CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210134Orig1s000

OTHER REVIEW(S)

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:	July 18, 2019
To:	Lisa Yanoff, M.D. Director **Division of Metabolism and Endocrinology Products (DMEP)**
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:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Samantha Bryant, PharmD, BCPS 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):	BAQSIMI (glucagon)
Dosage Form and Route:	nasal powder, for intranasal use
Application Type/Number:	210134
Applicant:	Eli Lilly and Company

1 INTRODUCTION

On June 28, 2018, Eli Lilly and Company submitted for the Agency's review a New Drug Application (NDA) for BAQSIMI (glucagon) nasal powder indicated for the treatment of severe hypoglycemia.

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 Metabolism and Endocrinology Products (DMEP) on July 13, 2018 and July 11, 2018, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for BAQSIMI (glucagon) nasal powder.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed May 24, 2019.

2 MATERIAL REVIEWED

- Draft BAQSIMI (glucagon) PPI and IFU received on June 28, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 10, 2019.
- Draft BAQSIMI (glucagon) Prescribing Information (PI) received on June 28, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 10, 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%. A reading ease score of 60% corresponds to an 8th grade reading level.

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. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

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.

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

---

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/

AMANPREET K SARAI
07/18/2019 03:58:44 PM

MARCIA B WILLIAMS
07/19/2019 06:03:51 AM

SAMANTHA E BRYANT
07/19/2019 06:06:31 AM

LASHAWN M GRIFFITHS
07/19/2019 07:34:58 AM

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

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

Memorandum

Date: July 17, 2019

To: Meghna M. Jairath, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

Monika Houstoun, Associate Director for Labeling, (DMEP)

From: Samantha Bryant, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for BAQSIMI (glucagon) nasal powder

NDA: 210134

In response to DMEP's consult request dated July 11, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI)/Instructions for Use (IFU), and carton and container labeling for the original NDA/BLA submission for BAQSIMI.

PI and PPI/IFU: OPDP's comments on the proposed labeling are based on the draft PI and PPI/IFU received by electronic mail from DMEP (Meghna Jairath) on July 10, 2019, and are provided below.

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

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DMEP on July 10, 2019, and our comments are provided below

Thank you for your consult. If you have any questions, please contact Samantha Bryant at (301) 348-1711 or Samantha.Bryant@fda.hhs.gov.

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

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

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:	June 27, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 210134
Product Name and Strength:	Baqsimi (glucagon) nasal powder, 3 mg
Applicant/Sponsor Name:	Eli Lilly and Company (Lilly)
FDA Received Date:	June 24, 2019
OSE RCM #:	2018-1387-2 and 2018-1416-2
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on June 24, 2019 for Baqsimi. We reviewed the revised container labels and carton labeling for Baqsimi (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.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Conrad A. Label and Labeling and Human Factors Results Review for Baqsimi (NDA 210134). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 May 24. RCM No.: 2018-1387-1 and 2018-1416-1.

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

---

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/

ARIANE O CONRAD
06/27/2019 10:08:06 AM

HINA S MEHTA
06/28/2019 08:36:01 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date of Consult Request:	March 13, 2019
From:	Jane Liedtka M.D., Medical Officer, Maternal Health, Division of Pediatric and Maternal Health (DPMH)
To:	Meghna Jairath, Regulatory project manager (RPM) Division of Metabolic and Endocrine Products (DMEP)
NDA Number:	210134
Drug:	BAQSIMI (glucagon nasal powder) 3mg
Applicant:	Eli Lily and Company
Indication:	treatment of severe hypoglycemia

DMEP submitted a consult request to DPMH on March 13, 2019, asking for assistance with the review of labeling language for the pregnancy and lactation sections for the above referenced NDA.

DPMH participated in a labeling meeting with DMEP on April 26,2019 and proposed labeling recommendations for the above referenced NDA.

DPMH- Maternal Health, has no further comments at this time, thus, this memorandum will close out the consult request.

DPMH Maternal Health MO Reviewer- Jane Liedtka, MD
DPMH Maternal Health Team Leader- Miriam Dinatale, DO
DPMH Division Director- Lynne Yao, MD
DPMH RPM-Kerri-Ann Jennings

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/

JANE E LIEDTKA
06/17/2019 11:33:39 AM

MIRIAM C DINATALE
06/17/2019 11:35:41 AM

LABEL AND LABELING AND HUMAN FACTORS RESULTS REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
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:	May 24, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 210134
Product Name and Strength:	Baqsimi (glucagon) nasal powder, 3 mg
Product Type:	Combination Product (Drug-Device), Single Ingredient
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly and Company
FDA Received Date:	April 2, 2019
OSE RCM #:	2018-1387-1 and 2018-1416-1
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS
DMEPA Associate Director:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

The Division of Metabolic and Endocrinology Products (DMEP) requested that DMEPA review the supplemental human factors (HF) validation study report and proposed labels and labeling submitted on April 3, 2019 under NDA 210134 for glucagon nasal powder.

1.1 PRODUCT INFORMATION

Lilly submitted NDA 210134 for Baqsimi (glucagon), which will be supplied as a nasal powder, for the emergency treatment of severe hypoglycemia in adult and pediatric patients. The proposed nasal delivery device is a prefilled, single-dose device that is intended to deliver one dose of glucagon to the nasal mucosa of a patient experiencing a severe hypoglycemic episode. Each device contains 3 mg of glucagon and will be supplied in a carton containing one device inside a shrink-wrapped sealed tube with printed instructions. Of note, users are expected to carry the sealed tube containing the nasal delivery device without the carton, so instructions are included on the outside of the device and tube when the printed IFU may be unavailable.

1.2 REGULATORY HISTORY

We evaluated Lilly's HF validation study results submitted June 28, 2018 in a prior review.[a] Our review determined that the failures associated with performing the critical task of depressing the plunger to administer the dose did not support safe use of the product. In addition, we identified areas of improvement and provided multiple recommendations to Lilly to the proposed labeling from a medication error perspective. We advised that Lilly implement changes to their user interface, including the labels/labeling, and conduct a supplemental HF study to validate that the revised user interface supports safe and effective use.

Thus, Lilly submitted additional HF study data and revised product labeling for review on April 2, 2019.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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
Human Factors Study	C
ISMP Newsletters	n/a

[a] Conrad A. Label and Labeling and Human Factors Results Review for Baqsimi (NDA 210134). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Jan 30. OSE RCM No.: 2018-1387 and 2018-1416.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
FDA Adverse Event Reporting System (FAERS)*	n/a
Labels and Labeling	D

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the supplemental human factors validation study results and we performed a risk assessment of the proposed labeling to identify areas of vulnerability that may lead to medication errors and other areas of improvement.

3.1 HUMAN FACTORS VALIDATION STUDY RESULTS

The sections below provide a summary of the study design, errors observed with the critical tasks (Table 2), and our analysis of the HF validation study results.

3.1.1 SUMMARY OF STUDY DESIGN

Lilly's previous HF study, submitted June 28, 2018, failed to demonstrate that the intended users could use the Baqsimi nasal powder device to administer doses and comprehend the product instructions in an emergency. For the newly submitted supplemental HF validation study, Lilly made labeling revisions and revised the study methodology to exclude use of the paper IFU and product carton to simulate actual use of the product as advised in our January 30, 2019 communication to the applicant.[b]

The supplemental HF validation study was conducted with 45 representative users: 15 adolescents aged 10-17 years (12 familiar with diabetes and 3 unfamiliar with diabetes), 15 adults ≥18 years of age (10 familiar with diabetes, 3 familiar with diabetes and trained to use injectable glucagon, and 2 unfamiliar with diabetes), and 15 healthcare providers (12 nurses and 3 emergency medical technicians). All study participants were untrained and were not shown the product prior to completing the study tasks; however, they were provided a general overview of the study's purpose.

