CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761215Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 17, 2021
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	BLA 761215
Product Name and Strength:	LY2963016 (insulin glargine-aglr)[a] injection, 100 units/mL (300 units/3 mL)
Applicant/Sponsor Name:	Eli Lilly and Company (Lilly)
OSE RCM #:	2020-2684-1
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader (Acting):	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised instructions for use (IFU), prescribing information (PI), patient package insert (PPI), container label and carton labeling, which were received on December 16, 2021 for LY2963016. Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised IFU, PI, PPI, container label and carton labeling for LY2963016 (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[b] and information requests issued by DDLO[c,d,e].

[a] LY2963016 has been developed as a proposed (b) (4) biosimilar to US-licensed Lantus. For the purpose of this review, LY2963016 is used throughout the review to refer to this product. The proposed proprietary name for this BLA, Rezvoglar KwikPen, was found conditionally acceptable on March 18, 2021. The nonproprietary name, insulin glargine-aglr, was found conditionally acceptable on September 13, 2021.
[b] Bhalodia, A. Label and Labeling Review for LY2963016 (BLA 761215). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 DEC 13. RCM No.: 2020-2684.

2 CONCLUSION

Although not specifically reflected in the label and labeling submitted to the BLA at that time, based on email communication dated December 13, 2021, Lilly confirmed following,

- The product will be marked with the product identifier (a standardized graphic that includes the standardized numerical identifier, lot number, and expiration date of the product in both human-readable and machine-readable format) in accordance with the Drug Supply Chain Security Act prior to release from Lilly.
- The expiration date format that will be used for the Rezvoglar KwikPen carton and container label is YYYY-MMM-DD.

Thus, based on the foregoing and review of the revised label and labeling, the Applicant implemented all of DMEPA's prior recommendations. We did not identify any new medication error concerns and have no recommendations for the revised label and labeling at this time.

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[c] Salartash, S. Information Request for BLA 761215. Silver Spring (MD): FDA, CDER, OSE (US); 2021 NOV 18. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80629cac&_afrRedirect=220613660735 2831

[d] Salartash, S. Information Request for BLA 761215. Silver Spring (MD): FDA, CDER, OSE (US); 2021 NOV 30. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8062d0b7&_afrRedirect=22062018052 38266

[e] Salartash, S. Labeling PMR/PMC Discussion for BLA 761215. Silver Spring (MD): FDA, CDER, OSE (US); 2021 DEC 7. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80630114&_afrRedirect=22074695922 34426

APPENDIX A. LABEL AND LABELING RECEIVED ON DECEMBER 16, 2021

Instructions for Use

- EDR link: \\CDSESUB1\evsprod\bla761215\0019\m1\us\proposed-ifu-clean.docx

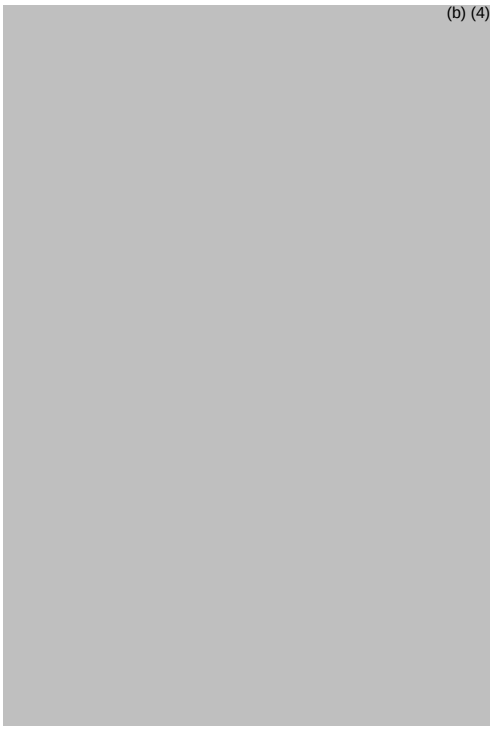
Prescribing Information

- EDR link: \\CDSESUB1\evsprod\bla761215\0019\m1\us\proposed-uspi-clean.docx

Patient Package Insert

- EDR link: \\CDSESUB1\evsprod\bla761215\0019\m1\us\proposed-ppi-clean.docx

Container labels



Carton labeling

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/s/

AVANI BHALODIA
12/17/2021 09:23:05 AM

OLUWAMUREWA OGUNTIMEIN
12/17/2021 09:25:27 AM

JASON A FLINT
12/17/2021 09:30:58 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	12/13/2021
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	BLA 761215
Product Name, Dosage Form and Strength:	LY2963016 (insulin glargine-aglr)[a] injection, 100 units/mL (300 units/3 mL)
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly and Company (Lilly)
FDA Received Date:	12/18/2020
OSE RCM #:	2020-2684
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader (Acting):	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Division Director	Irene Z. Chan, PharmD

