CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761109Orig1s000

PRODUCT QUALITY REVIEW(S)

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	June 15, 2020
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Andrea George, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 1
Application:	BLA 761109 NON-RESPONSIVE
Applicant:	Eli Lilly and Company
Submission Date:	August 15, 2019
Product:	insulin lispro-aabc
Dosage form(s):	Injection
Strength and Container-Closure:	100 units/mL (U-100) 10 mL multiple-dose vial 100 units/mL (U-100) 3 mL single-patient-use KwikPen 100 units/mL (U-100) 3 mL single-patient-use Junior KwikPen 100 units/mL (U-100) 3 mL single-patient-use Tempo Pen 100 units/mL (U-100) 3 mL single-patient-use cartridges 200 units/mL (U-200) 3 mL single-patient-use KwikPen
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information, patient labeling, and instructions for use (submitted on June 11, 2020), and container labels and carton labeling (submitted on May 27, and June 4, 2020) 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, patient labeling, and instructions for use (submitted on June 11, 2020), and container labels and carton labeling (submitted on May 27, and June 4, 2020) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted on August 15, 2019
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Medication Guide (N/A)

Patient Information labeling (submitted on August 15, 2019
\\cdsesub1\evsprod\bla761109\0001\m1\us\proposed-ppi-clean.docx)

Instructions for Use (submitted on August 15, 2019
\\cdsesub1\evsprod\bla761109\0001\m1\us\proposed-ifu-u100-10ml-vial-clean.docx ,
\\cdsesub1\evsprod\bla761109\0001\m1\us\proposed-ifu-u100-junior-kwikpen-clean.docx ,
\\cdsesub1\evsprod\bla761109\0001\m1\us\proposed-ifu-u100-kwikpen-clean.docx ,
\\cdsesub1\evsprod\bla761109\0001\m1\us\proposed-ifu-u100-tempo-pen-clean.docx)

Instructions for Use (submitted on December 12, 2019
\\cdsesub1\evsprod\bla761109\0016\m1\us\proposed-ifu-u200-kwikpen-clean.docx)

11 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 below the proper name)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: *Note in later communication DMEPA requested that the statement "For single patient use" appear immediately below the proper name and the applicant revised to appear below the proper name and dosage form*

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

Comment/Recommendation: For the cartridge, Junior KwikPen, U-100 KwikPen, U-200 KwikPen, and Tempo Pen container labels, revise the manufacturer information

[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."

to only include the manufacturer's name for partial label and space considerations. Consider also including the U.S. license number. *The Applicant revised as requested*

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

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

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

Comment/Recommendation: partial label

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: Consider revising the statement of dosage form (b) (4) to read as follows: "Dosage: See Prescribing Information" *The Applicant revised as requested*

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

Comment/Recommendation: partial label

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.

Applicant response: Lilly confirms that there is no visible text on the ferrule and cap overseal of the vials.

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

Comment/Recommendation: For all proposed container closure systems, 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 response:

The full length of the 100 units/mL 3 mL single-patient use cartridge for part of the circumference is visible

The entire circumference of the 100 units/mL 10 mL multiple dose vial is visible

Once the caps of 100 units/mL 3 mL prefilled pens are removed the full length and circumference of the 3 mL cartridge is visible. For the 200 units/mL prefilled pen, there is a yellow label that will cover part of the cartridge but the full length of the cartridge for part of the circumference and full circumference at top of cartridge are visible.

(b) (4)

A

B

C

D

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: partial label for pens and cartridges

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,	☐ Yes ☐ No

April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☒ N/A

Comment/Recommendation: partial label

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

Comment/Recommendation: space considerations

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

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

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

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

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No

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

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

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

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

Comment/Recommendation: see multiple dose comment above for the vial presentation

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

Comment/Recommendation: partial label

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

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 below the proper name)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Ensure that the approved suffix always appears with the proper name. Revise the ingredient statement from (b) (4) to read "Each mL contains insulin lispro-aabc…" *The Applicant revised as requested*

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

[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.

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

Comment/Recommendation: see recommendation for storage instructions

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

Comment/Recommendation: 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

Comment/Recommendation: Consider relocating the strength statement on the carton labeling to consistently appear after the dosage form as follows:
"Proprietary name
(insulin lispro-xxx)
injection
100 units per mL (U-100)"
The Applicant revised as requested
Note in later communication DMEPA requested that the statement "For single patient use" appear immediately below the proper name and the applicant revised to appear below the proper name and dosage form

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: Consider revising the storage information for the pens and cartridges to highlight the storage instruction so as not to be missed, to include a beyond use date, and to include instructions for the in-use pen or cartridge from (b) (4) to read as follows:
"**Storage:** Refrigerate unused pens at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do not freeze or expose to direct heat. Store opened pen [or cartridge] at room temperature below 86°F (30°C)."
The Applicant revised as requested

For cartridge carton labeling, consider adding spaces for the end-user to document the date each cartridge is removed from refrigeration for clarity:
"Discard unused portion of the cartridge 28 days after first opening. Date of first opening:

1: __/__/__.
2: __/__/__.
3: __/__/__.
4: __/__/__.
5: __/__/__."
The Applicant revised as requested

Consider revising the storage information for the multiple-dose vial (b) (4) to read as follows:
"**Storage:** Refrigerate unused (b) (4) vials at 36°F to 46°F (2°C to 8°C) (b) (4) in the original carton to protect from light. Do not freeze or expose to direct heat. Discard unused portions after 28 days."