Each participant was asked to simulate administering a dose of glucagon nasal powder after being presented with a manikin either lying on the floor or seated in an upright position. The tube containing the product, which included instructions on the tube labeling and device label, was on a table nearby. A sound machine was used to create beeping sounds, which increased in pitch, frequency, and intensity for the duration of the task to simulate a stressful

[b] Jairath M. Information Request for Glucagon Nasal Powder. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2019 Jan 30. NDA 210134.

environment. In addition, the moderator timed the participant's performance of the tasks and stressed the need to complete them quickly to induce a stress response. Participants failing to administer the product correctly were asked to read the instructions on the tube labeling prior before making a second attempt to administer a dose. After the administration tasks were completed, participants were asked knowledge questions related to information provided in the product labeling.

3.1.2 STUDY RESULTS AND ANALYSIS

Table 2 below summarizes and focuses on the results observed with the critical tasks, which were evaluated in the supplemental HF validation study along with the root cause analysis that Lilly provided for each failure. The table also includes our assessment of the critical task failures. Of note, Lilly did not propose any further mitigation strategies to address the failures identified in the study.

Table 2: Human Factors Validation Study Results				
Tasks[c]	Use Errors	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Usability Task: Place nozzle in nostril	3 errors: -3 adolescents familiar with diabetes Two of the adolescents delivered the dose to the manikin's mouth instead of the nose. The third adolescent attempted delivery to the manikin's mouth but failed to fully actuate the device. Each reported unfamiliarity with medications administered to the nose and assumed the medication would be delivered orally. In addition, one of these adolescents indicated that the manikin's open mouth contributed to the quick decision that the	The sponsor attributed these errors to the participants' age, lack of familiarity with the device, overlooking the instructional materials while under stress, and expectation that medications are usually delivered orally.	The sponsor expects that users, particularly adolescent caregivers, will receive some introduction to the device prior to use. In addition, the sponsor asserts that there is a low likelihood that an adolescent would randomly encounter an unresponsive person with a rescue medication that requires administration and would be able to identify an appropriate response for that situation with no prior knowledge of the product. The proposed paper IFU, tube label, nasal device label, and carton clearly state that Baqsimi is to be administered nasally and the sponsor determined that the current statements	Our assessment indicated that there is a risk for patient harm associated with this error as patients would not receive a therapeutic dose of glucagon. We note that there are multiple statements in the proposed labeling (nasal device label, tube label, carton label, paper IFU, and prescribing information) to indicate that the product is to be administered to the nose. Based on our evaluation of the labels and labeling and the root cause of the use errors, we do not have any recommendations to further address these errors.

[c] All study tasks were classified as critical.

Table 2: Human Factors Validation Study Results				
Tasks[c]	Use Errors	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	medication was intended for oral administration. Of note, only one of these adolescents referred to the product labels before attempting to administer the dose, reportedly only glancing at the images on the tube label without reading any of the text.		on the product labeling are sufficient. Thus, they determined that no further mitigation is required.	
Usability Task: Depress plunger to administer the dose	<u>4 errors:</u> -2 adolescents familiar with diabetes -1 adult familiar with diabetes -1 nurse These participants failed to push the plunger far enough to actuate the device (i.e., until the green line was no longer visible). Of note, the nurse and one of the adolescent	The sponsor attributed these errors to the participants' failure to read the instructions prior to attempting to administer the dose. In addition, the nurse attributed the error to a lack of familiarity with the device and the expectation that the nasal device would require repeated sprays into the nostril vs. one forceful spray.	The sponsor expects that caregivers will be familiar with the device prior to use, unlike in this simulated study, and will have either read the IFU or received counseling from the prescribing physician or pharmacist prior to use. The sponsor concludes that the device design and instructions are sufficient to mitigate for the failure to fully actuate the device; thus, they determined that	Our assessment indicated that there is a risk for patient harm associated with this error as patients would not receive the intended dose of glucagon. As noted with these failures, caregivers may not realize that they did not administer the full dose of glucagon. In addition, patients requiring glucagon therapy are typically unconscious and would not be able to communicate to the caregiver whether they received the dose.

Table 2: Human Factors Validation Study Results				
Tasks[c]	Use Errors	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	participants placed the device in the nostril and pushed the plunger repeatedly while alternating nostrils. The second adolescent and the adult did refer to the labeling, with the adolescent reportedly glancing at the pictures and the adult misreading the statement "dose is complete when the green line [redacted]" by overlooking the word [redacted]. Of note, each of these participants were able to successfully complete this task after they were asked to refer to the instructions printed on the tube label.		no further mitigation is required.	We acknowledge that the sponsor has included multiple statements in the labeling (nasal device label, tube label) to indicate that the plunger must be pressed until the green line is no longer showing to administer the full dose. As part of our evaluation, we also considered the results from the prior HF validation study reviewed.[a] We acknowledge that study participants in both HF validation studies experienced failures with the critical task "[redacted] plunger [redacted] however, we identified a methodology concern in the first study (i.e., users had the option to also refer to the paper IFU) that did not represent the highest risk scenario where the users only have access to the instructions on the nasal device and tube label. This might have

Table 2: Human Factors Validation Study Results				
Tasks[c]	Use Errors	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				confounded the results of the first study. For the second study, the sponsor employed a methodology that reflects the highest risk use scenario per our recommendation. In addition, the subjective feedback from this second study indicated that the user might have misread the word (b) (4) in this task; thus, we determined that additional clarity is needed to highlight that information on the nasal device label and tube label. In addition, based on the subjective feedback indicating that users did not realize that force was needed to actuate the device, we determined that additional clarity is needed to highlight that information on the nasal device label and tube label as well. These recommendations do not require additional HF validation data because the changes are

Table 2: Human Factors Validation Study Results				
Tasks[c]	Use Errors	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				intended to use affirmative language and do not change the critical tasks for product use. Please see our recommendations in Section 4.1 (bullets A2, A3, B2, and B3).

Furthermore, per additional discussion with medical officer with regards to the considerations of risk and benefit evaluation, we note that the glucagon products currently available require user reconstitution and are administered via injection during an emergency hypoglycemic episode. Based on postmarketing experience, we note that dose omission errors have occurred when users inadvertently inject the diluent only instead of using the diluent to reconstitute glucagon, resulting in patients not receiving the drug product. Thus, we believe that having the proposed nasal product as an alternative option may be beneficial for those patients with diabetes who require doses of glucagon with caregivers that are uncomfortable administering injectable medications. When considering the totality of the data submitted, the errors that occurred, and the public health benefit associated with this administration option, we find the residual risks associated with the use of Baqsimi to be acceptable.

3.2 LABELS AND LABELING

In addition to the supplemental human factors study evaluation, DMEPA reviewed the revised proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We noted that additional modifications are needed to improve the clarity and readability of important information on the proposed labeling and we provide recommendations in Section 4.1 for the container labels and carton labeling.

Our recommendations for the container labels and carton labeling do not require additional HF validation data because the changes are intended to use affirmative (rather than negative) language and do not change the critical tasks for product use.

4 CONCLUSION & RECOMMENDATIONS

The supplemental HF validation study results identified use errors with critical tasks. However, given our evaluation of the subjective feedback and our expert and heuristic review of the proposed product labels and labeling, we recommend the sponsor to implement additional revisions to the product labels and labeling. Given the nature of the revisions, we do not require additional human factors validation data. Please see our recommendations in Section 4.1.

4.1 RECOMMENDATIONS FOR ELI LILLY

We recommend the following be implemented prior to approval of this NDA.

A. Container Labeling (attached to sealed outer tube)
    1. We recommend revising the statement "contains 1 single dose" to "contains 1 dose" for clarity and consistency with the prescribing information.
    2. Revise the statement "Dose is complete when (b) (4)." to use affirmative language (e.g., "Dose is complete when green line disappears.") because the word "(b) (4) may be overlooked in the current location, as noted in the HF study.

3. We recommend revising the statement “Push plunger all the way in” to read “Push plunger firmly all the way in.” to improve user understanding that the device plunger requires a firm push to actuate the device due to errors noted in the HF study.

