, perform, and assess work affecting quality of the product and related controls to ensure that your quality policies are appropriately implemented and followed, and the product appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements met, per 21 CFR 820.20. b. Provide a summary of your design control system under 21 CFR 820.30 for the device constituent part and combination product. The design control information should include initial design, planning and development, design input, design output, design review, design transfer, design verification, design validation that meets the proposed intended use of the final combination product, design changes, and design history file. For changes made to the device constituent part of the combination product, the impact of the design changes on the overall combination product performance should be considered and documented. All the design control activities must be documented in the Design History File (DHF) and subjected for	

	design reviews. In addition, identify the facility containing the DHF so that the Agency inspection planning activities are appropriately determined. c. Provide a summary of your purchasing control system per 21 CFR 820.50 to demonstrate controls and documentation for components, products, or services (e.g., sterilization) received at your facility for use in the manufacture of the combination product. The summary should include your evaluation process of your suppliers that meet the manufacturing acceptance criteria of the combination product specifications. Notification of changes made by the suppliers should be considered in your Purchasing/Supplier agreement as changes to incoming specification that can impact the safety and effectiveness of the final combination product. d. Provide a summary of your corrective and preventive actions (CAPA) system per 21 CFR 820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of nonconformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions must be documented under your CAPA System as described in 21 CFR 820.100.
Sponsor Response	Mylan acknowledges the Agency's request. Please refer to Section 1.11.1 of the Information Request Response provided on September 9, 2020 (SEMGLEETM [insulin glargine] Solution for Subcutaneous Injection, 100 Units/mL, BLA 761201, Sequence Number 0004 [Response to Information Request dated August 28, 2020]) in which updates were made to Module 3 in alignment with the response to deficiencies and Information Requests for BLA 210605, as requested by the Agency. As part of the Module 3 updates the applicable 21 CFR Part 820 regulations for this combination product were provided in Annexure 13, included in Section 3.2.P.2.4.1 Introduction and Device Description (of Section 3.2.P.2.4 Container Closure System – Design and Development) of BLA 761201.
Reviewer Comments	The Sponsor cross-referenced the GMP information that was previously provided under BLA 210605, Seq 004 in response to a CDRH information request. This information was originally missing in this application. The provided information was reviewed and is substantially similar to what was provided in the previously approved submission. This information was reviewed by Habacuc Barrera under ICC1700725 (see memo in Appendix B).
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent: **11/11/2020**	**Date/Sequence Received:** **11/30/2020**
Information Request #3	You are proposing to remove the Biocon Biologics India facility (FEI: 3003981475) from the submission and keep the Biocon Malaysia site (FEI: 3011248248) as the sole facility for pen injector assembly. However, it is unclear if pen injector assembly and release testing have been validated at the Malaysia site and if any performance data from devices manufactured at the Malaysia site has been provided to the Agency for review. Clarify whether the pen injector assembly and release test methods have been validated at the Malaysia site. In	

	addition, confirm if device data of devices manufactured at this facility has been submitted to the Agency before and provide the location of this data. Otherwise, provide performance data of the essential performance requirements of the pen injector (dose accuracy, injection force) from devices manufactured at the Malaysia facility.
Sponsor Response	Mylan confirms that Process Validation (PV) for Pre-Filled Pen (PFP) assembly was performed for the Biocon, Malaysia (L2) site and details, including the PV protocol and report, were provided in Section 3.2.P.3.5.2 of both BLA 210605 and BLA 761201. Three consecutive batches of the proposed commercial pen configuration of the PFP were assembled for the PV study, each at a batch size of (b) (4) units. Test results, against the finished combination product specification, for the three PV batches of PFP were provided in Section 3.2.P.3.5.2 along with the results of physicochemical (quality attribute) testing of the drug product cartridge before and after PFP assembly. The batch analysis data for the three PV batches of PFP were also provided in Section 3.2.P.5.4 of both BLA 210605 and BLA 761201. All acceptance criteria for the both the finished combination product testing and the drug product cartridge testing, before and after PFP assembly, for the three PV batches of PFP were met. The three PV batches of PFP manufactured at the Biocon, Malaysia (L2) site were placed on long term and accelerated functional stability and the stability data available at the time of submission (long term functional stability data up to 18 months and accelerated stability data up to 6 months) were presented in Section 3.2.P.8.3 of BLA 761201. All associated test methods were transferred from the Biocon Biologics, India (L1) site to the Biocon, Malaysia (L2) site and a method qualification study conducted to confirm the transfer process had been completed appropriately, as documented in Section 3.2.P.5.3 of BLA 210605. In addition to the PV study conducted an assembly verification study was performed in support of the assembly of the PFP at the Biocon, Malaysia (L2) site the results of which were presented in Section 3.2.P.2.4.2.4.3 of the 3.2.P.2.4 Container Closure System – Design and Development Section of BLA 761201. The results demonstrated that the finished combination product met the key performance and functional requirements after final assembly at the Biocon, Malaysia (L2) site. With respect to the Essential Performance Requirements (EPRs) of dose accuracy and injection force: • Dose accuracy data for the three PV batches of PFP were provided with the batch analysis data in Section 3.2.P.5.4 of both BLA 210605 and BLA 761201 • While the combination product injection force is considered an EPR of the MYL-1501D PFP at the point of dosing, the design verification data in Table 3.2.P.2.4/ 33 of BLA 761201 demonstrates that the mean injection force is less than or equal to the sustaining forces of the cartridge when both parameters are tested with a needle attached. As such Mylan would like to confirm that injection force of the PFP will be controlled at the cartridge level through testing of the initiating and sustaining forces both at cartridge release and on stability. Cartridge initiating and sustaining forces were monitored at cartridge release testing and met specification for all batches (refer to Section 3.2.P.5.4 of BLA 761201). Cartridge initiating and sustaining forces were also monitored on stability through to end of cartridge shelf-life and have been shown to meet specification up to the proposed shelf-life of (b) (4) months at the long term (5 [± 3]ºC) storage condition (refer to Section 3.2.P.8 of BLA 761201). (Note: Mylan would like to clarify that

	design verification testing was performed with a needle attached to both the PFPs and the cartridge. The MYL-1501D cartridge stability data was generated by a different technique with cartridges open to the atmosphere [i.e., no needle was attached] in accordance with the requirements of ISO 11608-3:2012 - Needle-based Injection Systems for Medical Use - Requirements and Test Methods, Part 3: Finished Containers [Recognition Number: 6-294].)
Reviewer Comments	The Sponsor stated that process validation for the pen injector has been performed at the Malaysia site. In addition, the Sponsor clarified that performance data from validation batches was previously provided in BLA 210605 Section 3.2.P.3.5.2. Hence, the removal of the India manufacturing site from the application is acceptable from a device perspective. The Sponsor noted that a "refined" commercial version of the Product was developed and that information about these refinement were provided in 3.2.P.2.4.2.3 of this submission. While reference to the refined commercial version of the pen were found in BLA 210605, the Sponsor intends to formally introduce this version in the next annual report as design refinements. Per the applicant, the refinements do not impact the pen performance. The following list of changes from the initial to the refined commercial version of the pen were found in 3.2.P.2.4.2.3 (Sequence 0004): *The minor design refinements included:* • (b) (4) • • *The material changes included:* • (b) (4) • • The Sponsor has conducted a full set of performance tests (including an assessment of the essential performance requirements) of the initial and the refined version of the device. The following is a comparison of the dose accuracy and injection forces of the two versions (top data: initial commercial version; bottom data: refined commercial version): **Dose Accuracy**

Table 3.2.P.2.4/ 11: Dose Accuracy and Device Functionality in Cool In-Use Conditions

DRS Requirement		The pen must maintain volumetric accuracy in accordance with ISO 11608-1:2014 under the operating conditions 5°C ± 3°C/uncontrolled RH				Met requirements
Mechanical Function	Sample Size and Configuration	Functionality: Number of mechanical failures (for 97.5% reliability) = 0 (Initial and refined commercial pen configurations)				Pass
Dose Accuracy (Needle BD Ultra-Fine 31G x 5 mm)	n = 60 pens (MYL-1501D cartridge) (Initial commercial pen configuration)	Requirement (b) (4)	Results (mL)			
			Dose	V_{min} (0.01 mL)	V_{mid} (0.40 mL)	V_{max} (0.80 mL)
			Mean	0.01	0.40	0.80
			SD*	0.001	0.004	0.005
			Min	0.01	0.39	0.79
			Max	0.02	0.41	0.81
			k_{actual}	6.076	5.170	8.663
	n = 60 pens (MYL-1501D cartridge) (Refined commercial pen configuration)		Results (mL)			
			Dose	V_{min} (0.01 mL)	V_{mid} (0.40 mL)	V_{max} (0.80 mL)
			Mean	0.01	0.40	0.80
			SD*	0.001	0.002	0.004
			Min	0.01	0.40	0.79
			Max	0.01	0.41	0.81
			k_{actual}	7.15	8.61	9.26

Met requirements
Pass
Pass
Pass
Pass
Pass

*Standard deviation reported to 3 decimal places for information.

Please note that dose accuracy testing was done with different needles, and after preconditioning (including free fall and vibration). Not all data is shown here for brevity.