The Applicant revised with modification to clarify that unused vials should be stored in the refrigerator and opened vials can be stored refrigerated or at room temperature as follows:
Storage: Refrigerate unused vials at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do not freeze or expose to direct heat. Store opened vial at either refrigerated or room temperature below 86°F (30°C). Discard unused portion after 28 days.
Acceptable

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

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

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

Comment/Recommendation: Add the route of administration "For subcutaneous use" to the principal display panel of the carton labeling for cartridges
The Applicant revised as requested

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

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

Comment/Recommendation: Revise the ingredient list to include the suffix in the proper name and to include quantitative amounts provided per BLA submission as follows:

Each mL of TRADENAME U-100 contains 100 units of insulin lispro-aabc and the inactive ingredients: glycerol (12.1 mg), magnesium chloride hexahydrate (1.02 mg), metacresol (3.15 mg), sodium citrate dihydrate (4.41 mg), treprostinil sodium (1.06 mcg), zinc oxide (content adjusted to provide 39 mcg zinc ion) and Water for Injection, USP.

Each mL of TRADENAME U-200 contains 200 units of insulin lispro-aabc and the inactive ingredients: glycerol (12.1 mg), magnesium chloride hexahydrate (1.02 mg), metacresol (3.15 mg), sodium citrate dihydrate (4.41 mg), treprostinil sodium (1.06 mcg), zinc oxide (content adjusted to provide 52 mcg zinc ion), and Water for Injection, USP.

The Applicant revised as requested and will also include the pH adjuster statement "Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH. LYUMJEV has a pH of 7.0 to 7.8".

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

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 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: For the pen and cartridge carton labeling, add the package type term to at least one of the net quantity statements as the package type term is intended to describe the container. For example, consider revising the statement to read as "5 x 3 mL single-patient use prefilled pens (or cartridges)". Refer to FDA's 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, which is available from: https://www.fda.gov/media/117883/download.

Applicant response:

Lilly does not intend to make this change on the pen and cartridge carton labeling, because the statement "**For Single Patient Use Only**" with a dark blue box is already prominently displayed on the PDP.

OBP labeling response: At this time, we acknowledge that in general, FDA's guidance documents do not establish legally enforceable responsibilities.

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

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

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

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

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

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

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

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

Comment/Recommendation: Consider revising the statement of dosage form "See enclosed literature for full prescribing information and instructions for use" to read as follows: "Dosage: See Prescribing Information"
The Applicant revised as requested

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

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

Prescribing Information Evaluation

PRESCRIBING INFORMATION

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

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

Comment/Recommendation: Sodium Chloride Injection, USP or 5% Dextrose Injection, USP were revised to USP nomenclature for clarity
This information was deleted from this section

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

Comment/Recommendation: the dosage form has been added per 21 CFR 201.57(a)(8)
The Applicant revised as requested

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 drug; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes); confirm product's incompatibilities, and 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	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The verbatim statement for visual inspection has been added per 21 CFR 201.57(c)(3)(iv).
Division preference includes a similar statement

Sodium Chloride Injection, USP or 5% Dextrose Injection, USP were revised to USP nomenclature for clarity
The Applicant revised as requested

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

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

Comment/Recommendation: Deleted the proprietary name from this paragraph since this first paragraph discusses the drug substance
The Applicant revised as requested

Deleted the mechanism of action from section 11 as it is already provided in the appropriate section 12 below
Applicant response: Lilly accepted revisions in Section 11, with one exception. Lilly proposes retaining "used to lower glucose" as originally proposed because the wording is consistent with labeling of similar products (e.g., Fiasp and NovoLog). The Applicant request is acceptable.

Relocated the dosage form to appear in the paragraph discussing the drug product
The Applicant revised as requested

Revised the ingredient list to include the suffix in the proper name and to include quantitative amounts provided per your BLA submission
The Applicant revised as requested

Full Prescribing Information	
15 & 16 Cytotoxic 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 cytotoxic 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: revised the storage requirement information for clarity as follows:

Refrigerate unused (unopened) TRADENAME vials, pens, and cartridges between 36°F to 46°F (2°C to 8°C) until time of use and keep in the original carton to protect from light. Do not freeze or use TRADENAME if it has been frozen. Do not expose to direct heat. Discard unused (unopened) TRADENAME vials, pens, and cartridges stored at room temperature (below 86°F (30°C) after 28 days.