B. Carton Labeling
    1. We recommend revising the statement “1 (or 2) single dose nasal device(s)” to read “1 (or 2) nasal device(s)” on the cartons for improved clarity of the product contents and for consistency with the prescribing information.
    2. Revise the statement “Dose is complete when [redacted (b) (4)].” to use positive language (e.g., “Dose is complete when green line disappears.”) because the word “[redacted (b) (4)] may be overlooked in the current location, as noted in the HF study.
    3. We recommend revising the statement “Push plunger all the way in” to read “Push plunger firmly all the way in.” to improve user understanding that the device plunger requires a firm push to actuate the device due to errors noted in the HF study.

C. Instructions for Use
    1. Due to the above requested recommendations for the container labeling and carton labeling, please revise the Instructions for Use as necessary for consistency.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Baqsimi received on June 28, 2018 from Eli Lilly.

Table 3. Relevant Product Information for Baqsimi	
Initial Approval Date	n/a
Active Ingredient	glucagon
Indication	treatment of severe hypoglycemia in adult and pediatric patients with diabetes
Route of Administration	intranasal
Dosage Form	Nasal powder
Strength	3 mg
Dose and Frequency	A single 3 mg dose delivered intranasally
How Supplied	single-use nasal dosing device containing 3 mg of glucagon available in a shrink-wrapped packaging containing 1 device or 2 devices
Storage	temperatures up to 30°C (86°F); keep in the shrink-wrapped packaging until ready to use

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 18, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, glucagon AND 110674. Our search identified 1 previous review.[d]

[d] Conrad A. Label and Labeling and Human Factors Results Review for Baqsimi (glucagon nasal powder, NDA 210134). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Jan 30. OSE RCM No.: 2018-1387 and 2018-1416.

APPENDIX C. HUMAN FACTORS STUDY

The following HF study documents can be assessed in the EDR via the following links:

HF Results report: \\cdsesub1\evsprod\nda210134\0033\m1\us\ly900018-nda-210134-seq0033-rtq07-2019-04.pdf

APPENDIX D. LABELS AND LABELING

D.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 Baqsimi labels and labeling submitted by Eli Lilly.

- Container label received on April 2, 2019
- Carton labeling received on April 2, 2019
- Instructions for Use received on April 2, 2019
    - o \\cdsesub1\evsprod\nda210134\0036\m1\us\proposed-usermanual-clean.docx

D.2 Label and Labeling Images

Container Label (attached to inhaler)

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

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

---

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/

ARIANE O CONRAD
05/24/2019 08:17:16 AM

MISHALE P MISTRY on behalf of HINA S MEHTA
05/24/2019 08:55:39 AM

QUYNHNHU T NGUYEN
05/24/2019 10:08:14 AM

MISHALE P MISTRY
05/24/2019 10:09:56 AM

OFFICE OF DEVICE EVALUATION
DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM

Date	April 19, 2019
To	Anika Lalmansingh CDER/OPQ/OPRO/DRBPMI/RBPMBI
Requesting Division	CDER/OPQ/OPRO
From	Matthew Ondeck CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	Consult for Submission # NDA 210134 ICCR2018-03234 ICC1800591
Recommendation	**CDHR/ODE Recommendation:** Device Constituents Parts of the Combination Product are Approvable with a (b) (4) month shelf life. If the sponsor would like to extend the shelf life to (b) (4) month, as originally proposed, we recommend that they submit a shelf-life extension protocol to propose the device performance testing that would be needed to extend the shelf life as a part of a supplement. **CDRH/OC Recommendation:** • Quality Systems Recommendation: The QS information is adequate to support approval. • Facilities Inspections Recommendation: Facilities information is adequate. Inspection recommendations are below: ***Combination Product Applicant:*** Firm Name: Eli Lilly and Company A pre-approval inspection is required and was completed ***Finished Combination Product Manufacturer:*** Firm Name: (b) (4) A post-approval inspection is required

Digital Signature Concurrence Table

Reviewer	
Team Lead	
Branch Chief	

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2018-03234
ICCR SharePoint Link	SP link
ICC tracking # (Lead)	ICC1800591
Submission Number	NDA 210134
Sponsor	Eli Lilly and Company
Drug/Biologic	BAQSIMI (Glucagon nasal powder)
Indications for Use	Treatment of severe hypoglycemia
Device Constituent	Nasal Spray
Related Files	IND 110674

Table 2. Review Team	
CDER/CBER Lead Review Division	CDER/ODEII/DMEP
Submission RPM	Meghna Jairath
Lead Device Reviewer	Matthew Ondeck
The CDRH review is being managed under ICC1800591	
Below is a list of the Discipline Specific ICCR#, ICC# and CON#. The CON# are under ICC1800591 in CTS.	

Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	ICCR #	ICC #	CON #
Compliance	Leslie E. Dorsey/ Nikhil Thakur CDRH/OC/DPLC/SEB II	ICCR2018-03380; SP Link	ICC1800591	CON1820113

Table 3. Important Dates		
Interim Due Dates	**Meeting Date**	**Due Date**
Filing	8/16/2018	8/27/2018
Mid-Cycle	10/28/2018	N/A
Wrap Up Meeting	3/20/2019	N/A
Primary Review	N/A	3/22/2019
Secondary Review	N/A	3/28/2019

2. PURPOSE/BACKGROUND

2.1. Scope

The purpose of this review is to provide a review of the device constituent for NDA 210134. There was not scope provided in the request details of the consult. Therefore, a full device review will be provided. The review will cover:

- Device Performance
- Device Biocompatibility (Non-primary container closure, non-fluid path)
- Human Factors
- Quality System/Inspection Review

2.2. Prior Interactions

CDRH previously issued comments regarding device reliability comments under IND110674

- Type B Meeting held 5/29/2015
- Type C Meeting WRO – 9/16/2016

2.3. Indications for Use

Combination Product	Indications for Use
BAQSIMI (glucagon nasal powder)	BAQSIMI™ is an antihypoglycemic agent indicated for the treatment of severe hypoglycemia.
Nasal Spray	Administration of drug product

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Location
Proposed-uspi-clean	0000(1)_1.14.1.13 Draft Labeled Text
Proposed-usermanual-clean	0000(1)_1.14.1.13 Draft Labeled Text
Type B Meeting Minutes 29May2015	0000(1)_1.6.3 Correspondance Regarding Meetings
Type C Meeting FDA Written Response- 16 September 2016	0000(1)_1.6.3 Correspondance Regarding Meetings
Specifications	0000(1)_3.2.P.5.1 Specification(s)
Batch-analyses	0000(1)_3.2.P.5.6 Batch Analyses
Medical-device	0000(1)_3.2.R Regional Information
Medical-device-app-a-hfe	0000(1)_3.2.R Regional Information
Contain-tube	0000(1)_1.14.1.1 Draft Carton and Container Labels
Contain-device	0000(1)_1.14.1.1 Draft Carton and Container Labels
Cntrl-critical-steps	0000(1)_3.2.P.3.4. Controls of Critical Steps and Intermediates
Particle-size –g2065-valid-analyt-proc	0000(1)_3.2.P.5.2 Analytical Procedures
Shotweight-pds00496-analyt-prc	0000(1)_3.2.P.5.2 Analytical Procedures
Shotweight-pds00496-valid-analyt-proc	0000(1)_3.2.P.5.2 Validation of Analytical Procedures
Particle-size-g2065-valid-analyt-proc	0000(1)_3.2.P.5.2 Validation of Analytical Procedures
Justifif-specs	0000(1)_3.2.P.5.6 Justification of Specifications
Medical-device-app-c-rrr	0000(1)_3.2.R Regional Information
Quality-response-to-questions-25-sep 2018	0008(8)_1.11.1 Quality Information Amendment
Medical-device-sac-full	0008(8)_3.2.R. Regional Information
Container-closure-dev	0000(1)_3.2.P.2. Pharmaceutical Development
Quality-rtq-jan2019-followup	0023(24) 1.11.1 Quality Information Amendment
Medical-device-sac-reliability	0023(24)_3.2.R Regional Information
1111-quality-response-to questions-27-nov-2018	0016(21) 1.11.1 Quality Information Amendment

Quality-response-to-questions- oct-2018	0009(10) 1.11.1 Quality Information Amendment
Quality-response-to-questions-sept-2018	0010(12) 1.11.1 Quality Information Amendment
111-quality-response-to questions-21 feb2019	0027(26) 1.11.1 Quality Information Amendment
Quality-response to questions 28-feb-2019	0029(29) 1.11.1 Quality Information Amendment

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

The nasal glucagon delivery device is a prefilled, single-use, delivery device that is intended to deliver a single dose of glucagon to the nasal mucosa of a patient experiencing severe hypoglycemia. Figure 3.2.R.3.2-1 is an image of the device and functional secondary packaging.