[a] LY2963016 has been developed as a proposed (b) (4) biosimilar to US-licensed Lantus. The proposed proprietary name for this BLA, Rezvoglar KwikPen, was found conditionally acceptable on March 18, 2021. The nonproprietary name, insulin glargine-aglr, was found conditionally acceptable on September 13, 2021.

1 REASON FOR REVIEW

As part of the 351(k) BLA approval process for LY2963016 (insulin glargine-aglr) injection, 100 units/mL (300 units/3 mL) the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the proposed LY2963016 instructions for use (IFU), patient package insert (PPI), prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 PRODUCT DESCRIPTION

LY2963016 is a proposed combination product with a prefilled pen (PFP) device constituent part that is intended for the treatment of improving glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. LY2963016 will be supplied in a carton containing five, 3 mL single patient use LY2963016 prefilled pens.

1.2 REGULATORY HISTORY

Lilly submitted comparative analyses on 9/15/2020 under IND 140889 for the proposed LY2963016 to determine whether Lilly needs to submit the results of a comparative use human factors (CUHF) study to support their 351(k) application seeking licensure as (b) (4) biosimilar with US-licensed Lantus (BLA 021081). We refer you to our comparative analyses review dated 12/10/2021. The comparative analyses determined that additional data from a CUHF study did not need to be submitted to support this marketing application.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed LY2963016 instructions for use (IFU), patient package insert (PPI), and prescribing information (PI) did not identify areas of vulnerability that may lead to medication errors. Thus, we do not have any recommendations at this time for the LY2963016 IFU, PPI and PI.

However, the proposed container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for Eli Lilly and Company. We ask that the Division convey Section 4 in its entirety to Eli Lilly and Company so that recommendations are implemented prior to approval of this BLA.

4 RECOMMENDATIONS FOR ELI LILLY AND COMPANY

Table 2. Identified Issues and Recommendations for Eli Lilly and Company (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The format for expiration date is not defined.	Clearly define the expiration date to minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or

Table 2. Identified Issues and Recommendations for Eli Lilly and Company (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			a space be used to separate the portions of the expiration date.
Carton Labeling			
1.	The carton labeling is not consistent with prescribing information with regards to storage information. The PI states, "Store in-use Pen at room temperature up to 86ºF [30ºC]." while the carton labeling states, (b) (4)	Inconsistency between carton labeling and PI with regards to storage information may lead to confusion.	Revise the in-use storage statement to read, "Store in-use Pen at room temperature up to 86ºF [30ºC]." to be consistent with the storage information in the Prescribing Information.
2.	The carton labeling does not include a 2D data matrix barcode.	In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act.[b] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling.

[b] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. Food and Drug Administration. 2021. Available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for LY2963016 that Eli Lilly and Company submitted on 12/18/20 and US-licensed Lantus.

Table 3. Relevant Product Information for US-licensed Lantus and LY2963016		
Product Name	US-licensed Lantus[c]	LY2963016
Initial Approval Date	4/20/2000	N/A
Nonproprietary Name	Insulin glargine	Insulin glargine-aglr
Indication	to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus	
Route of Administration	Subcutaneous	
Dosage Form	Injection	
Strength	100 units/mL (300 units/3 mL)	
Dose and Frequency	Once daily at any time of day, but at the same time every day	
How Supplied	• Carton containing one 10 mL multiple dose vial • Carton containing five 3 mL single patient use SoloStar prefilled pens	• Carton containing five 3 mL single patient use Rezvoglar KwikPen prefilled pens
Storage	• Not in-use (unopened): refrigerate (36°F to 46°F [2°C to 8°C]) until expiration date • Not in-use (unopened): room temperature (up to 86°F [30°C]) for up to 28 days • In-use (opened) pen: room temperature for up to 28 days (do not refrigerate)	
Container Closure	• 10 mL multiple-dose vial • 3 mL single-patient-use SoloStar prefilled pen	• 3 mL single-patient-use Rezvoglar KwikPen prefilled pen

[c] Lantus [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 April 16. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021081s073s074lbl.pdf.

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 16, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, BLA 761215, IND 140889 and LY2963016. Our search identified one previous review[d] and we considered our previous recommendations to see if they are applicable for this current review.