The Applicant revised as requested but retained the language opened and unopened and deleted "unused" and "used" to be consistent with Table 9

Added the Celsius temperature to the storage table.
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

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 to USP nomenclature
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: Add the dosage form to appear after the proper name for the pens and cartridges
The Applicant revised as requested
Add the route of administration in the title for the multiple-dose vial.
The Applicant revised as requested

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

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

INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). *21 CFR 610.61 (add the US license number for consistency with the carton labeling),* *21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised to the qualifying phrase "Manufactured by"
The Applicant revised as requested

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information (submitted on June 11, 2020
\\cdsesub1\evsprod\bla761109\0041\m1\us\proposed-uspi-clean.docx)

Instructions for Use (submitted on June 11, 2020
\\cdsesub1\evsprod\bla761109\0041\m1\us\proposed-ifu-10ml-vial-clean.docx,
\\cdsesub1\evsprod\bla761109\0041\m1\us\proposed-ifu-u100-junior-kwikpen-clean.docx,
\\cdsesub1\evsprod\bla761109\0041\m1\us\proposed-ifu-u100-kwikpen-clean.docx,
\\cdsesub1\evsprod\bla761109\0041\m1\us\proposed-ifu-u100-tempo-pen-clean.docx,
\\cdsesub1\evsprod\bla761109\0041\m1\us\proposed-ifu-u200-kwikpen-clean.docx)

Patient Information (submitted on June 11, 2020
\\cdsesub1\evsprod\bla761109\0041\m1\us\proposed-ppi-clean.docx)

Container Labels

Per 27May20 submission- The timing of the Tempo Pen launch is uncertain; the Professional Sample labeling sample will be submitted once the timing is confirmed

100 units/mL (U-100) 10 mL multiple-dose vial (submitted on May 27, 2020)

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

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 6/15/2020 09:35:26AM
GUID: 50814c7000007a3d59329f660d8ddf02

Andrea George

Digitally signed by Andrea George
Date: 6/15/2020 02:46:30PM
GUID: 59b99181005cc7b0a3e954078ede1be9

Recommendation: Approval

BLA Number: 761109
Review Date: May 29, 2020

Drug Name/Dosage Form	insulin lispro-aabc (LYUMJEV)/injection
Strength/Potency	100 units/mL (U-100) in a 10 mL vial and 3mL cartridge 200 units/mL (U-200) in a 3 mL cartridge
Route of Administration	subcutaneous injection and intravenous infusion
Rx/OTC dispensed	Rx
Indication	Improve glycemic control in adults with type 1 and type 2 diabetes mellitus.
Applicant/Sponsor	Eli Lilly and Company

Product Overview:

LYUMJEV (insulin lispro-aabc) is a new formulation of insulin lispro that has a faster time-action profile than the approved insulin lispro formulation. Insulin lispro is a recombinant, human insulin analog composed of a two-chain peptide that contains 51 amino acids; the A-chain is composed of 21 amino acids and the B-chain is composed of 30 amino acids. The amino acid sequence of insulin lispro differs from human insulin at positions 28 (P28K) and 29 (K29P) of the B-chain. As with human insulin, insulin lispro contains two interchain disulfide bonds and one intrachain disulfide bond within the A-chain. Insulins, including insulin lispro, bind insulin receptors and lower blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and inhibit hepatic glucose production, lipolysis, and proteolysis.

Insulin monomers form dimers and trimers, which then combine into hexamers. Monomers are the physiologically-relevant form of insulin as this form binds insulin receptors, whereas hexamers are naturally occurring higher order structures that stabilize insulins. The time-action profile of an insulin depends on the propensity of hexamers to dissociate into monomers in vivo. The Pro(B28), Lys(B29) to Lys(B28), Pro(B29) switch in insulin lispro leads to faster hexamer dissociation relative to normal human insulin, and as a result, a faster time-action profile. The new formulation of LYUMJEV (insulin lispro-aabc) includes two additional excipients, treprostinil and sodium citrate, (b) (4) resulting in a faster insulin time-action profile and, consequently, an earlier reduction in glucose compared to the approved insulin lispro formulation. Treprostinil is a prostacyclin analog that is present in the formulation at a sub-therapeutic concentration (b) (4) sodium citrate (b) (4)

Insulin lispro drug substance (DS) is produced in genetically engineered *Escherichia coli*. LYUMJEV (insulin lispro-aabc) drug product (DP) is further formulated from insulin lispro DS and supplied at the following dosage forms and strength for subcutaneous injection and/or intravenous infusion:

- (b) (4) 100 units/mL (U-100):
  - 10 mL multiple-dose vial
  - 3 mL single-patient-use KwikPen®
  - 3 mL single-patient-use Junior KwikPen®

- 3 mL single-patient-use Tempo Pen™
- 3 mL single-patient-use cartridges
- (b) (4) 200 units/mL (U-200):
- 3 mL single-patient-use KwikPen®

Quality Review Team:

Discipline	Reviewer	Branch/Division
Drug Substance/Drug Product/ Immunogenicity	Andrea George	DBRRI/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Drug Substance Microbiology and Facility	Amy Devlin	DBM/OPMA/OPQ
Drug Substance Quality Assessment Lead	Thuy Thanh Nguyen	DBM/OPMA/OPQ
Drug Product Microbiology and Facility	Michael Shanks	DBM/OPMA/OPQ
Drug Product Quality Assessment Lead	Candace Gomez-Broughton	DBM/OPMA/OPQ
Application Team Lead	Riley Myers	DBRRI/OBP/OPQ
Tertiary Reviewer for OBP	Qing (Joanna) Zhou	DBRRI/OBP/OPQ
Business Project Manager	Shamika Brooks	RBPMBI/OPRO/OPQ

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Callie Cappel-Lynch	CDER/OND/OCHEN/DDLDO
Cross-disciplinary Team Lead	Patrick Archdeacon	CDER/OND/OCHEN/DDLDO
Medical Officer	Dolly Misra	CDER/OND/OCHEN/DDLDO
Pharmacology/Toxicology	Dan Minck	CDER/OND/OCHEN/DPTCHEN
Clinical Pharmacology	Manoj Khurana	CDER/OTS/OCP/DIIP
Statistics	Anna Ketterman	CDER/OTS/OB/DBII

Names:
a. Proprietary Name: LYUMJEV
b. Trade Name: LYUMJEV
c. Non-Proprietary Name/USAN: insulin lispro-aabc
d. CAS Name: 133107-64-9
e. Common Name: insulin lispro
f. INN Name: insulin lispro
g. Compendial Name: insulin lispro
h. OBP systematic name: N/A

Submissions Reviewed:

Submission(s) Reviewed	Document Date

STN 0001/1	August 15, 2019
STN 0006/5 (response to IR#1)	September 26, 2019
STN 0014/12 (response to IR#2)	November 26, 2019
STN 0015/13 (response to IR#2)	November 27, 2019
STN 0017/14 (response to IR#3)	December 6, 2019
STN 0016/15 (response to IR#2)	December 12, 2019
STN 0020/20 (response to IR#4)	January 17, 2020
STN 0022/21 (response to IR#5)	January 24, 2020
STN 0023/22 (response to IR#6)	January 27, 2020
STN 0025/23 (response to IR#7)	January 28, 2020
STN 0027/26 (response to IR#8 and stability update)	March 2, 2020
STN 0030/29 (response to IR#9)	March 17, 2020
STN 0031/30 (response to IR #10)	March 20, 2020
STN 0032/31 (withdraw comparability protocol)	March 26, 2020
STN 0033/32 (response to IR #11)	April 15, 2020
STN 0034/33 (response to IR #12)	April 28, 2020
STN 0035/34 (response to IR #13)	May 12, 2020
STN 0037/36 (response to IR #14)	May 18, 2020
STN 0038/37 (response to IR #15)	May 22, 2020
STN 0039/39 (response to IR #16)	May 27, 2020

Quality Review Data Sheet:

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Comments
(b) (4)	III		(b) (4)	2	Adequate	
	III			2	Adequate	
	III			2	Adequate	
	III			2	Adequate	
	II			3	N/A	
	III			2	Adequate	
	III			2	Adequate	
	V			3	N/A	
	V			3	N/A	

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient

information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

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

B. Other documents: IND 127210

3. Consults: None.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761109 for insulin lispro-aabc (LYUMJEV) manufactured by Eli Lilly and Company. The data submitted in this application are adequate to support the conclusion that the manufacture of insulin lispro-aabc (LYUMJEV) is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance: Fermentation, Granule Recovery, and Purification: Lilly del Caribe, Inc. 12.3 KM 65th Infantry Road (PR05) Carolina, Puerto Rico, United States

    Purification only: Eli Lilly and Company Lilly Corporate Center Indianapolis, Indiana, United States
  - Drug Product: Eli Lilly and Company Lilly Corporate Center Indianapolis, Indiana, United States and Lilly France 2, rue du Colonel Lilly 67640 Fegersheim, France
- Fill size and dosage form: 100 units/mL (U-100) in a 10 mL vial and 3 mL cartridge
  200 units/mL (U-200) in a 3 mL cartridge
- Dating period:
  - Drug Product: 24 months: 2°C to 8°C
  - Drug Substance: (b) (4) months: (b) (4) °C
  - For packaged products: N/A
  - Stability
    - 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: specified product in accordance with 21 CFR 601.2a
    Note: insulin lispro-aabc (LYUMJEV) is exempted from lot release per FR 95-29960.

Benefit/Risk Considerations: Insulin lispro-aabc (LYUMJEV) is indicated for improvement of glycemic control in adults with type 1 and type 2 diabetes mellitus. Diabetes mellitus is a group of metabolic disorders characterized by high blood glucose over a prolonged period of time that is caused by either the pancreas not producing a sufficient amount of insulin due to loss of beta cells (type 1) or cells not responding properly to the insulin produced (i.e. insulin resistance; type 2). Without proper management of blood glucose, patients with type 1 or type 2 diabetes mellitus develop a broad range of comorbidities that ultimately lead to death.