.3.2-1 Nasal Glucagon Device and Secondary packaging

The single use device is prefilled with one dose of glucagon drug powder and is provided non-sterile and ready-to-use. The device may be used by lay persons, emergency medical technicians, or health care providers to administer an intranasal dose of glucagon. The dose may be delivered in multiple environments including home, work, school, recreation, ambulance, or health care facility.

Device operation is relatively simple. After removing the device from the secondary packaging, the user inserts the device nozzle into the patient's nostril and presses the button on the bottom of the device (b) (4) expels the drug product into the nose. In contrast, the current standard of care requires multiple steps to reconstitute and deliver glucagon by injection to treat severe hypoglycemia.

The figures below show the primary container closure system, assembled delivery device, and functional secondary packaging. The filled primary container closure system fits inside the assembled delivery device, which is comprised of (b) (4) The device is stored in functional secondary packaging comprised of a tube with desiccant to (b) (4).

(b) (4)

Primary Container Closure

The primary container closure for nasal glucagon is a (b) (4)

(b) (4)

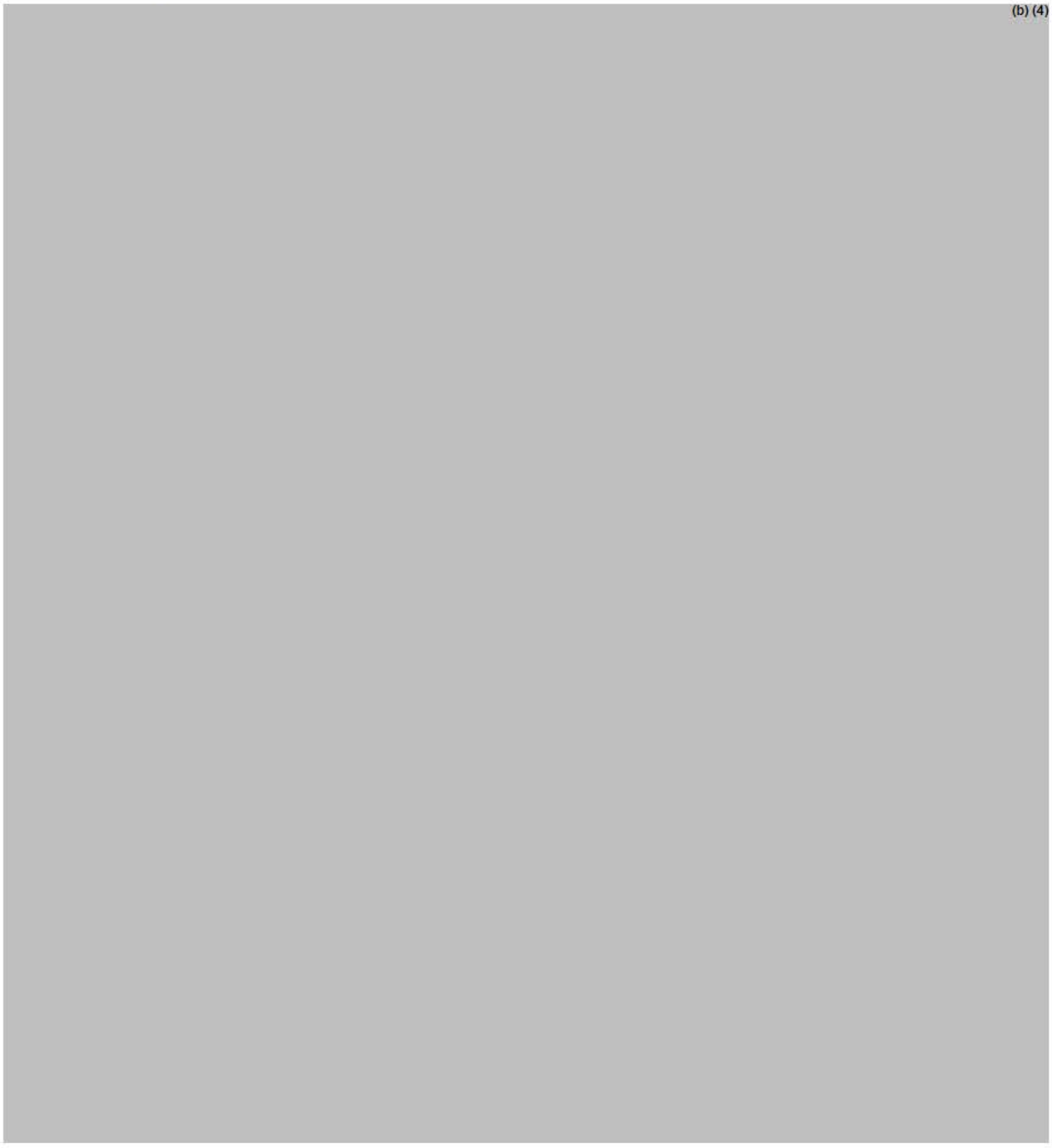
Nasal Glucagon Delivery Device

In addition to the primary container closure, the nasal glucagon delivery device consists of (b) (4)

Drug product contact does not occur with the other device components.


(b) (4)


(b) (4)



DMF related to the components above are listed below:

(b) (4)

Reviewer Note:

For nasal sprays, we expect the EPRs to include, at a minimum, the following (These are evaluated in Section 6.3)

- Pump Delivery (Spray Weight)
- Spray Pattern and Plume Geometry Shape
- Spray Content Uniformity (SCU)
- Droplet / Particle Size Distribution
- Actuation Force

Steps for Using the Device:

The delivery device containing drug powder is stored in the functional secondary packaging (b) (4) Prior to use, the user must remove the delivery device from the packaging.

To operate the device, the user performs the following steps:

1. Hold the delivery device between fingers and thumb.
2. Insert the tip of the actuator gently into one nostril of the patient until the fingers touch the outside of the nose.
3. Push the button all the way into the bottom. The dose is complete when the green stripe is no longer showing.

When the user pushes the button into the bottom, the following steps take place within the device:

(b) (4)

Figure 3.2.R.3.3.2-1 shows component movements during drug delivery.

The table below is a summary description of the device characteristics:

Device Characteristic	Subject Device
Injector Platform Name	(b) (4)
Fill Volume	3 mg glucagon
Injection Site	Intranasal (b) (4) spray
Audible / visual feedback	Button is retained in device after delivery
Visibility of medication container	No
Last Dose Specifications and Safety Features	N/A (single use)
Type of Use (e.g. single use, disposable, reusable, other)	Single use
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Lay persons, emergency medical technicians, or health care providers
Injection/Spray mechanism (e.g., manual piston, spring, gas, etc.)	Manual actuation
Method of actuation	Manual actuation
Automated Functions	N/A
Residual Medication	N/A
Drug Container Type	(b) (4) nasal spray
Environments of use	Emergency use: hospital/home use
Expiry	(b) (4)
Preparation and administration (describe all that are applicable) • Warm to room temp prior to injection • Assembling components • Prime steps	See Steps for using device section

• Setting dose • Skin preparation steps (e.g., pinch skin, inject through clothing, etc.)	

Device Description Recommendation:
The device description is adequate.