[d] Barlow, M. Comparative Analyses Review for LY2963016 (IND 140889). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 DEC 10. RCM No.: 2020-1934.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

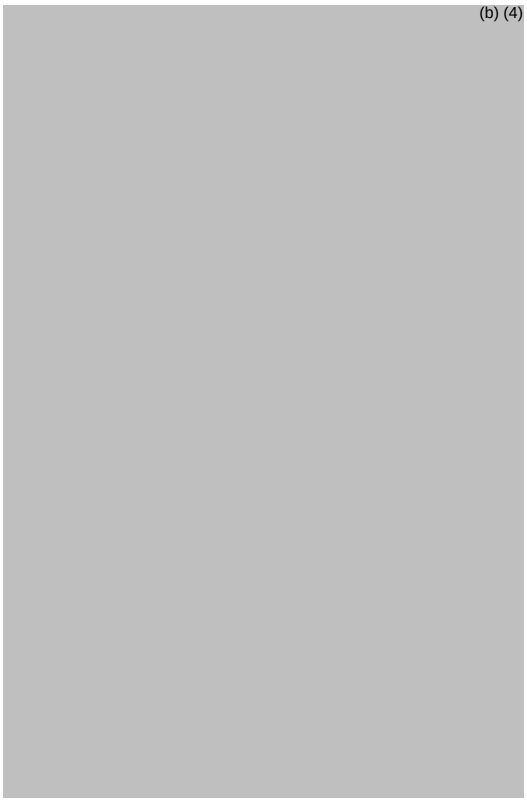
Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following LY2963016 labels and labeling submitted by Eli Lilly and Company.

- Container label(s) received on 12/18/20
- Carton labeling received on 12/18/20
- Instructions for Use received on 12/18/20, available from \\CDSESUB1\evsprod\bla761215\0001\m1\us\proposed-ifu.docx
- Prescribing Information (Image not shown) received on 12/18/20, available from \\CDSESUB1\evsprod\bla761215\0001\m1\us\proposed-uspi.docx
- Patient Package Insert received on 12/18/20, available from \\CDSESUB1\evsprod\bla761215\0001\m1\us\proposed-ppi.docx

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

F.2 Label and Labeling Images

Container label



Carton labeling

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/s/

AVANI BHALODIA
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12/13/2021 10:37:01 AM

IRENE Z CHAN
12/13/2021 10:43:25 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 9, 2021
To:	Shiva Salartash Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ankur Kalola, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	REZVOGLAR (insulin glargine-aglr)
Dosage Form and Route	injection, for subcutaneous use
Application Type/Number:	BLA 761215
Applicant:	Eli Lilly and Company

1 INTRODUCTION

On December 31, 2020, Eli Lilly and Company submitted for the Agency's review Biologics License Application (BLA) #761215 REZVOGLAR (insulin glargine-aglr) injection. The proposed indication is to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. This is an application for a biosimilar product (b) (4) to the reference product LANTUS Solostar. (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) on January 8, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for REZVOGLAR (insulin glargine-aglr) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft REZVOGLAR (insulin glargine-aglr) injection PPI and IFU received on December 31, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 6, 2021.
- Draft REZVOGLAR (insulin glargine-aglr) injection Prescribing Information (PI) received on December 31, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 6, 2021.
- Approved BASALGAR (insulin glargine) injection labeling dated July 20, 2021.
- Approved LANTUS SOLOSTAR (insulin glargine) injection labeling dated November 15, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible

- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
12/09/2021 09:35:40 AM
DMPP-OPDP review of insulin glargine-aglr (REZVOGLAR) BLA 761215 PPI and IFU

ANKUR S KALOLA
12/09/2021 09:42:16 AM

MARCIA B WILLIAMS
12/09/2021 09:57:01 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 1, 2021

To: Michelle Carey, M.D.
Division of Diabetes, Lipid Disorders, and Obesity Products (DDLO)

Shiva Salartash, Regulatory Project Manager, (DDLO)

Monika Houstoun, Associate Director for Labeling, (DDLO)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda Wilson, Team Leader, OPDP

Subject: OPDP Labeling Comments for REZVOGLAR (insulin glargine-aglr) injection, for subcutaneous use

BLA: 761215

In response to DDLO's consult request dated December 31, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original BLA submission for REZVOGLAR (insulin glargine-aglr) injection, for subcutaneous use (Rezvoglar).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DDLO (Shiva Salartash) on August 26, 2021, and we have no additional comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 26, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Ankur Kalola at (301) 796-4530 or Ankur.Kalola@fda.hhs.gov.