Therapeutic strategies for type 1 and type 2 diabetes mellitus typically include the administration of exogenous insulin. Purified canine and swine insulin were used for glycemic control since the early 20th century until recombinant human insulin was approved in 1982. The first insulin analog engineered to modulate the time-action profile of human insulin, insulin lispro, was approved in 1996. Despite these insulins available to patients, in clinical practice, many patients do not administer their mealtime insulin as prescribed. As such, the time-action profile of currently available rapid-acting insulin analogs do not adequately mimic the physiological post-meal insulin secretion profile in non-diabetics (Heinemann L and Muchmore DB *J Diabetes Sci Technol*2012). LYUMJEV is an alternative formulation of insulin lispro that was developed to provide a faster prandial insulin time-action profile to more acutely control blood glucose.

The overall control strategy for insulin lispro-aabc (LYUMJEV) manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process controls, process monitoring tests, release testing, and stability testing ensures overall process consistency that results in drug substance and drug product that is pure, potent, and safe.

The compatibility study results support the in-use conditions specified in the label with respect to protein recovery and purity. From a product quality perspective, because lispro-aabc drug product is to be diluted in a significant amount of saline or D5W for IV infusion, leading to the loss of an excipient-mediated effect on PK, lispro-aabc is unlikely to fulfill the "faster time-action" product performance as compared to Humalog. However, the final decision on whether the IV route of administration of lispro-aabc for the specified indications is appropriate is being deferred to the Clinical Division for additional benefit-risk considerations from the clinical perspective.

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

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management (see example in Attachment 1)

CQA (type)	Risk	Origin	Control Strategy	Other
Strength and Potency	Efficacy	Intrinsic to the molecule.	(b) (4)	Strength of insulin lispro-aabc is

			(b) (4)	
		Impacted by aggregation, fragmentation, and deamidation. Minimal change is expected during storage through expiry.		defined by the relative main peak area using RP-HPLC.
Identity (insulin lispro-aabc)	Safety and Efficacy	Intrinsic to the molecule.		Identity is confirmed through HPLC retention time of the insulin lispro peak.
Fingerprint (insulin lispro-aabc)	Safety and Efficacy	Intrinsic to the molecule.		The peptide map chromatogram of the digested sample must conform to that of the reference standard.
High Molecular Weight (HMW) species/Aggregates (product-related impurities)	PK and Safety (Immunogenicity)	Manufacturing process and exposure to elevated temperature, light exposure, addition of metals, changes in pH (acidic and basic), physical stresses including shaking. Minimal change is expected during storage under recommended conditions through expiry.		N/A

Deamidation (b) (4) species (product-related impurities)	Efficacy and PK	Manufacturing process and exposure to low pH.	(b) (4)	N/A
Other Related Substances (ORS) (product-related impurities)	Efficacy and PK	Manufacturing process, changes in pH (acidic and basic), elevated temperature.		(b) (4)
Lispro Proinsulin (product-related impurities)	Safety and Efficacy	DS manufacturing process		N/A

			(b) (4)	
pH	Safety, Efficacy, and PK	Formulation process		N/A
Zinc	Efficacy and PK	Manufacturing and formulation process		(b) (4)
Metacresol	Safety, Efficacy, and PK	Formulation process		
Treprostinil (Identity)	Safety and Efficacy	Formulation process		
Treprostinil (Concentration)	Safety, Efficacy, and PK	Formulation process		

Magnesium	Efficacy and PK	Formulation process	(b) (4)	(b) (4)
Citrate	Safety, Efficacy, and PK	Formulation process		

B. Drug Substance [insulin lispro] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA (type)	Risk	Origin	Control Strategy	Other
(b) (4)	Strength	(b) (4)	(b) (4)	N/A
E. coli cell proteins (ECP) (process-related impurities)	Safety and Immunogenicity	Production cell line		N/A
Bacterial Endotoxin	Safety and Purity	Production cell line		N/A

(process-related Impurity, Contaminant)			(b) (4)	
Total Microbial Count (Contaminant)	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Production cell line, raw materials, and the manufacturing process		N/A
(b) (4) (Process-related impurity)	Purity	Process-related impurity (b) (4)		N/A
(b) (4) (Process-related impurity)	Safety and Purity	Process-related impurity (b) (4)		N/A
(b) (4) (process-related impurities)	Safety	DS manufacturing process		N/A

- Description: Insulin lispro is a recombinant, human insulin analog manufactured in *Escherichia coli* cells, consisting of two peptide chains, the A-chain which is composed of 21 amino acids, and the B-chain which is composed of 30 amino acids, for a total 51 amino acids. Insulin lispro is identical in structure to human insulin except for an amino acid conversion at positions 28 and 29 of the B-chain from Pro(B28), Lys(B29), to Lys(B28), Pro(B29). As with human insulin, insulin lispro contains two interchain disulfide bonds and one intrachain disulfide bond within the A-chain.