5. DESIGN CONTROL REVIEW

5.1. Design Review Summary

5.1.1. *Design Control Documentation Check/Filing Review:*

Lead reviewer Matthew Ondeck was included in the Filing Review/Meeting with CDER. It appeared that there was adequate information to continue with the application filing. However, deficiencies were included in the 74 day letter. See Section 11.1 for the deficient material at the time of filing.

5.1.2. *Design Control Documentation Check*

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	X		3.2.R Regional Information_medical-device
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		3.2.P.5.4 Batch Analysis
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		3.2.R Regional Information _3.2.R "medical device rrr"
Validation Data	X		3.2.R Regional Information_medical-device
• Human factors • Clinical data	X		

Design Control Review Recommendation:
The design control review is adequate.

6. DESIGN VERIFICATION AND VALIDATION REVIEW

6.1. Summary of Design V&V Attributes

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial		X*	
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		

* See Section 6.2.1. Minor device modifications were made that would not appear to affect the device EPRs. Therefore while the to-be-marketed device was not used, I believe that it is acceptable to demonstrate clinical validation of the device constituent.

Discipline -Specific Design Verification / Validation adequately addressed*						
	Consult needed			Consultant	Attributes Acceptable	
	Yes	No	N/A		Yes	No
Engineering (Materials, Mechanical, General)		X			X	
Biocompatibility		X			X	
Sterility			X		N/A	
Software / Cybersecurity		X				
Electrical Safety / EMC			X		N/A	
Human Factors	X			CAPT. Mary Brooks	X	
Quality Systems	X			Leslie Dorsey/Nihkil Thakur	X	

6.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device		X*	
Bioequivalence Study utilized to-be-marketed device			X
Simulated Actual Use Study utilized to-be-marketed device	X		

* See Section 6.2.1. Minor device modifications were made that would not appear to affect the device EPRs. Therefore while the to-be-marketed device was not used, I believe that it is acceptable to demonstrate clinical validation of the device constituent.

6.2.1. *Clinical Validation*

The sponsor states that there have been minor device changes to the device compared to what was used in the clinical study. They discuss the risks of these changes to the device performance in response to question 3. The sponsor has clarified the differences in the clinical use device and the to-be-marketed version of the device. These are also the same stability lots versions of the device.

While it is unlikely that the changes to the device from the primary stability lots would affect the performance requirements of the device, given that the internal assembly of the device are not changing, it is unclear if this would

affect the drug stability or device performance requirements. A deficiency was sent to the sponsor and they responded with the following:

"Delivery performance of the device (i.e., Pump Delivery (spray/shot weight), Spray Pattern, Plume Geometry, and SCU) is dependent on only two factors:

(b) (4)

In contrast to solution-based nasal sprays, particle size distribution for nasal glucagon is not dependent on the device, but is an inherent property of the drug powder. Therefore, particle size distribution is not affected by this change. Device actuation force is (b) (4) generated during actuation. The primary constituents of actuation force are the (b) (4). As there were no changes to the primary container closure system, the changes have no effect on drug product compatibility.

The sponsor has provided an adequate response. I do not believe that the minor design changes listed above will change the device essential performance requirements and are adequate as far as clinically validating the device.

6.2.2. *Human Factors Validation (completed by Lead Reviewer)*

The sponsor provided a human factors validation study. The review of the adequacy of the study is deferred to CDER/DMEPA and CDRH/DAGRID (CAPT. Mary Brooks completed a review). However a cursory review of the HF study by the lead reviewer is provided below. **For the CDRH/DAGRID review please see Section 7.3 of the review in which CAPT Mary Brooks completed a full HF validation review.**

The tasks that the sponsor identified are below. They were identified using a use-related risk analysis. See below:

Table 7. Critical Tasks for Nasal Glucagon

Task (use step)	Potential use error	Potential hazard	Potential harm	Mitigations	Evaluative method
User transport/stores product	User opens tube prior to emergency scenario requiring use	Degraded drug product	Continued SEVERE HYPOGLYCEMIA, may result in Death	Instructions on the tube state to not remove the shrink wrap until ready to use and to call for medical help right away after giving a dose.	Knowledge assessment
	User exposes device to moisture	Degraded drug product	Continued SEVERE HYPOGLYCEMIA, may result in Death	Instructions on the tube state to not remove the shrink wrap until ready to use and to call for medical help right away after giving a dose.	Knowledge assessment
	User carries a device that is expired	Degraded drug product	Continued SEVERE HYPOGLYCEMIA, may result in Death	Tube label states expiration date and to call for medical help right away after giving a dose.	Knowledge assessment
Open the tube	User is unable to open the tube	No dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	Tube is designed to be opened by intended users	Simulated Administration
Remove device from tube	User is unable to remove device from tube	No dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	The tube and device are designed to afford it to be removed by intended users	Simulated Administration
Hold device between fingers and thumb	User inadvertently actuates device	No dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	Force to actuate device affords use by intended users while mitigating inadvertent actuation, and instructions state to call for medical help right away after giving a dose.	Simulated Administration
	User actuates the device attempting to 'test' it prior to use	No dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	In the step "Hold device between fingers and thumb", the tube label instructions state "Do not press plunger", and to call for medical help right away after giving a dose.	Simulated Administration
Place nozzle in nostril	User places nozzle in a location that is not the nostril	No dose or partial dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	Instructions on the tube indicate to administer into the nostril, and to call for medical help right away after giving a dose.	Simulated Administration
	User does not push the nozzle far enough into the nostril	No dose or partial dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	Instructions state to insert the tip gently in one of the nostrils until finger(s) touch the outside of the nose, and to call for medical help right away after giving a dose.	Simulated Administration
Depress plunger to administer a dose	User does not fully depress plunger	No dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	Device designed for actuation force low enough for intended users, and high enough to prevent accidental actuation. Instructions state to depress plunger until the green line at the bottom is no longer visible, and to call for medical help right away after giving a dose.	Simulated Administration
After giving a dose	User does not dispose of device and carries a used device with them	No dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	Device is designed to visually indicate when it is used (plunger stays down, and green line is hidden when actuated). Tube label states nasal glucagon is a single use product, to throw away the used device.	Knowledge Assessment

The sponsor provided information regarding the validation study. The testing was done with 45 users, listed below. The range of users appear adequate, given that they are expanding upon age groups, lay users, and HCPs

Test Participants

The study included a total of 45 representative users, including:

[n=15] Adolescent lay users (10-17 years of age), including:

[n=7] familiar with diabetes (e.g., living with someone with diabetes)

[n=8] not familiar with diabetes

[n=15] Adult lay users (≥18 years of age), including:

[n=11] familiar with diabetes (including n=7 previously trained on injectable glucagon)

[n=4] not familiar with diabetes

[n=15] Healthcare providers, including:

[n=3] Emergency room physicians

[n=7] Nurses

[n=5] EMTs

The summary results are below:

Table 9. Summary of Results, Simulated Use Test

			Task 1: Open Tube		Task 2: Remove Device		Task 3: Insert tip		Task 4: Depress plunger	
Participant Group	**Subgroup**	**n**	**Success**	**Failure**	**Success**	**Failure**	**Success**	**Failure**	**Success**	**Failure**
Adolescent lay users (n=15)	Familiar	7	7	0	7	0	7	0	5	2
	Not familiar	8	8	0	8	0	8	0	8	0
Adult lay users (n=15)	Familiar, no inj. glucagon exp.	4	4	0	4	0	4	0	4	0
	Familiar, Prior inj. glucagon training	7	7	0	7	0	7	0	6	1
	Not familiar	4	4	0	4	0	4	0	4	0
Healthcare providers (n=15)	E.R. Physicians	3	3	0	3	0	3	0	3	0
	Nurses	7	7	0	7	0	7	0	7	0
	EMT	5	5	0	5	0	5	0	5	0
	Totals	45	45	0	45	0	45	0	42	3

The sponsor provided a root cause anlaysis to anaylze the failure observerd in the HF validation study. Of note the only exhibited failures were in Task 4 “depress plunger”