Injection Force

Table 3.2.P.2.4/ 32: Injection Force (without Cartridge and Needle)

DRS Requirement		Injection force (without cartridge and needle)			Met requirements
Injection force (without cartridge and needle)	Sample Size n = 30 pens (Initial commercial pen configuration)	Number of failures (for 97.5% reliability) = 0 (Initial and refined commercial pen configurations)			Yes
		(b) (4)	Results (N)		
			Mean	2.6	Yes
			Range	2.3 to 2.7	
			SD	0.1	
Injection force (without cartridge and needle)	Sample Size n = 30 pens (Refined commercial pen configuration)		Results (N)		
			Mean	2.4	Yes
			Range	2.2 to 2.7	
			SD	0.1	

Table 3.2.P.2.4/ 33: Injection Force (with Cartridge and Needle)

Device Requirement		Injection Force (with Cartridge and Needle)			Met Requirements
Injection Force (with Cartridge and Needle)	Sample Size n = 30 PFPs (Water-filled cartridge) (Initial commercial pen configuration)	Number of failures (for 97.5% reliability) = 0 (Initial and refined commercial pen configurations)			Yes
		Requirement (b) (4)	Results (N)		
			Injection Force Mean	14	Yes
			Range	12 to 17	
Injection Force (with Cartridge and Needle)	Sample Size n = 30 PFPs (MYL-1501D cartridge) (Refined commercial pen configuration)		Results (N)		
			Injection Force Mean	9	Yes
			Mean Sustaining Force of Cartridge and Needle	12	

	Other performance attributes were also assessed (including cap removal force, dose dial torque, and dose selection override torque). No failures were reported by Mylan.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

<<END OF REVIEW>>

13.APPENDIX A (INFORMATION REQUESTS)

13.1. Filing/74-Day Information Requests

1. You have provided a comparative analysis of the Semglee prefilled pen and Lantus solostar. However, you have not addressed the comparison of performance. Provide a comparison of the dose accuracy, injection time, and activation force. Provide a comparison table that compares the performance of both device that you wish to interchangeable.

2. You have indicated that you are implementing a drug based CGMP streamlined approach. Please provide the following information related to the medical device Quality System for the device:

    a. Provide a summary of your management structure with executive responsibility for those who manage, perform, and assess work affecting quality of the product and related controls to ensure that your quality policies are appropriately implemented and followed, and the product appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements met, per 21 CFR 820.20.
    b. Provide a summary of your design control system under 21 CFR 820.30 for the device constituent part and combination product. The design control information should include initial design, planning and development, design input, design output, design review, design transfer, design verification, design validation that meets the proposed intended use of the final combination product, design changes, and design history file. For changes made to the device constituent part of the combination product, the impact of the design changes on the overall combination product performance should be considered and documented. All the design control activities must be documented in the Design History File (DHF) and subjected for design reviews. In addition, identify the facility containing the DHF so that the Agency inspection planning activities are appropriately determined.
    c. Provide a summary of your purchasing control system per 21 CFR 820.50 to demonstrate controls and documentation for components, products, or services (e.g., sterilization) received at your facility for use in the manufacture of the combination product. The summary should include your evaluation process of your suppliers that meet the manufacturing acceptance criteria of the combination product specifications. Notification of changes made by the suppliers should be considered in your Purchasing/Supplier agreement as changes to incoming specification that can impact the safety and effectiveness of the final combination product.
    d. Provide a summary of your corrective and preventive actions (CAPA) system per 21 CFR 820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of nonconformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions must be documented under your CAPA System as described in 21 CFR 820.100.

13.1.1. Interactive Information Requests sent on 11/11/2020

3. You are proposing to remove the Biocon Biologics India facility (FEI: 3003981475) from the submission and keep the Biocon Malaysia site (FEI: 3011248248) as the sole facility for pen injector assembly. However, it is unclear if pen injector assembly and release testing have been validated at the Malaysia site and if any performance data from devices manufactured at the Malaysia site has been provided to the Agency for review. Clarify whether the pen injector assembly and release test methods have been validated at the Malaysia site. In addition, confirm if device data of devices manufactured at this facility has been submitted to the Agency before

and provide the location of this data. Otherwise, provide performance data of the essential performance requirements of the pen injector (dose accuracy, injection force) from devices manufactured at the Malaysia facility.

13.2. Mid-Cycle Information Requests

4. In your response to Comment 2 of the 74 Day comment letter, you referred to your comparative analysis report and the three conducted threshold analyses (physical comparison, labeling, and comparative task analysis). However, you have not provided a comparison of the functional performance attributes of the two devices. Please note that differences in device performance can impact the usability and efficacy of your product. In order to establish interchangeability, provide a comparison of the essential performance requirements (i.e., dose accuracy and injection force) of the proposed product and the reference product.

13.3. Interactive Information Requests

13.3.1. Interactive Information Requests sent on 1/22/2021

5. In your response to Comment 13 of the information requested dated 21DEC2020, you provided a comparison of results of dose accuracy and injection forces of the Lantus SoloSTAR and the MYL-1501D Pre-filled Pen. However, you only provided the mean injection forces for each injector. More detail is needed to evaluate the provided response. Provide complete test results (i.e., data for each injector tested and a statistical analysis of the test results) for your injection force testing.

14.APPENDIX B (CONSULTANT MEMOS)

14.1. Original Device Review

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL, RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Date	March 19, 2018
To	Anika Lalmansingh CDER/OPQ/OPRO/DRBPMI/RBPMBI
Requesting Division	CDER/OND/ODEII/DMEP
From	Rong Guo CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Carolyn Dorgan CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRRID/GHDB
Subject	Consult for Submission # NDA 210605, SEMGLEE, MYL-1501D ICCR2017-01604 ICC1700398
Recommendation	Approval of the device constituent of the combination product

Digital Signature Concurrence Table	
Reviewer	
Team Lead	
Branch Chief	

Reference ID: 4746242

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2017-01604
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=1824
ICC tracking # (Lead)	ICC1700398
Submission Number	NDA210605
Sponsor	Mylan GmbH
Drug/Biologic	Insulin glargine
Indications for Use	Improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Device Constituent	pre-filled pen
Related Files	NDA210605 EDR 3.2.P.2; 3.2.P.7

Table 2. Important Dates	
Filling	Sept 15, 2017
Mid-Cycle Meeting	January 8, 2018
Wrap up Meeting	April 11, 2018
Final Discipline Specific Memos Due	April 9, 2018
Final Lead Device Review Memo Due	April 17, 2018
PDUFA date	May 17, 2018

2. PURPOSE/BACKGROUND

2.1. Scope

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH) regarding NDA 210605, MYL-1501D, Insulin glargine. The device consultant authoring this review memorandum has performed a design review of submission materials intended to support the safety and functionality of the pre-filled pen injector. This review did not cover manufacturing of the pen injector nor the human factors study.

This review covers the essential performance elements of the device under review:

- Dose accuracy
- Functional Performance
- Biocompatibility of non-primary closure components

Topics not covered in this review:

- Human factors deferred to CDER/OSE/DMEPA
- Device manufacturing review deferred to CDRH/OC
- Final combination product benefit / risk assessment
- Review of the prefilled cartridge (primary container closure) including biocompatibility and sterility deferred to CDER/OPQ

2.2. Background

Insulin glargine (Anatomical Therapeutic Chemical [ATC] code A10AE04) is a long-acting analog of human insulin, and is classified under the ATC group "drugs used in diabetes, insulins and analogues for injection, long-acting". The primary sequence of insulin glargine differs from that of insulin by 3 amino acids: asparagine at position A21 instead of glycine and 2 arginines added to the C-terminus of the B chain. Lantus® (insulin glargine [rDNA origin] injection; NDA# 021081; Sanofi-Aventis) is the reference listed product. The sequence of MYL-1501D was shown to be identical to that of insulin glargine (Lantus). MYL-1501D is a clear, colorless solution for injection, at pH 4.0. It is supplied in a pre-filled disposable pen integrated with a 3 mL cartridge, containing 100 U insulin glargine per mL.

2.3. Prior Interactions

GHDB received ICC1700398 on May 8, 2017. Rong Guo was the reviewer. The submission contained sufficient data for the device constituent part of the combination product. Device recommended filing. This application was issued a Refuse to File on 6/26/2017. The applicant has Filed over Protest and therefore the review clock has been restarted.

2.3.1. Related Files

NDA 210605 Sequence 0000 submitted on 04/27/2017
Sequence 30 submitted on 02/28/2018
(b) (4) Disposable pen

2.4. Indications for Use

Combination Product	Indications for Use
Insulin glargine	Improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
(b) (4) Disposable pen	To deliver a maximum of 80 insulin glargine units (U) per injection and the total deliverable content of the MYL-1501D cartridge is 300 U

2.5. Dosage and Administration

- Individualize dosage based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, prior insulin use
- Administer subcutaneously once daily at any time of day, but at the same time every day.
- Do not dilute or mix with any other insulin or solution.
- Rotate injection sites to reduce the risk of lipodystrophy.
- Closely monitor glucose when changing to SEMGLEE and during initial weeks thereafter.

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Date - Version	Location
(b) (4)	(b) (4) Disposable pen Device Master File	CDRH Image

NDA 210605	Sequence 0000 submitted on 04/27/2017	CDER EDR
NDA 210605	Sequence 30 submitted on 02/28/2018	CDER EDR

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

The device constituent part of the MYL-1501D combination product is composed of the [redacted] Disposable Pen Body Subassembly, the [redacted] Disposable Pen Cartridge Holder and the [redacted] Disposable Pen Cap [redacted] are the Design Authority for the device and the holder of the device master file [redacted] Disposable Pen Device Master File).