  Insulin lispro is soluble in dilute acid and solutions with a pH of 7 or higher and has an isoelectric point of approximately 5.6.

- Mechanism of Action (MoA): Insulin lispro binds membrane bound insulin receptors on liver, skeletal muscle, and fat cells to stimulate peripheral glucose uptake, reduce blood glucose, and inhibit hepatic glucose production, lipolysis, and proteolysis.

- Potency Assay: RP-HPLC is utilized to determine potency of insulin lispro. Potency is reported as insulin units per milliliter in which 1 unit is equal to 0.0347 mg protein that is captured by the RP-HPLC main peak.

- Reference Materials: (b) (4)

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

- Manufacturing process summary (b) (4)

(b) (4)

- Container closure: (b) (4)
- Dating period and storage conditions (b) (4)

C. Drug Product [LYUMJEV; insulin lispro-aabc] 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
Sterility (Contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination introduced throughout DP manufacturing process	(b) (4)	N/A

			(b) (4)	
Container Closure Integrity (Contaminant)	Safety (loss of sterility due breaches in CCI during shelf-life	Container closure breaches during DP shelf-life.		N/A
Bacterial Endotoxin (Contaminant)	Safety, Purity, and Immunogenicity	Raw materials and the DP manufacturing process.		N/A
Particulate Matter (Visible and Subvisible) (Product of Process Related Impurities)	Safety (Immunogenicity))	Manufacturing process and container closure system		N/A
Color	Safety and Efficacy	Formulation or degradation		N/A
Clarity	Safety and Efficacy	Formulation, contamination, or degradation		N/A
Description	Safety and Efficacy	Formulation, contamination, or degradation		N/A
Extractable Volume	Efficacy and Strength	Manufacturing process		(b) (4)

				(b) (4)

- Potency and Strength: LYUMJEV is supplied as a 3 mL cartridge (100 U/mL and 200 U/mL) and a 10 mL vial (100 U/mL). Potency is defined as the concentration of insulin lispro-aabc captured in the RP-HPLC main peak. The potency assay is the same as described for DS.

- Summary of Product Design: LYUMJEV is supplied as a sterile, multi-dose liquid in a 3 mL cartridge for subcutaneous injection or in a 10 mL vial for subcutaneous injection and intravenous infusion. LYUMJEV is formulated in 4.41 mg sodium citrate dihydrate, 1.02 mg magnesium chloride hexahydrate, 12.1 mg glycerol, and 3.15 mg metacresol in water for injection (WFI) with 1.06 μg Treprostinil and zinc oxide to provide a final zinc concentration of 39 μg for 100 U/mL or 52 μg for 200 U/mL.

- List of Excipients: Excipients include Treprostinil, sodium citrate dihydrate, zinc oxide, magnesium chloride hexahydrate, metacresol, and glycerol. Except for Treprostinil, all excipients are compendial.

- Reference Materials: The same reference material is used for DS and DP.

- Manufacturing process summary: (b) (4)

(b) (4)

(b) (4)

- Container closure: The primary container closure for LYUMJEV consists of a 3 mL (b) (4)

- Dating period and storage conditions: The dating period for all presentations of LYUMJEV is 24 months when stored at 2-8°C, protected from light.

- List of co-package components, if applicable: N/A

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

a. Storage at 2-8°C.
b. Protect from direct light or sunlight.
c. Do not freeze.
d. Protect from direct heat.
e. (b) (4).

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture of drug substance (fermentation, granule recovery, and purification), in-process testing of drug substance, release/stability testing of drug substance, raw material testing	Lilly del Caribe, Inc. 12.3 KM 65th Infantry Road (PR05) Carolina, Puerto Rico (PR) 00985 United States	FEI 3004525072 DUNS 828519616	Performed a FDCA 704(a)(4) review of requested inspection documents. Most recent inspection (ORA), facility history, District File	N/A	Approve

and approval, microbiological testing			Review, and FDAC 704(a)(4) are all adequate. OMPQ PLI waived.		
Manufacture of drug substance (purification only), in-process testing of drug substance, release/stability testing of drug substance, raw material testing and approval, preparation and storage of master cell bank and working cell bank	Eli Lilly and Company Lilly Corporate Center Indianapolis, Indiana (IN) 46285 United States	FEI 1819470 DUNS 006421325	Most recent inspection, facility history, and District File Review were adequate. OMPQ PLI waived.	N/A	Approve
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture of cartridge and vial drug product, primary and secondary packaging, assembly of pre-filled pen injectors, release testing (vial only), in-process testing, stability testing, raw material testing and approval	Eli Lilly and Company Lilly Corporate Center Indianapolis, Indiana (IN) 46285 United States	FEI 1819470 DUNS 006421325	Most recent inspection, facility history, and District File Review were adequate. OMPQ PLI waived.	N/A	Approve

Secondary drug product packaging (cartridge only), assembly and testing of pre-filled pen injector, drug product release and stability testing	Lilly France 2, rue du Colonel Lilly 67640 Fegersheim, France	FEI 3002807475 DUNS 395346919	A Part 4 Medical Device QSIT inspection on 1/16/2020 was performed with no FDA Form 483 issued for this product. A District File Review was approve based on the inspection.	No FDA Form 483 issued.	Approve

G. Facilities: Adequate descriptions of the facilities, equipment, environmental controls, process equipment cleaning, and contamination control strategy were provided for Eli Lilly and Company Lilly Corporate Center (FEI: 1819470) and Lilly del Caribe, Inc. (FEI: 3004525072) proposed for insulin lispro-aabc DP and DS manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facility standpoint.