Participant	Test Scenario	Observation	Participant comments	Root Cause	Clinical Consequence
Y03 [Female, Age 16, REALM- Teen 64, familiar with diabetes]	Test Scenario 1: Simulated Use	Did not fully depress the plunger – she pushed part way, but not far enough to actuate the device. Y03 opened and followed the IFU during the scenario. After the task (and before root cause investigation), when asked to give another dose, she was successful.	User said that the first time she used the device, she didn't know when to stop pushing the plunger.	User did not know to fully depress the plunger until the green line is no longer visible	Delay of therapy
Y06 [Male, Age 15, REALM- Teen 66, familiar with diabetes]	Test Scenario 1: Simulated Use	Did not fully depress the plunger – repeatedly went back and forth between the nostrils, partially depressing the plunger each time (similar to OTC nasal sprays). He opened and followed the IFU during the scenario. After the task (and before root cause investigation), when asked to follow the IFU to give another dose, he was successful.	User said that the first time he used the device, he didn't know that had to push down until the green line was not visible. He also said he expected it to work like a typical nasal spray, or syringe-like device (where repeatedly pressing it sprays medicine into the nostril).	User did not know to fully depress the plunger until the green line is no longer visible.	Delay of therapy
A10 [Male, Age 58, REALM 60, familiar with diabetes, prior training on injectable glucagon]	Test Scenario 1: Simulated Use	Placed the nozzle firmly into the nostril, but did not press the plunger. He then placed the device on the floor and stated he was finished. After the task (and before root cause investigation), when asked to follow the IFU to give another dose, he was successful.	User said he expected to push the device into the nose and it would actuate automatically like an EpiPen.	User did not know to fully depress the plunger until the green line is no longer visible.	Delay of therapy

Participant	Test Scenario	Observation	Participant comments	Root Cause	Clinical Consequence
Y09 [Female, Age 12, REALM-Teen 47, not familiar with diabetes]	IFU Knowledge assessment, Q2: According to the materials, when should you open the tube?	The participant could not locate the information on the tube.	The participant could not locate the answer to the question. She showed confusion over whether the yellow blocks of information on the label were separate instructions.	User was confused over the apparent redundancy of the "Do not remove shrink wrap" and "Do not open tube" lines.	Potential to deliver degraded drug if the user opened the tube and exposed the product to moisture before use.
Y10 [Male, Age 15, REALM- Teen 65, not familiar with diabetes]	IFU Knowledge assessment, Q3: According to the materials, what are you supposed to do after giving the dose?	The participant briefly looked at the tube, then abandoned the task. He did not peel back the label, so did not locate the information on the tube. After the task (and before root cause investigation), when asked what he would do in this situation, he said he would call 911.	User said he not see the "peel back" instructions, because his attention on that part of the label was focused on the "Do not remove shrink wrap" and "Do not open tube" lines.	User did not see the "Peel for instructions after giving the dose" text on the label.	Little to no clinical consequence, as it did not prevent the participant from successfully delivering the drug.
A07 [Male, Age 31, REALM 55, familiar with diabetes]	IFU Knowledge assessment, Q3: According to the materials, what are you supposed to do after giving the dose?	The participant did not peel back the label, so did not locate the information on the tube. After the task (and before root cause investigation), when asked what he would do in this situation, he said he would call 911.	Participant did not peel back the label to read the information underneath. He did not pay attention to the "peel back" instructions, saying that he felt like it was an anxious situation, and assumed that under the peel would be instructions he didn't need, such as drug or chemical information. He indicated that he would call 911 after giving a dose.	User assumed that the information in the "peel back" section label was nonessential or irrelevant to the task.	Little to no clinical consequence, as it did not prevent the participant from successfully delivering the drug.

Participant	Test Scenario	Observation	Participant comments	Root Cause	Clinical Consequence
A09 [Male, Age 55, REALM 51, familiar with diabetes, prior training for injectable glucagon]	IFU Knowledge assessment, Q3: According to the materials, what are you supposed to do after giving the dose?	The participant did not peel back the label, so did not locate the information on the tube. After the task (and before root cause investigation), when asked what he would do in this situation, he said he would call 911.	User said he expected instructions on what to do after giving a dose to be sequential with the steps on the tube, and was not expecting to find it under the peeled label.	User assumed that the information in the "peel back" section label was nonessential or irrelevant to the task.	Little to no clinical consequence, as it did not prevent the participant from successfully delivering the drug.
A15 [Female, Age 63, REALM 66, familiar with diabetes, prior training for injectable glucagon]	IFU Knowledge assessment, Q3: According to the materials, what are you supposed to do after giving the dose?	The participant did not peel back the label, so did not locate the information on the tube.	User said she would expect to be trained on this device by the doctor before even getting it.	User did not know to peel back the label to find what to do after giving a dose and assumed she would be trained to use it before getting it.	Little to no clinical consequence, as it did not prevent the participant from successfully delivering the drug.
Y08 [Female, Age 12, REALM-TEEN 52, familiar with diabetes]	IFU Knowledge assessment, Q5: According to the materials, how many times can a device be used?	The participant could not locate the information on the tube.	When directed to the phrase "For single use only" and asked to interpret, she said it was confusing and that she didn't know what it meant.	User did not understand the meaning of the phrase "For Single Use Only"	Potential for delay of therapy if the user kept a used device thinking it could be used again.

3 failures were noted during the actuation of the device in the simulated use study. The sponsor states:

The task failures shown in Table 11 reflect a risk of delay of therapy if users do not fully depress the plunger in actual use. The participants who experienced this task failure included 2 adolescents (16 year old female, and 15 year old male) and 1 adult (a 58 year old male) who did not know how far to depress the plunger.

- In the first case, the participant (a 16 year old female) did not see the instruction that the dose is complete when the green line is no longer visible.
- In the other 2 cases, the participants expected the device to work differently than described in the labeling (i.e., like nasal spray and an autoinjector, respectively). Before performing root cause investigation, these participants were asked to repeat the scenario while reading along with the IFU.

In all three cases, the participants successfully administered a dose, indicating as expected that emergency situations contribute to lay user errors. Lilly intends for users to read the instructions, and the results show that the instructions serve as sufficient mitigation for the failure to activate the device. In light of the success of all participants in delivering a dose under conditions that they had read the instructions, Lilly concludes that no further mitigations are necessary.

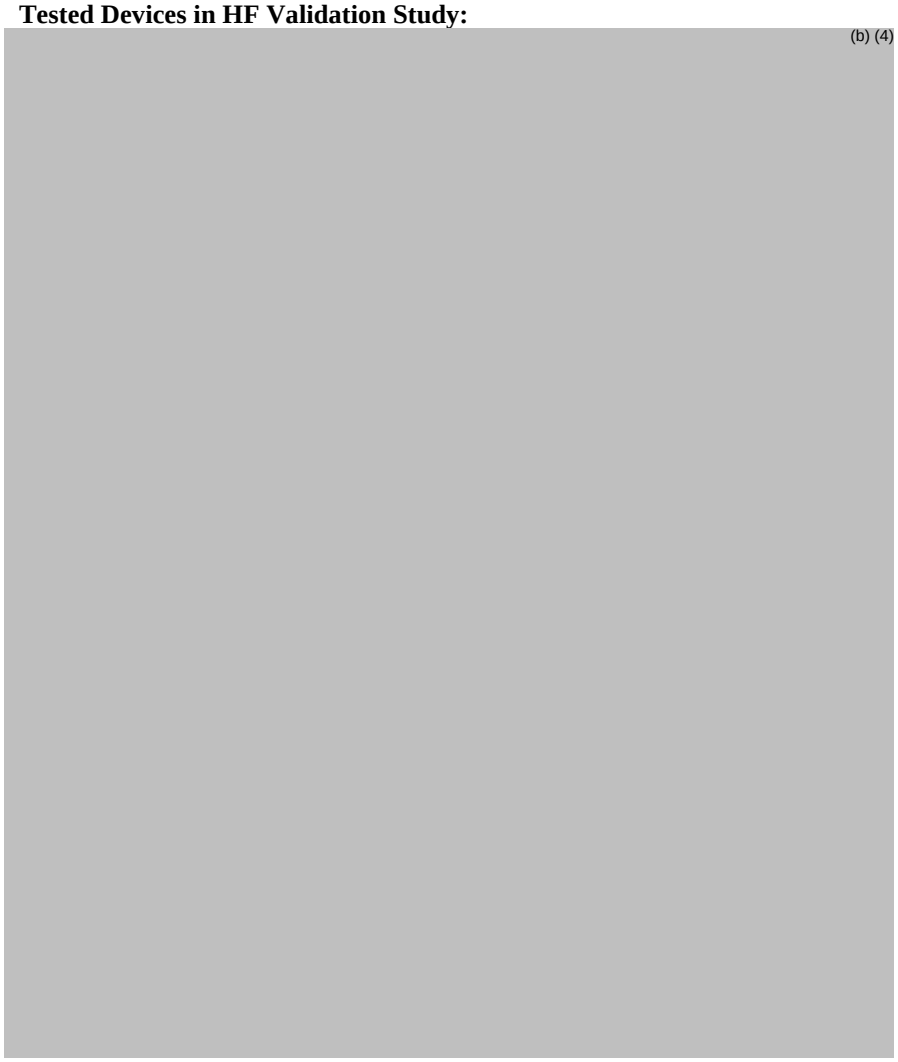
Reviewer Note:
The reasoning that the sponsor provides is noted for the device. However, in most cases the user will not be looking for the instructions to administer the device in an emergency situation. They also note that the instructions are on the spray carton, as shown below and a folded IFU is within the carton.