Figure 3.2.P.2.4/ 1: An Illustration of the MYL-1501D Combination Product, as Received by the User[1]

Table 3.2.P.7/7: Overview of the MYL-1501D PFP Components

Device Component	Constituent Component	Material	DMF/MAF Reference	Supplier
Pen body subassembly	(b) (4)			
Cartridge holder				
Pen cap				

Principles of Operation

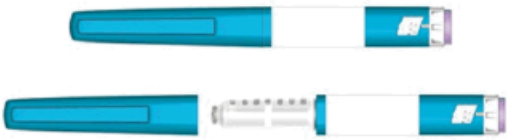
Each MYL-1501D PFP contains in total 300 insulin glargine units (U) (in 3 mL of 100 U/mL solution for injection). The MYL-1501D PFP is designed to deliver a maximum of 80 U per injection. Doses from 1 to 80 U can be set in increments of 1 U. These are consistent with the reference product Lantus

Prior to injection, the pen cap is removed and a new pen needle is attached to the front end of the cartridge holder. In its initial position, the DSK (located at the rear end of the device) is flush with the body and "0" is displayed in the dose window. The dose is pre-selected by rotating the DSK and the number of insulin glargine units (U) is displayed in the dose window. Numerals on the outside of the DSK are visible through the dose window of the body to indicate the selected dose. The dialing mechanism allows dosage increments of 1 U.

The injection is then performed by pushing the dose button. The user pushes on the button, which locks the set back and DSK, so that they rotate and translate together. The rotation of the set back is transmitted to the lead screw, and the rotation of the lead screw drives the plunger rod forward to push the cartridge plunger stopper and deliver the dose. During dose delivery, the DSK rotates, clicking down through each unit administered. Once the injection is complete, the dose button will have returned to its original position and "0" is displayed in the dose window. The display of "0" assures the user that the injection is complete.

Comparison between the RLD (Lantus® SoloSTAR®, Sanofi-Aventis) and the proposed MYL-1501D

Table 3.2.P.2.4/ 1: Comparison of the User Interfaces for Lantus SoloSTAR and the MYL-1501D Combination Product

Company	Sanofi-Aventis	Mylan Inc
Name	Lantus SoloSTAR	MYL-1501D Combination Product
Composition	Lantus SoloSTAR is a disposable pre-filled pen (PFP) for the injection of insulin glargine. The PFP is approximately 16 to 17 cm in length with the pen cap attached. Each Lantus SoloSTAR contains in total 300 insulin glargine units (U) (in 3 mL of 100 U/mL solution for injection). Doses from 1 to 80 U can be set in increments of 1 U. An indicative scale is printed on the cartridge holder of the PFP with graduations from 20 U to 260 U in increments of 40 U.	The MYL-1501D combination product is a disposable pre-filled pen (PFP) for the injection of insulin glargine. The PFP is approximately 16 to 17 cm in length with the pen cap attached. Each MYL-1501D PFP contains in total 300 insulin glargine units (U) (in 3 mL of 100 U/mL solution for injection). Doses from 1 to 80 U can be set in increments of 1 U. An indicative scale is printed on the cartridge holder of the PFP with graduations from 20 U to 260 U in increments of 40 U.
Component Color	The Lantus SoloSTAR is grey with a purple injection button.	The MYL-1501D PFP is blue with a purple injection button.
Disposable Pen	 Image representative of Lantus SoloSTAR	 Image representative of the MYL-1501D PFP
Packaging Configuration	Provided in a package of 5 Lantus SoloSTAR PFP	Provided in a carton containing 1 MYL-1501D PFP.[2]

Company	Sanofi-Aventis	Mylan Inc
Package Insert	PIL and IFU	PIL and IFU
Carton	(b) (4)	
Storage		

***Reviewer Comment**: The device description is comparable to the reference product Lantus, and is acceptable.*

Device Characteristic	Description / Specification
Injector Name	(b) (4) Disposable pen
Injector Platform Name	n/a
Priming Dose / Volume	2 U
Dose accuracy	Comply with ISO 11608-1: 2014
Injection Time	User dependent; Hold 10 seconds after injection
Injection Site	subcutaneous injection
Injection tissue and depth of injection	Depends on the commercial needle used
Audible / visual feedback	yes
Cap Removal Force	(b) (4) N
Activation Force	User dependent
Visibility of medication container	yes
Last Dose Specifications and Safety Features	Comply with ISO 11608-1: 2014
Needle Specifications • Length(s) • Gauge(s) • Connection type o ISO 11608-2:2012 o Prestaked	Commercial needle (BD Ultra-Fine™ needles are compatible with this pen). Comply with ISO 11608-2:2012
Type of Use (e.g. single use, disposable, reusable, other)	Multi-use, disposable

Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Self-administer for adult patients with diabetes mellitus, or healthcare provider
Injection mechanism (e.g., manual piston, spring, gas, etc.)	manual piston
Method of actuation	Pressing the purple injection button
Automated Functions	n/a
Residual Medication	n/a
Delivered Volume (for single dose or selectable volume range for multidose pens)	Up to 80 U per injection
Drug Container Type	Clear, colorless, Type I borosilicate glass cartridges
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	U
Environments of use	home
Storage conditions and expiry	(b) (4)
Graduation marks / fill lines	yes
Preparation and administration (describe all that are applicable) • Warm to room temp prior to injection • Assembling components • Prime steps • Setting dose • Skin preparation steps (e.g., pinch skin, inject through clothing, etc.) • Changing / disposing needles • Etc.	(b) (4)
Safety Features • Needle safety	no

Electronics / Data transmission • Display • Control functions • Data transmission technology • Data being transferred	n/a
Material composition of injector	(b) (4)

5. DESIGN CONTROL REVIEW

5.1. Design Review Summary

The device design, development, verification and validation data contained in this submission provide a summary of the device development conducted with a consideration of 21CFR Part 820.30 and EN ISO 13485:2012 – Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes.

5.1.1. Design Control Documentation Check

Design Control Requirement*	**Signed/Dated Document Present**		**Submission Location**
	Yes	**No**	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	x		EDR 3.2.P.5.1
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	x		EDR 3.2.P.2
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	x		EDR 1.11.1
Validation Data	x		EDR 3.2.P.2
• Human factors • Clinical data	x		EDR Module 5
Traceability Documentation	x		

5.1.2. Design Control Review

(b) (4)

. The submission complies with the following guidance and standards:

21 CFR Part 820.30 – Design Controls
Guidance for Industry Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (FDA, June 2013)
Guidance for Industry – Container Closure Systems for Packaging Human Drugs and Biologics (FDA, May 1999)
Guidance for Industry and Food and Drug Administration Staff – Applying Human Factors and Usability Engineering to Medical Devices (FDA, February 2016)
Guidance for Industry and Food and Drug Administration Staff – Use of International Standard (ISO) 10993-1, "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing within a Risk Management Process" (FDA, June 2016)
ISO 10993-1:2009 – Biological evaluation of Medical Devices – Part 1: Evaluation and Testing within a Risk Management Process
EN ISO 13485:2012 Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes
ISO 14971:2007 - Medical Devices – Application of Risk Management to Medical Devices
ISO 11608-1:2014 Needle-based Injection Systems for Medical Use – Requirements and Test Methods - Part 1: Needle-based Injection Systems
ISO 11608-2:2012 Needle-based Injection Systems for Medical Use – Requirements and Test Methods – Part 2: Needles
ISO 11608-3:2012 Needle-based Injection Systems for Medical Use – Requirements and Test Methods - Part 3: Finished containers
EN ISO 62366-1:2015 – Medical Devices. Application of Usability Engineering to Medical Devices

***Reviewer Comment**: The design control is acceptable.*

6. DESIGN VERIFICATION AND VALIDATION REVIEW

6.1. Summary of Design V&V Attributes

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	x		
To-be-marketed device was used in the pivotal clinical trial?		x	
Selectable dose range on device matches the labeled dose range for the medication?	x		
Verification methods relevant to specific use conditions as described in design documents and labeling	x		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability	x		

study)				
Traceability demonstrated for specifications to performance data		x		
Conformance to applicable standards demonstrated	ISO 11608-1:2014 – Needle based injection systems – Requirements and Test Methods	x		
	ISO 11608-2:2012 – Needles	x		
	ISO 11068-4:2006 – Electronic and Electromechanical Pen Injectors			x
	ISO 11608-5:2012 – Automated Functions	x		
Adherence to FDA Guidance: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products		x		
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry		x		
Discipline -Specific Design Verification / Validation adequately addressed	Biocompatibility	x		
	Sterility			x
	Software / Cybersecurity			x
	Electrical Safety / EMC			x
	Human Factors	x		

6.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device		x	
Bioequivalence Study utilized to-be-marketed device	x		
Simulated Actual Use Study utilized to-be-marketed device	x		

Design changes between the clinical and commercial pen configurations:

(b) (4)

(b) (4)

All these changes did not impact the Device Requirement Specification (DRS) between the clinical and commercial pen configurations. Both clinical pen and commercial pen met the performance requirement specifications. The comparison table is provided in Response to CMC IR dated January 10 located in EDR Sequence 30 submitted on 02/28/2018

6.3. Design Verification Review

Essential Performance Requirement	Specification	Verification	Validation	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)
Injection Depth	(b) (4)	n/a				
Injection Time		Y	Y	Y	Y	N
Dose Accuracy		Y	Y	Y	Y	Y
Visual/Audible Feedback		Y	Y	N	N	Y

	(b) (4)					
Activation Force		Y	Y	Y	Y	Y
Needle Length		n/a				
Needle Gauge		n/a				
Needle Connection Type		n/a				
Needle Resistance to Bend / Fracture		n/a				
Cap Removal Force		Y	Y	Y	Y	N

Table 3.2.P.2.4/ 35: Design Verification Test Rationale for MYL-1501D PFP Manufactured on (b) (4) Assembly Line Biocon, Bangalore.