H. Lifecycle Knowledge Management:

a. Drug Substance:
   i. Protocols approved: Annual stability protocol for DS
   ii. Outstanding review issues/residual risk: none
   iii. Future inspection points to consider: Adequacy of the stability program for reprocessed and reworked batches, adequacy of corrective actions relating to foreign contaminants and particles in the manufacturing process, adequacy of root cause and product quality investigations of deviations from the validated manufacturing process, reliability of power supply to the facility and the impact of power failures on product quality, adequacy of lot disposition and IRL procedures, and conformance of the insulin lispro-aabc sampling plan with the license

b. Drug Product
   i. Protocols approved: Annual stability protocol for DP and stability protocol for first three commercially manufactured DP batches at each site.
   ii. Outstanding review issues/residual risk: none
   iii. Future inspection points to consider: none

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/

RILEY C MYERS
05/29/2020 08:00:42 AM

QING ZHOU
05/29/2020 08:49:27 AM

KATHLEEN A CLOUSE STREBEL
05/29/2020 10:21:10 AM

BLA STN 761109
insulin lispro-aabc (LYUMJEV)/injection
Eli Lilly and Company

OBP CMC Review Data Sheet

1. BLA#: 761109
2. Review Date: May 28, 2020
3. Primary Review Team

A. Medical Officer:	Dolly Misra, Patrick Archdeacon (TL)
B. Pharm/Tox:	Dan Minck, Federica Basso (TL)
C. Product Quality Team:	Andrea George, Riley Myers (ATL), Qing (Joanna) Zhou (Review Chief)
D. DS Micro/Facilities:	Amy Devlin, Thuy Thanh Nguyen (Branch Chief)
E. DP Micro/Facilities:	Michael Shanks, Candace Gomez-Broughton (TL)
F. Clinical Pharmacology:	Sury Sista, Manoj Khurana (TL)
G. Statistics:	Anna Ketterman, Yun Wang (TL)
H. OBP Labeling:	Vicky Borders-Hemphill
I. CDRH	David Wolloscheck, Rumi Young (TL)
J. RBPM:	Shamika Brooks

4. Major GRMP Deadlines

A. Filing Meeting:	October 14, 2019
B. Mid-cycle Meeting:	January 15, 2020
C. Wrap-up Meeting:	May 6, 2020
D. Primary Review Due:	April 20, 2020
E. Secondary Review Due:	May 4, 2020
F. PDUFA Action Date:	June 15, 2020

5. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request #1	September 23, 2019
Filing Meeting	October 14, 2019
Exclusivity Meeting 1	October 31, 2019
Information Request #2	November 12, 2019
Team Meeting 1	December 3, 2019
Information Request #3	December 4, 2019
Exclusivity Meeting 2	December 11, 2019
CMC-only inspection teleconference will Lilly Information Request #4	January 14, 2020
Mid-cycle Meeting	January 15, 2020
Information Request #5	January 22, 2020
Type C Meeting under IND 127210	January 23, 2020
Information Request #6	January 24, 2020
Information Request #7	January 28, 2020
Information Request #8	February 18, 2020
Information Request #9	March 4, 2020
Team Meeting 2	March 11, 2020
Information Request #10	March 11, 2020

Information Request #11	March 26, 2020
Inspection status update via email	April 2, 2020
Information Request #12	April 21, 2020
Labeling Meeting 1	April 22, 2020
IV administration compatibility update via email	April 24, 2020
Wrap Up and Labeling Meeting 2	May 6, 2020
Information Request #13	May 8, 2020
Information Request #14	May 14, 2020
Information Request #15	May 20, 2020
Information Request #16	May 26, 2020
Labeling Meeting 3	June 3, 2020