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

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/s/

ANKUR S KALOLA
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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	8/16/2021		
To:	Shiva Salartash		
Requesting Center/Office:	CDER/OND	**Clinical Review Division:**	Other
From	Kathleen Fitzgerald OPEQ/OHT3/DHT3C		
Through (Team)	Rumi Young, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Choose an item., Choose an item. OPEQ/OHT3/DHT3C		
Subject	BLA761215, Insulin Glargine ICC2100026		
Recommendation	**Filing Recommendation Date:** Click or tap to enter a date. ☐ 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: Click or tap to enter a date. ☐ 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: 8/16/2021 ☐ 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)
Kathleen E. Fitzgerald -S Digitally signed by Kathleen E. Fitzgerald -S Date: 2021.08.16 14:34:09 -04'00'	Suzanne J. Hudak -S Digitally signed by Suzanne J. Hudak -S Date: 2021.08.16 21:10:20 -04'00'	

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA761215
Sponsor	Eli Lily and Company
Drug/Biologic	Insulin Glargine
Indications for Use	Improvement of glycemic control in adults and pediatrics patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Device Constituent	Pen-Injector
Related Files	ICC1300540 – CDRH review of Basaglar Kwikpen (60U device) ICC1500700 – CDRH review of Basaglar Kwikpen (80U device) ICC1600339 – CDRH review of Basaglar Kwikpen (80U device) – addition of pen needle sample pack ICC1900371 – CDRH review of Basaglar TempoPen (80U device) ICC2000115-CDRH review meeting questions 3 & 4 ICC2000612-PIND 140889

Review Team		
Lead Device Reviewer	*Kathleen Fitzgerald*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
None		

Important Dates	
Discipline-Specific Review Memos Due	
Final Lead Device Review Memo Due	8/18/2021
Interim Due Dates	**Meeting/Due Date**
Filing	
74-Day Letter	6/4/2021
Mid-Cycle	5/18/2021
Primary Review	8/18/2021
Internal Meeting(s)	
Sponsor Meeting(s)	

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			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation			X	
Human Factors Validation			X	Reviewed by DMEPA
Facilities & Quality Systems	X			

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

Eli Lily and Company is requesting approval of Insulin Glargine. The device constituent of the combination product is a Pen-Injector.

CDER/OND has requested the following consult for review of the device constituent of the combination product:

Pen injector

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:

Pen injector information and device performance.

This review will not cover the following review areas:

Drug product, drug contacting device constituent parts, human factors

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

ICC1300540 – CDRH review of Basaglar Kwikpen (60U device)
ICC1500700 – CDRH review of Basaglar Kwikpen (80U device)
ICC1600339 – CDRH review of Basaglar Kwikpen (80U device) – addition of pen needle sample pack
ICC1900371 – CDRH review of Basaglar TempoPen (80U device)
ICC2000115-CDRH review meeting questions 3 & 4
ICC2000612-PIND 140889

3.3. Indications for Use

Combination Product	Indications for Use
Insulin Glargine	Improvement of glycemic control in adults and pediatrics 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)**
BLA761215-Medical Device	3.2.R.3
Container Closure pen injec	3.2.P.7
Stability data	3.2.P.8.3
Medical device (b) (4)	3.2.R

4. DEVICE DESCRIPTION

4.1. Device Description

The device constituent part of the combination product is a pen-injector- LY2963016 80U KwikPen. The user interface of the LY2963016 80U KwikPen is identical to the 60U KwikPen except for the 80U KwikPen is approximately 0.5 inches longer and allows for dosing in 1-unit increments from 1-unit to 80-units in a single injection.

LY2963016 80U KwikPen is a prefilled pen-injector designed to provide subcutaneous injection of L Y2963016 Insulin for treatment of diabetes mellitus. The product may be used for self-administration by the patient, by health care providers, or by caregivers to administer the medicine. The pen-injector can be used more than once with the same drug cartridge and is discarded after the cartridge is empty. The product may be used in health care, institutional, and home settings.