Input Design Requirement	Specification	Attribute Tested on Mikron Final Assembly MYL-1501D PFPs	Rationale
Dose accuracy in standard in-use conditions	(b) (4)	Yes	Ensures dose accuracy compliance at ambient operating conditions following (b) (4) (b) (4) assembly
Dose accuracy following freefall		Yes	Ensures dose accuracy compliance at ambient operating conditions after freefall following (b) (4) assembly
System resistance to freefall		Yes	Ensures dose accuracy compliance at ambient operating conditions after freefall following correct assembly on (b) (4) assembly line, therefore verification is required
Cartridge holder removal force – axial load		Yes	Verification required of the fitment and security of the cartridge holder in body post (b) (4) assembly, therefore verification is required
Cartridge holder removal force – side load		Yes	Verification required of the fitment and security of the cartridge holder in body post (b) (4) assembly, therefore verification is required
Cap attachment force		Yes	Verification required confirming the fitment security post (b) (4) assembly
Cap detachment force		Yes	Verification required confirming the fitment security post (b) (4) assembly

Dose Accuracy

The MYL-1501D PFP contains 3 mL of 100 U/mL insulin glargine equating to 300 U (i.e. each 0.01 mL of 100 U/mL insulin glargine equates to 1 U). The lowest selectable dose is 1 U (i.e. a volume of 0.01mL) and the highest selectable dose is 80 U (i.e. a volume of 0.80mL).

Dose accuracy performance and functionality/robustness testing was performed in accordance with ISO 11608-1:2014. The MYL-1501D PFP was subjected to in-use cool, ambient (standard) and warm environmental conditions, cold and hot storage conditions, freefall and vibration robustness, each followed by both functional and performance (dose accuracy) assessment. The BD Ultra-Fine 31G x 5 mm needle was used throughout the DVT as the "standard test needle".

Table 3.2.P.2.4/ 10: Dose Accuracy and Device Functionality in Cool In-Use Conditions

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under the operating conditions 5°C ± 3°C/uncontrolled RH				Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for 97.5% reliability) = 0				Pass
Dose Accuracy (Needle BD Ultra-Fine 31G x 5 mm)	n = 60 pens (MYL-1501D cartridge) (Commercial pen configuration)	Requirement (b) (4)	Results (mL)			
			Dose	v_{min} (0.01 mL)	v_{mid} (0.40 mL)	v_{max} (0.80 mL)	Pass
			Average	0.01	0.40	0.80	
			SD*	0.001	0.004	0.005	
			Min	0.01	0.39	0.79	
			Max	0.02	0.41	0.81	
			k_{actual}	6.076	5.170	8.663	Pass

*Standard deviation reported to 3 decimal places for information

Table 3.2.P.2.4/ 15: Dose Accuracy in Warm In-Use Conditions

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under the operating conditions 40°C ± 2°C/50% ± 10% RH				Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for 97.5% reliability) = 0				Pass
Dose Accuracy (Needle BD Ultra-Fine 31G x 5 mm)	n = 60 pens (MYL-1501D cartridge) (Commercial pen configuration)	Requirement (b) (4)	Results (mL)			
			Dose	v_{min} (0.01 mL)	v_{mid} (0.40 mL)	v_{max} (0.80 mL)	Pass
			Average	0.01	0.40	0.80	
			SD*	0.002	0.005	0.006	
			Min	0.01	0.39	0.79	
			Max	0.01	0.41	0.82	
			k_{actual}	5.078	3.797	5.983	Pass

* Standard deviation reported to 3 decimal places for information

Table 3.2.P.2.4/ 16: Dose Accuracy Following Freefall

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 following freefall testing				Met requirements
Mechanical Function	Sample Size n = 30 pens	Functionality: Number of mechanical failures (for 95% reliability) = 0				Pass
Dose Accuracy (Needle BD Ultra-Fine 31G x 5 mm)	n = 30 pens (MYL-1501D cartridge) (Commercial pen configuration - Mylan PMS 306C blue)	Requirement (b) (4)	Results (mL)			
			Dose	v_{min} (0.01 mL)	v_{mid} (0.40 mL)	v_{max} (0.80 mL)	Pass
			Average	0.01	0.40	0.80	
			SD*	0.001	0.002	0.003	
			Min	0.01	0.40	0.80	
			Max	0.01	0.41	0.81	
			k_{actual}	11.480	11.940	12.860	Pass

* Standard deviation reported to 3 decimal places for information

Table 3.2.P.2.4/ 17: Dose Accuracy Following Vibration (Needle BD Ultra-Fine 31G x 5 mm)

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 following vibration testing				Met requirements
Mechanical Function	Sample Size n = 20 pens	Functionality: Number of mechanical failures (for 95% reliability) = 0				Pass
Dose Accuracy (Needle BD Ultra-Fine 31G x 5 mm)	n = 20 pens (Water filled cartridge) (Commercial pen configuration)	Requirement (b) (4)	Results (mL)			
			Dose	v_{min} (0.01 mL)	v_{mid} (0.20 mL)	v_{max} (0.80 mL)
			Average	0.01	0.20	0.80
			SD*	0.001	0.002	0.005
			Min	0.01	0.20	0.79
			Max	0.02	0.21	0.81
			k_{actual}	5.167	3.827	6.869
						Pass

* Standard deviation reported to 3 decimal places for information

Table 3.2.P.2.4/ 18: Dose Accuracy Following Cold Storage Conditions (Needle BD Ultra-Fine 31G x 5mm)

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under storage at 5°C ± 3°C/uncontrolled RH conditions for 96 hours and allowed to equilibrate to Room Temperature (RT) for a minimum of 4 hours				Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for 97.5% reliability) = 0				Pass
Dose Accuracy (Needle BD Ultra-Fine 31G x 5mm)	n = 60 pens (Water filled cartridge) (Commercial pen configuration)	Requirement (b) (4)	Results (mL)			
			Dose	v_{min} (0.01 mL)	v_{mid} (0.20 mL)	v_{max} (0.80 mL)
			Average	0.01	0.20	0.80
			SD*	0.001	0.002	0.006
			Min	0.01	0.20	0.79
			Max	0.01	0.21	0.81
			k_{actual}	7.200	4.582	7.004
						Pass

* Standard deviation reported to 3 decimal places for information

Table 3.2.P.2.4/ 19: Dose Accuracy Following Hot Storage Conditions (Needle BD Ultra-Fine 31G x 5 mm)

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under storage at 40°C ± 2°C/50% ± 10% RH conditions for 96 hours and allowed to equilibrate to RT for a minimum of 4 hours				Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for 97.5% reliability) = 0				Pass
Dose Accuracy (Needle BD Ultra-Fine 31G x 5 mm)	n = 60 pens (Water filled cartridge) (Commercial pen configuration)	Requirement (b) (4)	Results (mL)			
			Dose	v_{min} (0.01 mL)	v_{mid} (0.20 mL)	v_{max} (0.80 mL)
			Average	0.01	0.20	0.80
			SD*	0.002	0.003	0.006
			Min	0.01	0.19	0.77
			Max	0.02	0.21	0.81
			k_{actual}	4.775	3.150	6.299
						Pass

* Standard deviation reported to 3 decimal places for information

Dose accuracy at last dose

Table 3.2.P.2.4/ 20: Dose Accuracy at Last Dose, in Standard In-Use Conditions (Needle BD Ultra-Fine 31G x 5 mm)

DRS Requirement		The pen must maintain volumetric accuracy at last dose as per ISO 11608-1:2014 under the operating conditions 23°C ± 5°C/50% ± 25% RH			Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for 97.5% reliability) = 0			Pass
Dose Accuracy (Needle BD Ultra-Fine 31G x 5 mm)	n = 60 pens (Water filled cartridge) (Commercial pen configuration)	Requirement (b) (4)	Results (mL)		
			Dose	0.20 mL (last dose)	Pass
			Average	0.20	
			SD*	0.003	
			Min	0.19	
			Max	0.20	
			k_{actual}	3.061	Pass

* Standard deviation reported to 3 decimal places for information

Volume expelled during dose selection

Table 3.2.P.2.4/ 22: Volume Expelled During Dose Selection

DRS Requirement		Volume expelled during dose selection is minimal			Met requirements
Volume expelled during dose selection	Sample Size n = 30 pens (Water filled Cartridge in Commercial pen configuration)	Number of failures (for 95% reliability) = 0			Yes
		Requirement (b) (4)	Results (µL)		
			Average	1	Yes
			Range	0 to 2	
			SD	1	

***Reviewer Comment**: The dese accuracy testing complies with ISO 11608-1:2014, which is the same as the reference product Lantus, and another approved insulin glargine pen (NDA208722, Lusduna). Per ISO 11608-1:2014, three dose sizes were used such that Vset is delivered from the front 1/3, middle 1/3 and rear 1/3 divisions of the container closure. The dose accuracy acceptance criteria were determined from ISO 11608-1:2014 requirements,* (b) (4)

(b) (4)

Dose accuracy testing was performed using drug product-filled cartridges for cool, ambient (standard) and warm conditions, and following freefall testing. Water was used within the cartridges in the dose accuracy assessment for vibration, dry heat and cold storage studies. As the density of insulin glargine is 1.0024 g/mL at standard temperature [23°C] against water of 0.9975 g/mL at the same temperature, the two liquids have similar density and viscosity, the use of water in some of the dose accuracy testing (vibration, dry heat and cold storage studies) is acceptable.

The reviewer agrees that the above dose accuracy performance of the pen following conditioning as prescribed by ISO 11608-1:2014 (in-use cool, storage in dry heat and cold conditions, free fall and vibration) and last dose all met the ISO 11608-1:2014 prescribed dose accuracy acceptance criteria, with no mechanical function failures. In use standard conditions testing with different commercial needles are shown under Needle compatibility testing, which also passed

acceptance criteria. These demonstrate acceptable delivery performance of the commercial pen configuration MYL-1501D PFP.