I believe that the outer packaging on the device is relatively clear, despite the failures that were observed. The labeling on the device states: "**Push** the Plunger all the way in (b) (4) I defer to CDRH reviewer HF review Mary Brooks. Mary Brooks had no additional deficieincies; therefore there is no outstanding deficeincies.

Additionally, there does not appear to be any failures related to difficulties in the amount of force needed to actuate the device.

Tested Devices in HF Validation Study:

(b) (4)



Instructions/Labeling on Nasal Spray Device:

Folded IFU in carton:

Design Validation Recommendation:
Please see Section 7.3 of the review, which includes the full review of the Human Factors study. CAPT. Mary Brooks had no outstanding deficiencies regarding the HF study.

6.3. Design Verification Review

For a nasal spray device, the Agency expects that the following should be considered essential performance requirements:

- Pump Delivery (Spray Weight)
- Spray Pattern and Plume Geometry Shape
- Spray Content Uniformity (SCU)
- Droplet / Particle Size Distribution
- Actuation Force

All of the performance parameters (except for actuation force) are required by the CDER Spray Guidance. However, the sponsor that only dose accuracy is an essential performance requirement of the device:

Table 3.2.R.3.5.4-1 Essential Performance Requirements Evaluation

Performance Function	Essential Performance (Yes/No)	Rationale
Delivered Dose (Shot Weight)	Yes	Delivered Dose is a direct relationship to clinical function of delivering the drug powder to the nasal cavity for absorption of glucagon through the nasal mucosa. A failure of this performance function could result in an underdose or no dose delivered and continued severe hypoglycemia (Hazard severity = 4 or 5).
Spray Pattern	No	Spray Pattern may be used to characterize device performance, but does not impact the ability of the device to deliver a dose. For this product design, a failure of this performance function is not associated with any hazard.
Plume Geometry	No	Plume Geometry may be used to characterize device performance, but does not impact the ability of the device to deliver a dose. For this product design, a failure of this performance function is not associated with any hazard.
Particle Size Distribution (PSD)	No	PSD of the delivered dose is determined and controlled by the drug powder manufacturing process, and not by the actuation of the device. No meaningful difference in PSD has been observed between the drug powder as filled and the drug powder as collected from the actuated device. A failure of this performance function could result in severe hypoglycemia (Hazard severity = 4 or 5) if particles were large enough that they couldn't pass through the device following actuation, however, the delivered dose (Shot Weight) method would detect this failure.
Actuation Force	No	Actuation force is not directly related to clinical function of dose delivery as long as a minimum force required to compress the air in the device chamber and to displace the centerpiece and ball is applied. Forces beyond this minimum required force will not affect the dose delivery as a full dose would still be delivered. An excessively high actuation force could result in the user having difficulty or being unable to actuate the delivery device in which case they could use two hands to deliver the dose. The most likely scenario is user dissatisfaction (Hazard severity = 1), and least likely scenarios include delay in therapy or no dose delivered with indication (Hazard severity = 5).

Design Verification Testing Summary

Device Performance Requirement	Specification	Test Methods	Primary Spec Verified	Spec Verified to Expiry ((b) (4) months)**	Spec Verified after Shipping	Lot Release Specification Included
Dose Accuracy	Each individual shot weight is NLT (b) (4)% of the mean fill weight The mean shot weight is NLT (b) (4)% of the mean fill weight *	Adequate	Yes	Yes**	Yes	Yes
Delivered Dose Uniformity	NLT (b) (4)%	Adequate	Yes	Yes**	Yes	Yes
Spray Pattern Diameter/Shape	NLT (b) (4)mm and Ovality (Dmax/Dmin) NMT (b) (4)	Adequate	Yes	Yes**	Yes	No***

Plume Geometry/Plume Angle	NLT (b) (4) deg NMT deg	Adequate	Yes	Yes**	Yes	No***
Particle Size Distribution	X90 NMT (b) (4) microns	Adequate	Yes	Yes**	Yes	Yes
Actuation Force	<u>At Room Temperature:</u> NLT: (b) (4) kgF NMT: (b) (4) kgF <u>At -20 deg C</u>: NLT: (b) (4) kgF NMT: (b) (4) kgF	Adequate	Yes	Yes**	Yes	Yes

* Regarding the shot weight specification, the sponsor has provided an adequate justification for why the dose accuracy does not include the fill weight. See Section 6.3.1.1.
** The sponsor is proposing a (b) (4) month shelf life, but has not verified the device EPRs up the (b) (4) month shelf life. I have spoken to OND and OPQ and only a (b) (4) month shelf life will be granted if the product is approved. This is acceptable.
*** OPQ Reviewer Muthukumar Ramaswamy has stated that CDER does not recommend that plume geometry and spray pattern be included as lot release specs/tests as this is a quality control test and does not need to be included. While, I do not agree with this decision to exclude these device performance requirements from lot release as it is important that the device is able to administer the drug product in the correct fashion to achieve the clinical affect, CDER is the lead center on this product; therefore I defer to CDER/OPQ. Additionally, the sponsor has included testing for these specific device EPRs in their reliability testing and has demonstrated that they can be met with 99.99% reliability, which supports the consistency of the delivery.

6.3.1. *Test Methods/Results:*

6.3.1.1. *Dose Accuracy:*

The sponsor states that the specification for dose accuracy is:

"each individual shot weight is NLT (b) (4) % of the mean fill weight The mean shot weight is NLT (b) (4) % of the mean fill weight."

This specification appears to be in line with the shot weight specification meets the intent of the Food and Drug Administration (FDA) Guidance for Industry "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing and Controls Documentation, 2002". However, an (b) (4) is not proposed since it is controlled by a 100% (b) (4) that rejects filled primary container closures that fall outside the range of (b) (4) % of the target (b) (4) . Additionally, the sponsor refers to the mean fill weight in the specification, not the target fill weight as the CDER guidance recommends. The sponsor was asked why the target weight was not included in the shot weight specification. They state that this was because there are other in-process/release controls used, such as (b) (4) See reviewer note below:

Reviewer Note:
The sponsor has provided a rationale to support their shot weight specification:

Lilly acknowledges that fill weight and shot weight are important attributes for nasal products. Given the unique nature of nasal glucagon, we would like to clarify why the specification for shot weight is based on the mean fill weight of the drug product rather than on the target fill weight. In addition, a brief discussion is provided for the in-process and release controls that are in place to (b) (4)

Manufacturing Process Description

(b) (4)

In-Process Control

(b) (4)

Shot Weight/Mean Fill Weight Rationale

(b) (4)

Release Controls

(b) (4)

FDA Response:

The sponsor has described in process controls (b) (4) that (b) (4)

(b) (4)

Dose accuracy testing/shot weight verification testing was provided in 3.2.P.5.2 (Seq0000), and additionally provided up to stability (18 months)/shipping in 1.11.1 (Seq0023). Stability testing was completed with 3 lots and the shot weight met specification to (b) (4) months.