The system consists of two main components: the filled Lilly LY2963016 3 mL cartridges and the pen-injector.
Some of the key features of the device are:

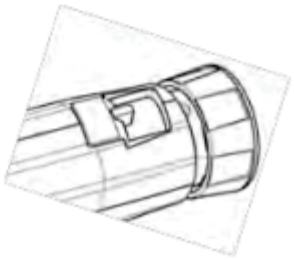
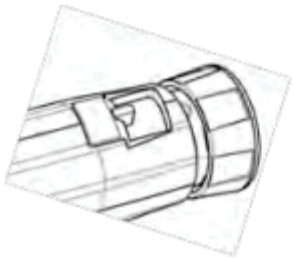
- utilizes the core drive mechanism and the standard Lilly LY2963016 3 mL cartridges as the existing KwikPen device platforms,
- same external features and patient contact materials as that of the L Y2963016 60U KwikPen, with the exception of added length,
- same color and body style as the LY2963016 60U KwikPen,
- delivery of doses from 1 to 80 units (0.01 mL to 0.80 mL) as a single injection,
- dosage amounts in 1-unit (0.01 mL) increments with audible or tactile clicks while setting dose,
- ergonomic design to facilitate control and stability,
- single-step dose setting; twist-to-set dose,
- low injection force.

The user interface of the LY2963016 80U KwikPen is identical to the approved LY2963016 60U KwikPen version, with the exception of the 80U KwikPen body length.

The body of the LY2963016 80U KwikPen is 0.5 inches (1.27 cm) longer than the LY2963016 60U KwikPen to accommodate the longer injection stroke associated with increasing the maximum dose by an additional 20U (80U versus 60U).

Table 3.2.R.3.2.2-1 Comparison of the LY2963016 60U KwikPen with the LY2963016 80U KwikPen

Feature	LY2963016 60U KwikPen	LY2963016 80U KwikPen	Explanation if a change
General Information			
Intended Use	Intended for the use by patients with diabetes for insulin injection from 3 ml cartridges.	Intended for the use by patients with diabetes for insulin injection from 3 ml cartridges	No change
Target Population	Target patients are adult persons 18 years of age and older with either Type 1 or Type 2 diabetes.	Target patients are adult persons 18 years of age and older with either Type 1 or Type 2 diabetes.	No change
Design and Features			
Technology	Mechanical pen-injector	Mechanical pen-injector	No change
Dosing mechanism design and components	Internal, non-user contact functional components	Internal, non-user contact functional components	No change
Overall length	LY2963016 60U KwikPen length- 6.1"	LY2963016 80U KwikPen length- 6.6"	0.5" increase in length
Label size	Width = 35mm Length = 58 mm	Width= 35mm Length = 58mm	No change
Dial Printing	1 to 60 units in 1 unit increments	1 to 80 units in 1 unit increments	Increase to accommodate 80U dose

Feature	LY2963016 60U KwikPen	LY2963016 80U KwikPen	Explanation if a change
Design and Features (Continued)			
Dose Volume Increment	0.01 mL per dose increment	0.01 mL per dose increment	No Change
Dose Indicator	Length and Shape are square and proud from the adjacent bezel surface. 	Length and Shape are square and proud from the adjacent bezel surface. 	No change
Performance			
Key specifications met	Compliance with ISO 11608-1:2014[a]	Compliance with ISO 11608-1:2014[a]	No change
Other			
Pen Body, Dose Knob, and Pen Cap color	Light gray	Light gray	No change
Bezel	5mm long 	5mm long 	No change

Feature	LY2963016 60U KwikPen	LY2963016 80U KwikPen	Explanation if a change
Pen Cap Shape	The device Pen Cap is rounded at the end.	The device Pen Cap is rounded at the end.	No change
Dose Knob features	Dose Knob side with cut outs.  Yellow ring aligning with the brand color is printed on the end of the Dose Knob. 	Dose Knob side with cut outs.  Yellow ring aligning with the brand color is printed on the end of the Dose Knob. 	No change

Feature	LY2963016 60U KwikPen	LY2963016 80U KwikPen	Explanation if a change
Cartridge Holder	Gauge with stripes 	Gauge with stripes 	No change
Draft Pen label	(b) (4) [redacted]		No change

Table 3.2.P.7.2-1 Device System Components

Attribute	Description
System	consists of the filled 3 mL cartridge and the pen-injector
External View	As presented in Figure 3.2.P.7.2-1
Dosage Delivery	80U Pre-Filled Pen Injector allows for delivery of doses from 1 to 80 units (0.01 mL to 0.80 mL) as a single injection
Dosage Units	1 unit (0.01 mL)

Table 3.2.R.3.2.4-1 Materials in the LY2963016 80U KwikPen*

Component		Material
External, Patient Contact Components	Dial	(b) (4)
	Housing	
	Cartridge Holder	
	Pen Cap	
	Dose Knob	
Internal Components		