Hold time Necessary after End of Injection

Injection time is largely user dependent, based upon applied force. The hold time following injection ensures that the entire dose is delivered once the plunger is pushed to the end of stroke and is within the time specified within the IFU.

Table 3.2.P.2.4/ 21: Hold Time Necessary After End of Injection (Terumo Nanopass 34G x 4 mm needle)

DRS Requirement		Hold time necessary after end of injection			Met requirements
Hold time after injection (Terumo Nanopass 34G x 4 mm needle)	Sample Size n = 60 pens (MYL-1501D cartridge) (Commercial pen configuration)	Number of failures (for 95% reliability) = 0			Yes
		Requirement	Results (seconds)		
		(b) (4)	Average	4	Yes
			Range	4 to 6	
			SD	1	

Needle Compatibility Testing

Verification of the finished cartridge and needles suitability for use with the MYL-1501D PFP were conducted on the following specific commercialized pen needles:

- BD Ultra-Fine™ 31G x 5 mm
- BD Ultra-Fine 32G x 4 mm
- Novo Nordisk NovoFine® 32G x 6 mm
- Terumo Nanopass® 34G x 4 mm

Dose accuracy, cartridge compatibility, needle thread pitch, needle attachment and needle detachment torque were tested with these four commercial needles. All test passed acceptance criteria.

Table 3.2.P.2.4/ 11: Dose Accuracy in Standard In-Use Conditions (Needle BD Ultra-Fine 31G x 5 mm)

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under the operating conditions 23°C ± 5°C/50% ± 25% RH				Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for 97.5% reliability) = 0				Pass
Dose Accuracy (Needle BD Ultra-Fine 31G x 5 mm)	n = 60 pens (MYL-1501D cartridge) (Commercial pen configuration - Mylan PMS 306C blue)	Requirement	Results (mL)			
		(b) (4)	Dose	V_{min} (0.01 mL)	V_{mid} (0.40 mL)	V_{max} (0.80 mL)	Pass
			Average	0.01	0.40	0.80	
			SD*	0.001	0.003	0.004	
			Min	0.01	0.39	0.79	
			Max	0.02	0.41	0.81	
			k_{actual}	5.294	5.983	8.412	Pass

* Standard deviation reported to 3 decimal places for information

Table 3.2.P.2.4/ 12: Dose Accuracy in Standard In-Use Conditions (Needle BD Ultra-Fine 32G x 4 mm)

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under the operating conditions 23°C ± 5°C/50% ± 25% RH				Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for 97.5% reliability) = 0				Pass
Dose Accuracy (Needle BD Ultra-Fine 32G x 4mm)	n = 60 pens (MYL-1501D cartridge) (Commercial pen configuration - Mylan PMS 306C blue)	Requirement (b) (4)	Results (mL)			
			Dose	v_{min} (0.01 mL)	v_{mid} (0.40 mL)	v_{max} (0.80 mL)
			Average	0.01	0.40	0.80
			SD*	0.001	0.003	0.013
			Min	0.01	0.39	0.70
			Max	0.01	0.41	0.81
			k_{actual}	12.310	7.626	3.015

Pass (Dose Accuracy rows); Pass (k_{actual})

* Standard deviation reported to 3 decimal places for information

Table 3.2.P.2.4/ 13: Dose Accuracy in Standard In-Use Conditions (Needle Novo Nordisk NovoFine 32G x 6 mm)

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under the operating conditions 23°C ± 5°C/50% ± 25% RH				Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for 97.5% reliability) = 0				Pass
Dose Accuracy (Needle Novo Nordisk NovoFine 32G x 6 mm)	n = 60 pens (MYL-1501D cartridge) (Commercial pen configuration - Mylan PMS 306C blue)	Requirement (b) (4)	Results (mL)			
			Dose	v_{min} (0.01 mL)	v_{mid} (0.40 mL)	v_{max} (0.80 mL)
			Average	0.01	0.40	0.80
			SD*	0.001	0.003	0.005
			Min	0.01	0.39	0.79
			Max	0.01	0.41	0.81
			k_{actual}	10.845	7.467	8.254

Pass (Dose Accuracy rows); Pass (k_{actual})

* Standard deviation reported to 3 decimal places for information

Table 3.2.P.2.4/ 14: Dose Accuracy in Standard In-Use Conditions (Needle Terumo Nonopass 34G x 4 mm)

DRS Requirement		The pen must maintain volumetric accuracy as per ISO 11608-1:2014 under the operating conditions 23°C ± 5°C/50% ± 25% RH				Met requirements
Mechanical Function	Sample Size n = 60 pens	Functionality: Number of mechanical failures (for 97.5% reliability) = 0				Pass
Dose Accuracy (Terumo Nonopass 34G x 4 mm)	n = 60 pens (MYL-1501D cartridge) (Commercial pen configuration - Mylan PMS 306C blue)	Requirement (b) (4)	Results (mL)			
			Dose	v_{min} 0.01 mL	v_{mid} (0.40 mL)	v_{max} (0.80 mL)
			Average	0.01	0.40	0.80
			SD*	0.001	0.003	0.005
			Min	0.01	0.39	0.79
			Max	0.01	0.41	0.82
			k_{actual}	6.698	6.138	7.637

Pass (Dose Accuracy rows); Pass (k_{actual})

* Standard deviation reported to 3 decimal places for information

Table 3.2.P.2.4/ 6: External Component Suitability

Input Design Requirement	Device Requirement Specification	Rationale	Verification Type (Configuration)	Reliability	Met Requirement
Cartridge compatibility	Must be compatible with Biocon insulin glargine 3 mL cartridge	As specified in ISO 11608-1:2014, Section 5.5 part m), the NIS shall be designed to function with its specified containers.	Tolerance analysis (Commercial pen configuration)	95.0%	Yes
Needle thread pitch (on cartridge holder)	(b) (4)	Needle compatibility requirement as specified in ISO 11608-2:2012 Section 4.2.1	Tolerance analysis (Commercial pen configuration)	95.0%	Yes
Needle attachment		As specified in ISO 11608-2:2012 Section 4.9, compatibility with any NIS shall be claimed only after testing in accordance with Clause 11. One type of needle from each manufacturer tested.	Test protocol n = 60 (Commercial pen configuration)	95.0%	Yes

Table 3.2.P.2.4/ 7: Needle Detachment Torque (BD Ultra-Fine 31G x 5 mm)

Test Requirement	Sample Size	Needle detachment torque (after attachment at 0.06 Nm – 0.08 Nm)			Met requirement
Needle detachment torque: BD Ultra-Fine 31G x 5 mm	n = 60 needles (Commercial pen configuration)	Number of mechanical failures (for 95.0% reliability) = 0			Yes
		Requirement	Results (Nm)		
		(b) (4)	Average	0.06	Yes
			Range	0.04 to 0.07	
			SD	0.01	

Table 3.2.P.2.4/ 8: Needle Detachment Torque (Novo Nordisk NovoFine 32G x 6 mm)

Test Requirement	Sample Size	Needle detachment torque (after attachment at 0.06 Nm – 0.08 Nm)			Met requirement
Needle detachment torque: Novo Nordisk NovoFine 32G x 6 mm	n = 60 needles (Commercial pen configuration)	Number of mechanical failures (for 95% reliability) = 0			Yes
		Requirement (b) (4)	Results (Nm)		
			Average	0.06	Yes
			Range	0.05 to 0.07	
			SD	0.01	

Table 3.2.P.2.4/ 9: Needle Detachment Torque (Terumo Nanopass 34G x 4 mm)

Test Requirement	Sample Size	Needle detachment torque (after attachment at 0.06 Nm – 0.08 Nm)			Met requirement
Needle detachment torque: Terumo Nanopass 34G x 4 mm	n = 60 needles (Commercial pen configuration)	Number of mechanical failures (for 95% reliability) = 0			Yes
		Requirement (b) (4)	Results (Nm)		
			Average	0.06	Yes
			Range	0.05 to 0.10	
			SD	0.01	

***Reviewer Comment**: The above data show that the four commercial needles tested (BD Ultra-Fine™ 31G x 5 mm, BD Ultra-Fine 32G x 4 mm, Novo Nordisk NovoFine® 32G x 6 mm and Terumo Nanopass® 34G x 4 mm) passed ISO 11608-2:2012 requirement for general fit (as assessed by dose accuracy at minimum and maximum doses per ISO 11608-1:2014 at standard atmosphere) and attachment and removal torque.*

The following are **user-related forces testing**. All testing passed the functionality requirement.