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
STN 0001/1	August 15, 2019	Yes (OBP/OPMA)
STN 0006/5 (response to IR #1)	September 26, 2019	Yes (OBP/OPMA)
STN 0014/12 (response to IR #2)	November 26, 2019	Yes (OBP/OPMA)
STN 0015/13 (response to IR #2)	November 27, 2019	Yes (OBP/OPMA)
STN 0017/14 (response to IR #3)	December 6, 2019	Yes (OPMA)
STN 0016/15 (response to IR #2)	December 12, 2019	Yes (OBP/OPMA)
STN 0020/20 (response to IR #4)	January 17, 2020	Yes (OBP/OPMA)
STN 0022/21 (response to IR #5)	January 24, 2020	Yes (OBP/OPMA)
STN 0023/22 (response to IR #6)	January 27, 2020	Yes (OBP/OPMA)
STN 0025/23 (response to IR #7)	January 28, 2020	Yes (OBP/OPMA)
STN 0027/26 (response to IR #8)	March 2, 2020	Yes (OBP)
STN 0030/29 (response to IR #9)	March 17, 2020	Yes (OBP)
STN 0031/30 (response to IR #10)	March 20, 2020	Yes (OPMA)
STN 0032/31 (CP withdraw)	March 26, 2020	Yes (OBP)
STN 0033/32 (response to IR #11)	April 15, 2020	Yes (OBP)
STN 0034/33 (response to IR #12)	April 28, 2020	Yes (OBP)
STN 0035/34 (response to IR #13)	May 12, 2020	Yes (OBP/CDRH)
STN 0037/36 (response to IR #14)	May 18, 2020	Yes (OPMA)
STN 0038/37 (response to IR #15)	May 22, 2020	Yes (OBP)
STN 0039/39 (response to IR #16)	May 27, 2020	Yes (OBP)

7. Drug Product Name/Code/Type:

Proprietary Name/Trade Name: LYUMJEV
Non-Proprietary Name/USAN: insulin lispro-aabc
CAS Name: 133107-64-9
Common Name: insulin lispro
INN Name: insulin lispro
Compendial Name: insulin lispro
OBP systematic name: N/A

8. Pharmacological Category: Antidiabetic agent for the treatment of Type I and Type II diabetes mellitus in adults (b) (4)

9. Dosage Form: Injection

10. Strength/Potency:

(i): The concentration/strength of the Drug Product: 100 Unit/mL 3mL cartridge; 200 Unit/mL 3 mL cartridge; 100 Unit/mL 10 mL vial

(ii): Type of potency assay(s): RP-HPLC is utilized to determine potency of insulin lispro. Potency is reported as insulin units per milliliter in which 1 unit is equal to 0.0347 mg protein as compared to reference standard.

11. Route of Administration: Subcutaneous and Intravenous injections

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Comments (status)
[redacted]	[redacted]	(b) (4)	Adequate
[redacted]	[redacted]	[redacted]	Adequate
[redacted]	[redacted]	[redacted]	Adequate
[redacted]	[redacted]	[redacted]	Adequate
[redacted]	[redacted]	[redacted]	Sufficient information in application
[redacted]	[redacted]	[redacted]	Adequate
[redacted]	[redacted]	[redacted]	Adequate

13. Inspectional Activities: In lieu of a pre-license on-site inspection (PLI) for the drug substance manufacturing facility Lilly del Caribe, Inc. (FEI: 3004525072) due to COVID-19 travel restrictions, a review of requested manufacturing site records under Section 704(a)(4) was conducted on April 20, 2020 by Amy Devlin (OPMA), Zhong Li (OPMA), Riley Myers (OBP) and Andrea George (OBP). Lilly del Caribe, Inc. (PR) is responsible, and previously licensed (BLA 020563), for the manufacture of insulin lispro drug substance. The document review did not identify conditions that would preclude approval.

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: None

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation: I recommend approval of STN 761109 for LY900014 manufactured by Eli Lilly and Co. (DS and DP), Lilly del Caribe, Inc. (DS), and Lilly France (DP). The data submitted in this application support the conclusion that the manufacture of LY900014 is well controlled and consistently leads to a product with the appropriate potency and purity.

Insulin lispro DS is stored at (b) (4)°C for (b) (4) months.

LY900014 DP is stored at 2-8°C for 24 months.

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

Environmental Assessment of Claim of Categorical Exclusion

Eli Lilly and Company claims categorical exclusion from the preparation of an Environmental Assessment pursuant to 21 CFR 25.15(d) allowed by 21 CFR 25.31(c). Insulin lispro for injection is metabolized and degraded in vivo and therefore has minimal risk for excretion into the aquatic environment. Similarly, other excipients including Treprostinil are present in micro-doses and therefore the expected levels are not considered to be an environmental risk and are categorically excluded from the environmental assessment requirement by 21 CFR 25.31(b). Further, no extraordinary circumstances exist for the manufacture of LY900014 DP.

Assessor comment: *The claim of categorical exclusion from an environmental assessment is acceptable.*

V. Primary Container Labeling Review:

The CMC review of DP labeling was generated by Vicky Borders-Hemphill, OBP.

VI. Review of Common Technical Document- Quality Module 3.2

The review of Module 3.2 is provided below.

VII. Review of Immunogenicity Assays- Module 5.3.1.4

The review of Module 5.3.1.4 is provided below.

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Andrea George

Digitally signed by Andrea George
Date: 5/28/2020 12:27:57PM
GUID: 59b99181005cc7b0a3e954078ede1be9

Riley C Myers

Digitally signed by Riley C Myers
Date: 5/28/2020 12:31:39PM
GUID: 57f6809300502f3978f97f5b5a09d128