* same materials as used in the approved LY2963016 60U KwikPen

4.2. Steps for Using the Device

(b) (4)

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

(b) (4)

[redacted]

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 an adequate device description and Method of operation. The materials and user interface of the LY2963016 80U KwikPen is identical to the approved LY2963016 60U KwikPen version, with the exception of the 80U KwikPen body length. The body of the LY2963016 80U KwikPen is 0.5 inches (1.27 cm) longer than the LY2963016 60U KwikPen to accommodate the longer injection stroke associated with increasing the maximum dose by an additional 20U (80U versus 60U).		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

5. FILING REVIEW

CDRH performed Filing Review ☐ **Finalize Filing Review Section**	☐
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

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 instructions for use and user interface of the LY2963016 80U KwikPen is similar to the approved LY2963016 60U KwikPen version, with the exception of the 80U KwikPen body length to accommodate the maximum dose by an additional 20U (80U versus 60U). The Sponsor was informed in a previous meeting with the FDA that they did not have to complete a usability/HF study for the 80U KwikPen and differences between 60 unit dial and 80 unit dial pen should be mitigated through labels and labeling.

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 instructions for use and user interface of the LY2963016 80U KwikPen is similar to the approved LY2963016 60U KwikPen version, with the exception of the 80U KwikPen body length to accommodate the maximum dose by an additional 20U (80U versus 60U). The provided labeling/instructions for use is adequate.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

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**		
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)			
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		
Bioequivalence Study utilized to-be-marketed device	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 study)			X
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments: LY2963016 80U KwikPen is identical to the approved LY2963016 60U KwikPen version, with the exception of the 80U KwikPen body length increase of .5 to accommodate the maximum dose by an additional 20U (80U versus 60U). Sponsor states that in previous communications with the FDA the agency stated that a new human factors study is not needed and differences between 60 unit dial and 80 unit dial pen should be mitigated through labels and labeling. The Sponsor demonstrated through functional performance testing that the LY2963016 80U KwikPen performs and delivers the drug product as indicated.

7.2. Design Inputs and Outputs

(b) (4)

Reviewer Comments-The Sponsor has adequately identified and completed the EPRs for pen injectors per ISO 11608-1. The device performed similar to their approved LY2963016 60U KwikPen. Testing was completed on the final finished aged device.

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	NA
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	NA
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	NA
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO 11608-1:2014 Needle-based injection systems for medical use Requirements and Test methods-Part 1: Needle-based injection systems	**Y**	**Y**

7.4. Design Control Review Conclusion

DESIGN CONTROL 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 provided an adequate design control and followed the appropriate standards for pen injectors/combination product.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

8. RISK ANALYSIS

8.1. Risk Management Plan

(b) (4)

[redacted]

Reviewer Comments – Full risk report is provided in section 3.2.R.2.4.3. The risk is similar to current 60U KwikPen (b) (4) Risk assessment is adequate.

8.2. 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 The Sponsor has provided an adequate risk assessment.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

(b) (4)

(b) (4)

Reviewer Comment The pen injector is not supplied with a needle but have demonstrated compatibility with BD pen needles. The Sponsor performed the required EPRs with adequate results.

(b) (4)

(b) (4)

Reviewer Comment

The pen injector design is the same as the approved LY2963016 60U KwikPen except for the longer length to accommodate the 80U dose. The Sponsor completed the the functional performance tests with adequate results for the EPRs. The Sponsor also followed ISO 11608-1:2014 requirements.

Additional tests completed per ISO 11608-1

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9.2. 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-The Sponsor has provided adequate design verification and test reports for review.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

9.3. 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

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors 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	☑

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☑
CDRH Quality Systems Documentation Review was not conducted	☐

12.2.1. Description of the Device Manufacturing Process

(b) (4)

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(b) (4)

Reviewer Comments
The Sponsor provided adequate information summary of the manufacturing process/production flow.

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☒Yes	☐No

12.2.2. cGMP Review

(b) (4)

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(b) (4)

Reviewer Comments
The quality systems documentation is adequate and in compliance with ISO 13485.

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	Yes	No

12.2.3. Corrective and Preventive Action Review

(b) (4)

Reviewer Comments
The Sponsor provided adequate information for corrective/preventative actions.

CAPA Conclusion		
The Sponsor provided adequate information for corrective and preventive actions.	☒Yes	☐No

12.3. 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-The Sponsor has provided adequate quality systems documentation.		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

<<END OF REVIEW>>

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/s/

SHIVA SALARTASH
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