Pen Cap Attachment Force

Table 3.2.P.2.4/ 25: Pen Cap Attachment Force

DRS Requirement		Pen Cap Attachment Force			Met requirements
Pen cap attachment force	Sample Size n = 30 pens (Commercial pen configuration - Mylan PMS 306C blue)	Number of failures (for 97.5% reliability) = 0			Yes
		Requirement	Results (N)	Pen Cap Attachment Force	
		(b) (4)	Average	5.7	Yes
			Range	3.7 to 7.7	
			SD	0.9	

Pen Cap Detachment Force

Table 3.2.P.2.4/ 26: Pen Cap Detachment Force

DRS Requirement		Pen Cap Detachment Force			Met requirements
Pen cap detachment force	Sample Size n = 30 pens (Commercial pen configuration - Mylan PMS 306C blue)	Number of failures (for 97.5% reliability) = 0			Yes
		Requirement (b) (4)	Results (N)	Pen Cap Detachment Force	
			Average	5.0	Yes
			Range	3.8 to 5.7	
			SD	0.5	

Dose Selection Torque (Dose Increase and Dose Decrease)

Table 3.2.P.2.4/ 27: Dose Selection Torque (Dose Increase and Dose Decrease)

DRS Requirement		Dose selection torque (dose increase and dose decrease)				Met requirements
Dose selection torque (dose increase and dose decrease)	Sample Size n = 30 pens (each) (Commercial pen configuration)	Number of failures (for 95% reliability) = 0				Yes
		Requirement (b) (4)	Results (ozf.in)	Dose increase	Dose decrease	Yes
			Average	0.8	0.6	
			Range	0.6 to 1.3	0.4 to 0.8	
			SD	0.2	0.1	

Dose Selection Override Torque (at 0 Volume and at Last Dose)

Table 3.2.P.2.4/ 28: Dose Selection Override Torque (at 0 Volume and at Last Dose)

DRS Requirement		Dose selection torque (at 0 volume and at last dose)				Met requirements
Dose selection override torque (at 0 volume and at last dose)	Sample Size n = 30 pens (Commercial pen configuration)	Number of failures (for 97.5% reliability) = 0				Yes
		Requirement (b) (4)	Results (ozf.in)	at 0 volume	at last dose	Yes
			Average	95.9	33.9	
			Range	87.6 to 103.1	32.1 to 52.2	
			SD	3.3	5.7	

Dose Selection Override Torque (at Maximum Selectable Volume)

Table 3.2.P.2.4/ 29: Dose Selection Override Torque (at Maximum Selectable Volume)

DRS Requirement		Dose selection torque (at max volume)			Met requirements
Dose selection override torque (at max volume)	Sample Size n = 30 pens (Commercial pen configuration)	Number of failures (for 97.5% reliability) = 0			Yes
		Requirement (b) (4)	Results (ozf.in)	at max volume	
			Average	51.3	Yes
			Range	42.6 to 59.2	
			SD	5.1	

Clip Stiffness (when Lifting)

Table 3.2.P.2.4/ 30: Clip Stiffness (when Lifting)

DRS Requirement		Clip stiffness (when lifting)			Met requirements
Clip stiffness (when lifting)	Sample Size n = 30 pens (Commercial pen configuration - Mylan PMS 306C blue)	Number of failures (for 95% reliability) = 0			Yes
		Requirement	Results (N/mm)		
		(b) (4)	Average	0.493	Yes
			Range	0.479 to 0.506	
			SD	0.007	

Injection Force (without Cartridge and Needle)

Table 3.2.P.2.4/ 31: Injection Force (without Cartridge and Needle)

DRS Requirement		Injection force (without cartridge and needle)			Met requirements
Injection force (without cartridge and needle)	Sample Size n = 30 pens (Commercial pen configuration – Mylan PMS 306C blue)	Number of failures (for 97.5% reliability) = 0			Yes
		Requirement	Results (N)		
		(b) (4)	Average	2.6	Yes
			Range	2.3 to 2.7	
			SD	0.1	

An IR was sent on 01/10/2018:

You provided design verification for Injection Force (without Cartridge and Needle) and mentioned that Injection Force (with Cartridge and Needle) are tested in the stability protocol. Please provide verification and validation for Injection Force (with Cartridge and Needle).

The Sponsor responded on 02/28/2018 and provided the injection force (with cartridge and needle) data generated at the initial timepoint and after storage of the MYL-1501D PFP at 5°C, 25°C and 40°C for 18 months. This data demonstrates that the force required to push down on the button (and dose setting knob) to make an injection (into air) is such that the user can administer the dose without having to use excessive force.

Device Requirement		Injection Force (with Cartridge and Needle)						Met Requirements
Injection Force (with Cartridge and Needle)	Sample Size n = 30 PFPs[6]	Number of failures (for 95% reliability) = 0						Yes
		Requirement	Results (N)	DVT (Initial T=0)	Stored at 5°C (18 months)	Stored at 25°C (18 months)	Stored at 40°C (18 months)	
		(b) (4)	Mean	14	15	15	15	Yes
			Range	12 to 17	13 to 17	12 to 18	12 to 24	

[6] - Water filled cartridge; commercial pen configuration – Mylan PMS 306C blue; injected into air

***Reviewer Comment**: Water was used in this testing, instead of the final drug product. As insulin glargine has similar density (1.0024 g/mL at room temperature) with water (0.9975 g/mL at room temperature), it's acceptable to use water in this testing.*

Cartridge Holder Removal Force

Table 3.2.P.2.4/ 33: Cartridge Holder Removal Force – Axial Load

Test Requirement	Sample Size	Cartridge Holder Removal Force – Axial Load			Met Requirements
Cartridge holder removal force – axial load	n = 30 pens (Water filled Cartridge) (Commercial pen configuration - Mylan PMS 306C blue)	Number of failures (for 95% reliability) = 0			Yes
		Requirement	Results (N)		
		(b) (4)	Average	362.1	
			Range	266.2 to 385.0	
			SD	20.4	

Table 3.2.P.2.4/ 34: Cartridge Holder Removal Force – Side Load

Test Requirement	Sample Size	Cartridge Holder Removal Force – Side Load			Met Requirements
Cartridge holder removal force – side load	n = 30 pens (Water filled cartridge) (Commercial pen configuration - Mylan PMS 306C blue)	Number of failures (for 95% reliability) = 0			Yes
		Requirement	Results (N)		
		(b) (4)	Average	67.6	
			Range	62.1 to 75.7	
			SD	2.9	

Additional testing

The following physical attributes further demonstrate that the MYL-1501D PFP meets specific requirements of ISO 11608–1:2014 and ISO 11608-5:2012 – Needle-based Injection Systems for Medical Use – Requirements and Test Methods – Part 5: Automated Functions, as well as those attributes specific to the MYL-1501D PFP required in the DRS.

Table 3.2.P.2.4/ 32: Design Requirements of the MYL-1501D PFP Verified by Design Verification Tests

Design Requirement	Device Requirement Specification	Rationale	Verification Type	Sample Number	Reliability	Meets Criteria
Dose selection near end of use	(b) (4)	Compliance to ISO 11608-1:2014, General Requirements Part j.1	Design rationale	n/a	n/a	Yes
Product contact with device		ISO 11608-5:2012 4.1(d)	Design rationale	n/a	n/a	Yes
System with pen cap does not roll on a surface of ≥ 5 degrees incline		The injector must include anti roll features in its design to prevent rolling during use or storage	Verification Test (Commercial pen configuration - Mylan PMS 306C blue)	n = 60	95.0%	Yes
Ready for injection indicator: visual		Compliance to ISO 11608-1:2014, General Requirements Part f	Verification Test (Commercial pen configuration)	n = 120	97.5%	Yes

Design Requirement	Device Requirement Specification	Rationale	Verification Type	Sample Number	Reliability	Meets Criteria
Ready for injection indicator: visual	(b) (4)	Compliance to ISO 11608-1:2014, General Requirements Part f	Verification Test (Commercial pen configuration	n = 120	97.5%	Yes
Start of injection indicator: visual and tactile		Compliance to ISO 11608-1:2014, General Requirements Part g	Verification Test (Commercial pen configuration)	n = 120	97.5%	Yes
Start of Injection indicator: audible		Compliance to ISO 11608-1:2014, General Requirements Part g	Verification Test (Commercial pen configuration)	n = 120	97.5%	Yes
End of injection indicator: visual and tactile		Compliance to ISO 11608-1:2014, General Requirements Part h	Verification Test (Commercial pen configuration)	n = 120	97.5%	Yes
End of injection indicator: visual		Compliance to ISO 11608-1:2014, General Requirements Part h	Verification Test (Commercial pen configuration)	n = 120	97.5%	Yes
End of injection indicator: audible		Compliance to ISO 11608-1:2014, General Requirements Part h	Verification Test (Commercial pen configuration)	n = 60	95.0%	Yes

Design Requirement	Device Requirement Specification	Rationale	Verification Type	Sample Number	Reliability	Meets Criteria
End of last dose injection indicator: visual and tactile	(b) (4)	Compliance to ISO 11608-1:2014, General Requirements Part h	Verification Test (Commercial pen configuration)	n = 60	95.0%	Yes
Ready for injection and end of injection indicators different: visual		Compliance to ISO 11608-1:2014, General Requirements Part h	Verification Test (Commercial pen configuration)	n = 120	97.5%	Yes
Ready for injection and end of injection indicators different: visual		Compliance to ISO 11608-1:2014, General Requirements Part f	Verification Test (Commercial pen configuration)	n = 120	97.5%	Yes
Remaining drug indicator: visual		Compliance to ISO 11608-1:2014, General Requirements Part a	Verification Test (Commercial pen configuration)	n = 120	97.5%	Yes
Dose selection increment indicator: visual		Compliance to ISO 11608-1:2014, General Requirements Part e	Verification Test (Commercial pen configuration)	n = 120	97.5%	Yes
Dose increment indicator: audible and tactile		Compliance to ISO 11608-1:2014, General Requirements Part e	Verification Test (Commercial pen configuration)	n = 60	95.0%	Yes

Design Requirement	Device Requirement Specification	Rationale	Verification Type	Sample Number	Reliability	Meets Criteria
Marking present on DSK and cartridge holder	(b) (4)	As specified in ISO 11608-1:2014, Section 11.1	Verification Test (Commercial pen configuration)	n = 60	95.0%	Yes
Marking legibility		As specified in ISO 11608-1:2014, Section 11.1	Verification Test (Commercial pen configuration)	n = 60	95.0%	Yes
Marking permanency		Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 60	95.0%	Yes
Dose reset		Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 120	97.5%	Yes
Dose selection marking alignment		Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 30	95.0%	Yes
Pen cap attachment indicator		Ensures user awareness of correct fitment of pen cap. The pen cap provides protection for the rubber seal prior to and during use	Verification Test (Commercial pen configuration)	n = 60	95.0%	Yes
Font style		Compliance to ISO 11608-1:2014, Section 13.2.1	Design rationale	n/a	n/a	Yes

Design Requirement	Device Requirement Specification	Rationale	Verification Type	Sample Number	Reliability	Meets Criteria
DSK markings font character height	(b) (4)	Compliance to ISO 11608-1:2014, Section 13.2.1	Verification Test (Commercial pen configuration)	n = 30	95.0%	Yes
DSK markings font character height for minor increment		Compliance to ISO 11608-1:2014, Section 13.2.1	Design rationale	n/a	n/a	Yes
DSK markings font character stroke width to character height ratio		Compliance to ISO 11608-1:2014, Section 13.2.1	Verification Test (Commercial pen configuration)	n = 30	95.0%	Yes
DSK markings font character width to character height ratio		Compliance to ISO 11608-1:2014, Section 13.2.1	Verification Test (Commercial pen configuration)	n = 30	95.0%	Yes
DSK font orientation		Compliance to ISO 11608-1:2014, General Requirements Part d	Design rationale	n/a	n/a	Yes
Dose window alignment		Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 60	95.0%	Yes
Marking contrast (all markings)		Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration - Mylan PMS 306C blue)	n = 60	95.0%	Yes

Design Requirement	Device Requirement Specification	Rationale	Verification Type	Sample Number	Reliability	Meets Criteria
Font spacing between charters to character width ratio	(b) (4)	Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 30	95.0%	Yes
Font spacing between lines to character height ratio		Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 30	95.0%	Yes
Dose window width		Compliance to ISO11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 30	95.0%	Yes
Dose pointer marking		Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 60	95.0%	Yes
Dose pointer protrusion from surface of system		Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 60	95.0%	Yes
Dose pointer protrusion into window		Compliance to ISO 11608-1:2014, General Requirements Part d	Verification Test (Commercial pen configuration)	n = 60	95.0%	Yes

Design Requirement	Rationale	Verification Type	Sample Number	Reliability	Meets Criteria
Drug inspection window visibility: radial degrees	Compliance to ISO 11608-1:2014, General Requirements Part a	Verification Test (Commercial pen configuration)	n = 60	95.0%	Yes

Biocompatibility

Assessment of the fluid path (the cartridge and the needle) is the scope of the CMC discipline and is not covered in this review memo as those are part of the container closure system.

Biocompatibility of the user contacts of the pen injector is provided in the submission and follows ISO 10993.

Table 3.2.P.2.4/ 51: Biocompatibility Tests Conducted on the Skin Contacting Components of the MYL-1501D PFP Components

Component Description	Material	Color	Tests conducted	Result
Pen Cap	(b) (4)	Blue	*In vitro*: Cell Cytotoxicity Elution, 48 hour single point	Pass Score = 0
			In vivo: Primary Dermal Irritation (saline, polyethylene glycol [PEG])	Negligible irritant (saline, PEG)
			Murine Local Lymph Node Assay (saline, PEG)	Non-sensitizer (saline, PEG)
Cartridge Holder		Clear (with black ink printing)	*In vitro*: Cell Cytotoxicity Elution, 48 Hour Single point	Pass Score = 0
			In vivo: Primary Dermal Irritation (saline, PEG)	Negligible irritant (saline, PEG)
			Murine Local Lymph Node Assay (saline, PEG)	Non-sensitizer (saline, PEG)
Body		Blue	*In vitro*: Cell Cytotoxicity Elution, 48 hour single point	Pass Score = 0
			In vivo: Primary Dermal Irritation (saline, PEG)	Negligible irritant (saline, PEG)
			Murine Local Lymph Node Assay (saline, PEG)	Non-sensitizer (saline, PEG)
Dose Setting Knob (DSK)		White (with black ink printing)	*In vitro*: Cell Cytotoxicity Elution, 48 hour single point	Pass Score = 0
			In vivo: Primary Dermal Irritation (saline, PEG)	Negligible irritant (saline, PEG)
			murine local Lymph node Assay (saline, PEG)	Non-sensitizer (saline, PEG)
Button		Purple	*In vitro*: Cell Cytotoxicity Elution, 48 hour single point	Pass Score = 0
			In vivo: Primary Dermal Irritation (saline, PEG)	Negligible irritant (saline, PEG)
			Murine Local Lymph Node Assay (saline, PEG)	Non-sensitizer (saline, PEG)

saline: 0.9% sodium chloride (NaCl)

***Reviewer Comment**: The user contact of the pen injector is categorized as surface contact with intact skin. The provided biocompatibility information to evaluate cytotoxicity, sensitization and irritation endpoints of the user contacts is appropriate and acceptable for the intended use of the user contacting of the combination product.*

Stability

Based on available long term stability data from DP, a shelf-life of 24 months is proposed for the DP when stored at 5°C±3°C.

Table 3.2.P.2.4/ 46: Device Component Shelf Life and Use Life Storage Conditions

(b) (4)

[redacted]

Table 3.2.P.2.4/ 47: MYL-1501D PFP Stability Study

Type	Target Real Time		Accelerated Aging Equivalent	
	Time (Months)	At Temperature (°C)	Time (Months)	At Temperature (°C)
Component storage	36	5	3.2	40
	36	25	12.8	40
	36	30	18	40
PFP storage (unused)	60	5	5.3	40

Table 3.2.P.2.4/ 48: Functionality and Performance Tests Conducted During Devic Stability Studies

Design Input Requirement	Sample Number (n)	Reliability	Meets Criteria
Hold time necessary after end of injection	60	95.0%	Yes
Volumetric accuracy as per ISO 11608-1:2014 under the operating conditions 23°C ± 5°C/50% ± 25% RH	60	95.0%	Yes
Volumetric accuracy as per ISO 11608-1:2014 following freefall testing	30	95.0%	Yes
Volumetric accuracy as per ISO 11608-1:2014 following vibration testing	20	95.0%	Yes
Volume expelled during dose selection is minimal	30	95.0%	Yes
Cartridge holder removal force – Axial load	30	95.0%	Yes
Cartridge holder removal force – Side load	30	95.0%	Yes
Pen cap attachment and detachment force	30	95.0%	Yes
Dose selection torque (dose increase and dose decrease)	30	95.0%	Yes
Dose selection override torque (at 0 volume, at last dose and at maximum selectable volume)	30	95.0%	Yes
Injection force (with cartridge and needle)	30	95.0%	Yes
Dose reset	120	97.5%	Yes
Dose selection play (prior to increment change)	30	95.0%	Yes
Dose selection direction change hysteresis	30	95.0%	Yes

***Reviewer Comment**: The stability testing includes the essential performance requirements of the pen injector. The provided stability information is adequate for device performance.*

Shipping Verification

Shipping verification was performed according to ASTM D4169-16 DC13. (b) (4)

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(b) (4)

7. RISK ANALYSIS

7.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	x		

Mitigations are adequate to reduce risk to health	x		
Version history demonstrates risk management throughout design / development activities	x		

7.2. Summary of Risk Analysis

Risk management for the MYL-1501D combination product incorporates risk management relating to: design and molded component manufacture from BD as Design Authority and component supplier, final assembly from Biocon as manufacturer of the MYL-1501D combination product, and design and user risk management conducted by Mylan which considered the BD and Biocon risk management programs.

An IR was sent on 01/10/2018:

> *You only provided a user-related risk analysis per ISO 14971:2007. Risks should be categorized from a user and functional perspective (by outcome – over dose, etc. or by error type, user, device etc.). Please provide a complete risk analysis table which outlines each risk. In addition, the analysis should include traceability to associated risk mitigation validation/ verification.*

The Sponsor responded on 02/28/2018 and provided a risk analysis table. In addition to the User-Related Risk Assessment (URRA) provided already, the Sponsor conducted a Preliminary Hazard Analysis (PHA) to confirm the suitability of the design of the delivery system as an element of the combination product. The Sponsor states that the output of the device risk management program confirmed the suitability of the PFP, with no new or increased risks when compared to the RLD, for its intended use, by intended users, in the intended use environment. Risk control measures were considered, where possible, through implementation in the device design intent or as subsequent risk mitigation.
Portion of the risk analysis is shown below:

Table 2: Preliminary Hazard Analysis

Potential System Failure State or User Misuse Related to Design Feature (Leading to Hazardous Situation)	Outcome (Potential Harm Arising from System Failure)	Severity of Harm	Associated User Requirement(s)	Design Feature or PFP Component Contributing to System Failure	Is there a Misuse Scenario Contributing to System Failure? If so is it Foreseeable (F) or Deliberate (Del)?	Risk Control Measures: Inherent in Design (D) or Addressed Through Risk Mitigation (M).
Pen cap cannot be removed. (Missed dose – user aware)	Inconvenience	S1	The user shall be able to remove the cap without excessive force.	Pen cap	No	(b) (4)
Primary container cannot be inspected prior to injection. (Injection of foreign particulates – drug product)	Granuloma / pain / irritation	S2	The Pre-Filled Pen (PFP) shall allow the user to inspect the primary container contents prior to injection.	Cartridge holder	No	
Incompatible needle attached. (Multiple missed doses – user unaware)	Hyperglycemia	S4	The PFP shall be compatible with the following needles to allow for subcutaneous injection: BD Ultra-Fine™ 31G, 5mm; BD Ultra-Fine™ 32G, 4mm; Novofine® 32G, 6mm; Terumo Nanopass® 34G, 4mm.	PFP interaction with needle	(F) User unintentionally selects an incompatible needle	
Incompatible needle attached leading to multiple minor underdose. (Disease control incomplete but recoverable – inconvenience)	Hyperglycemia	S1			(F) User unintentionally selects an incompatible needle	
Incompatible needle attached. (Missed dose – user aware)	Inconvenience	S1			(Del) User intentionally selects an incompatible needle	
Needle cannot be attached to PFP. (Missed dose – user aware)	Inconvenience	S1			(Del) User intentionally selects an incompatible needle	
Needle cannot be attached to	Inconvenience	S1	The user must be able to	Cartridge holder	No – this is a	

***Reviewer Comment**: The MYL-1501D device risks have been managed to the point where it is appropriate for moving forward into commercial supply from the device point of view.*

8. LABELING

Draft pen label

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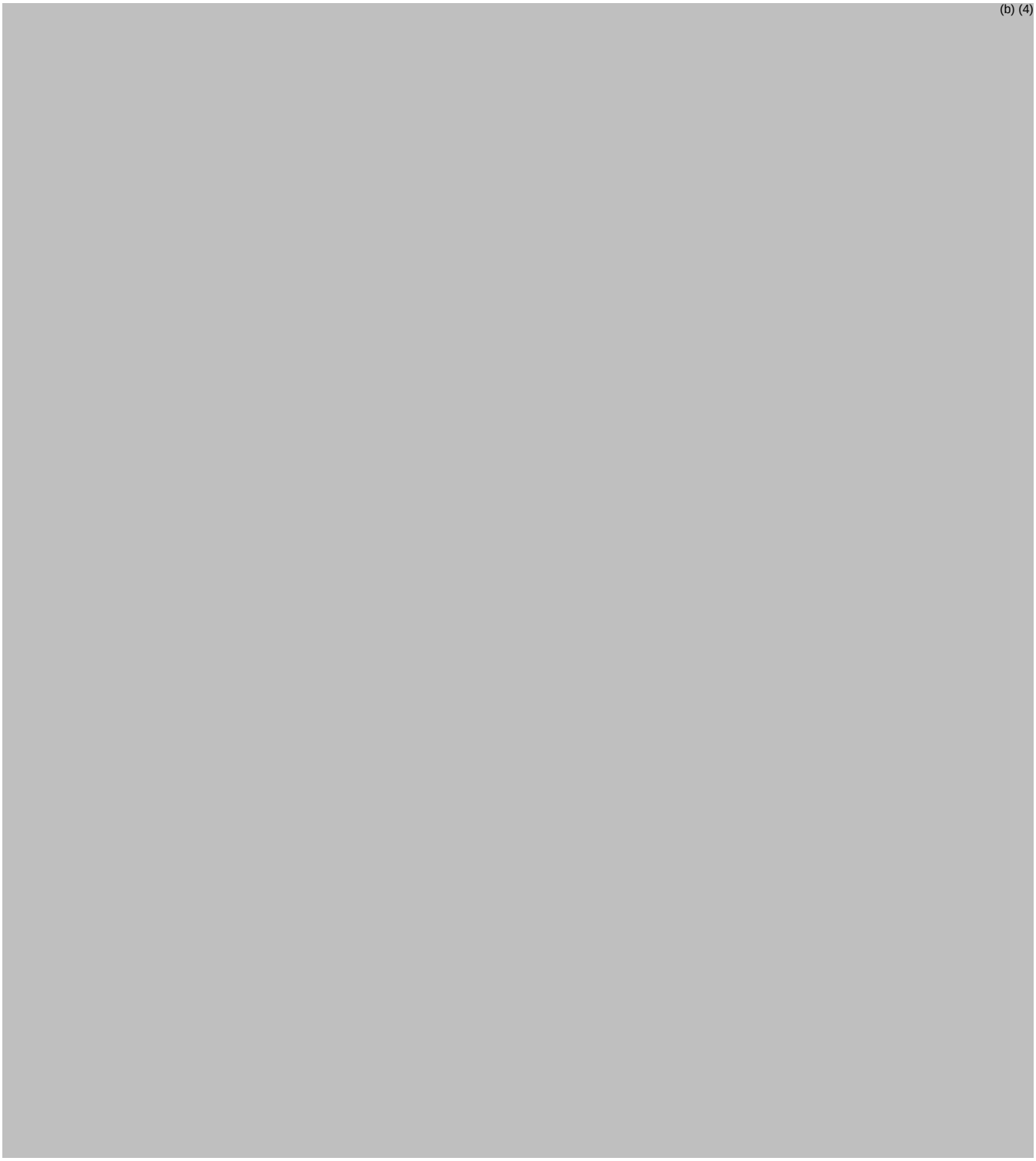

***Reviewer Comment**: The lot release specifications include the device essential performance requirement. The proposed lot release for the drug product is appropriate and acceptable from device point of view.*

10.INTERACTIVE REVIEW

Agency Information Request (sent on 01/10/2018)

- *You only provided a user-related risk analysis per ISO 14971:2007. Risks should be categorized from a user and functional perspective (by outcome – over dose, etc. or by error type, user, device etc.). Please provide a complete risk analysis which characterizes and evaluates the risks of the pen injector to the user or patient both during normal use, reasonable foreseeable mis-use, and potential system failure states. The risk analysis should include any risk control/mitigations as well as the residual risk remaining after any risk controls/mitigations are implemented.*

- *You indicated that there are design changes between the clinical and commercial pen configurations. Please provide a comparison of the verification and validation between the to be marketed presentation and the clinical studied pen injector, and justify how the design changes will not impact the essential performance specifications through a risk analysis.*

- *You provided design verification for Injection Force (without Cartridge and Needle) and mentioned that Injection Force (with Cartridge and Needle) are tested in the stability protocol. Please provide verification and validation for Injection Force (with Cartridge and Needle).*

The Sponsor responded on 02/28/2018. All responses are incorporated in the review memo and found adequate.

11.RECOMMENDATION

CDRH recommends approval based on review of the device constituent of the combination product. Review of this information found that there are sufficient verification activities for the safety and functionality of the device constituent part of the combination product to recommend approval.

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/s/

RONG GUO
03/27/2018

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/s/

ANIKA A LALMANSINGH
12/22/2017
Uploaded on behalf of Habacuc Barrera, CSO, CDRH/OC/DMQ/ASDB

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/s/

ANIKA A LALMANSINGH
02/12/2021 09:41:07 AM

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL, RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Device Constituent Review: CDER NDA210605 - CDRH ICC1900196

Date	July 26, 2019
To	Michael White
Requesting Division	CDER/OND/ODEII/DMEP
From	Rong Guo CDRH\OHT3\DHT3C\THT3C1
Through (Team Lead)	Sarah Mollo CDRH\OHT3\DHT3C\THT3C1
Through (Branch Chief)	CAPT Alan Stevens CDRH\OHT3\DHT3C
Subject	Device review for NDA210605
Combination product	insulin glargine (Semglee)
Recommendation	CDRH recommends **Approval** based on review of the device constituent of the combination product.

Digital Signature Concurrence Table	
Reviewer	
Team Lead	
Branch Chief	

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2019-04581
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=4934
ICC tracking # (Lead)	ICC1900196
Submission Number	NDA210605
Sponsor	Mylan
Drug	ICC1900196
Indications for Use	Indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Device Constituent	Pen injector
Route of Administration	S.C.

Table 2. Important Dates	
Information Requests Sent	n/a
Review Checkpoints	**Meeting / Due Date**
Primary Review / Lead Device Review	

2. PURPOSE/BACKGROUND

2.1. Scope

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH) regarding NDA210605 insulin glargine (Semglee). The device consultant authoring this review memorandum has performed a review of device constituent part of the combination product.

3. BACKGROUND

NDA210605 was issued a CR letter on 05/17/2018. Device constitute part was reviewed in the original submission with no deficiency. Review memo was uploaded into DARRTS by Rong Guo on 03/27/2018. The Sponsor re-submitted NDA210605 in response to FDA's major deficiencies, labeling comments, an updated proprietary name request, a safety update and information that addresses the additional comments regarding product quality.

The pen injector has no change in the resubmission. In addition to addressing the deficiencies to the CR letter, Biocon Sdn. Bhd. Facility (FEI 3011248248) is added as a new facility for pen assembly in addition to Biocon Limited (Bangalore, India). This new facility is responsible for activities related to manufacturing, filling, primary packaging, quality control testing [Chemical/Physical, Microbiological (sterility and non-sterility) testing] of the 3 mL cartridges and pre-filled pen assembly (secondary packaging), quality control testing [Chemical/Physical] of the pre-filled pens and secondary packaging in carton box. A desk review of the quality system was performed and there was no issue. Review memo was uploaded into DARRTS by Rong Guo on 05/28/2019. After a desk review of the facility inspection, CDRH recommended a pre-approval inspection of the facility Biocon Sdn. Bhd. Facility (FEI 3011248248).

An inspection to Biocon Sdn. Bhd. Facility was performed 06/24-07/05/2019. An FDA 483 letter was issued with 12 items. Observation 12 is device related: "Procedures for acceptance activities have not been adequately established.

Specifically, A. The rationale for the sample size of 25 (each) used in Friction Force testing performed as part of the acceptance of assembled Injection Insulin Glargine Injection 100 IU/mL Cartridge is not adequately documented". The Sponsor submitted response to the 483 letter on 07/26/2019, and "promised to correct". The response is acceptable since this observation will not pose any significant safety concerns. CDRH review team recommends the inspection is acceptable. This recommendation is made without reading the EIR.

4. RECOMMENDATION

CDRH recommends Approval based on review of the device constituent of the combination product.

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/s/

MICHAEL G WHITE
07/30/2019 01:19:01 PM
Filed on behalf of Rong Guo, CDRH reviewer, CDRH\OHT3\DHT3C\THT3C1