Amended 4/18/2019:

In addition to the testing described above, the sponsor has provided test results on 4/12/2019 of the subject EPR with preconditioning (at time = 0) to support the use of the product after the following preconditioning. All testing passed the acceptance criteria.

Table RF-2 Shot Weight Testing Results

Pre-Conditioning	Specification Limit Shot Weight (% Mean fill wt.)	Sample Size	Mean $\bar{x}$ (%)	SD σ (%)	Minimum (%)	Maximum (%)	Tolerance Limit $\bar{x}$ - Target k*σ	Pass/Fail
Standard	(b) (4)	60	98	2	93	101	(b) (4)	Pass
Vibration		60	98	1	95	101		Pass
In-Use Heat Exposure		60	99	2	95	101		Pass
In-Use Cold Exposure		60	97	2	90	101		Pass
Free Fall (Combination Product)		60	99	1	95	101		Pass
Free Fall (Packaged Combination Product)		60	98	1	95	101		Pass

Abbreviation: NLT = not less than.

6.3.1.2. *Particle Size Distribution:*

The sponsor states that the specification for particle size distribution is that the (b) (4)% of the measured particles are not more than (b) (4) microns. I defer the adequacy of the specification to the OPQ review division since this is a drug product characteristic, however this review will analyze the ability for the device to administer drug product at this specification.

Particle size distribution testing was provided for the mean, min, and max sizes up to 18 months and after shipping testing. All passed.

Amended 4/18/2019:

In addition to the testing described above, the sponsor has provided test results on 4/12/2019 of the subject EPR with preconditioning (at time = 0) to support the use of the product after the following preconditioning. All testing passed the acceptance criteria.

Table RF-5 Particle Size Distribution Testing Results

Pre-Conditioning	Specification Limit (Particle Size Distribution [µm])	Sample Size	Mean $\bar{x}$ (µm)	SD σ (µm)	Minimum (µm)	Maximum (µm)	Tolerance Limit $\bar{x}$ + Target k*σ	Pass/Fail
Standard	(b) (4)	30	279	19	221	306	(b) (4)	Pass
Vibration		30	306	30	226	371		Pass
In-Use Heat Exposure		30	311	20	266	354		Pass
In-Use Cold Exposure		30	295	34	220	381		Pass
Free Fall (Combination Product)		30	301	25	257	375		Pass
Free Fall (Packaged Combination Product)		30	306	30	226	371		Pass

Abbreviation: NMT = not more than.

6.3.1.3. *Delivered Dose Uniformity/Spray Content Uniformity*

The sponsor states that the specification for delivered dose uniformity is not less than (b) (4)% uniform. I defer the adequacy of the specification to the OPQ review division since this is a drug product characteristic, however this review will analyze the ability for the device to administer drug product at this specification. Delivered dose uniformity was provided for the mean, min, and max sizes up to 12 months and after shipping testing. All passed.

Amended 4/18/2019:

In addition to the testing described above, the sponsor has provided test results on 4/12/2019 of the subject EPR with preconditioning (at time = 0) to support the use of the product after the following preconditioning. All testing passed the acceptance criteria.

Table RF-4 (continued) Delivered Dose Uniformity Testing Results

Pre-Conditioning	Specification Limits (DDU)	Sample Size	Mean $\bar{x}$ (%LC)	Minimum (%LC)	Maximum (%LC)	Pass/Fail
Free Fall (Packaged Combination Product)	(b) (4)	30[a]	103	98	107	Pass

Abbreviations: DDU = delivered dose uniformity; LC = label claim; NLT = not less than; NMT = not more than.
[a] Tier 2 sample size and acceptance criteria applied for design verification testing. This was done to increase the sample size for DV testing.

6.3.1.4. *Spray Pattern:*

The sponsor initially states in Seq0000_3.2.P.5.6:
Spray pattern is not proposed as a release specification since it has been determined that (b) (4) are sufficient to ensure consistent batch to batch spray pattern of the combination product. However, after midcycle deficiencies the sponsor provided spray pattern verification testing. The sponsor states that the specification for spray pattern axis is not less than (b) (4) mm. I defer the adequacy of the specification to the OPQ review division since this is a drug product characteristic, however this review will analyze the ability for the device to administer drug product at this specification. Spray pattern was provided for the mean, min, and max sizes up to 12 months and after shipping testing. All passed.

Amended 4/18/2019:

In addition to the testing described above, the sponsor has provided test results on 4/12/2019 of the subject EPR with preconditioning (at time = 0) to support the use of the product after the following preconditioning. All testing passed the acceptance criteria.

Table RF-6 Spray Pattern Testing Results

Pre-Conditioning	Specification Limits (Spray Pattern)	Sample Size	Mean $\bar{x}$	SD σ	Minimum	Maximum	Tolerance Limit $\bar{x}$ - Target k*σ OR $\bar{x}$ + Target k*σ	Pass/Fail
Standard	(b) (4)	30	18	2	15	22	14	Pass
			1	0.2	1	2	2	Pass
Vibration		30	16	2	12	19	12	Pass
			2	0.2	1	2	2	Pass
In-Use Heat Exposure		30	15	2	12	19	11	Pass
			1	0.2	1	2	2	Pass
In-Use Cold Exposure		30	17	2	13	21	12	Pass
			2	0.2	1	2	2	Pass
Free Fall (Combination Product)		30	15	2	13	19	11	Pass
			1	0.2	1	2	2	Pass
Free Fall (Packaged Combination Product)		30	16	2	12	19	11	Pass
			2	0.2	1	2	2	Pass

Abbreviations: NLT = not less than; NMT = not more than.

6.3.1.5. *Plume Geometry/Ovality*

The sponsor states in 3.2.P.5.6:

Plume geometry is primarily a characterization technique and is not proposed as a release specification since it has been determined that [redacted] are sufficient to ensure consistent batch to batch plume geometry of the combination product. However, after midcycle deficiencies the sponsor provided plume geometry verification testing. The sponsor states that the specification for plume geometry relative axis is no more than [redacted] and the angle is in between [redacted] degrees. I defer the adequacy of the specification to the OPQ review division nce this is a drug product characteristic, however this review will analyze the ability for the device to administer drug product at this specification. Plume geometry/ovality was provided for the mean, min, and max sizes up to 12 months and after shipping testing. All passed.

Amended 4/18/2019:

In addition to the testing described above, the sponsor has provided test results on 4/12/2019 of the subject EPR with preconditioning (at time = 0) to support the use of the product after the following preconditioning. All testing passed the acceptance criteria.

Table RF-7 Plume Geometry Testing Results

Pre-Conditioning	Specification Limits (Plume Geometry)	Sample Size	Mean $\bar{x}$	SD σ	Minimum	Minimum	Tolerance Interval $\bar{x} \pm$ Target $k^*\sigma$	Pass/Fail
Standard	[redacted]	30	29	3	22	34	18 to 39	Pass
			31	4	23	37	19 to 43	Pass
Vibration		30	29	2	25	35	23 to 36	Pass
			32	3	27	38	25 to 39	Pass
In-Use Heat Exposure		30	30	4	24	37	20 to 41	Pass
			33	4	25	40	20 to 45	Pass
In-Use Cold Exposure		30	30	3	25	36	23 to 38	Pass
			33	3	27	39	24 to 42	Pass
Free Fall (Combination Product)		30	31	4	23	38	22 to 40	Pass
			33	4	24	42	23 to 43	Pass
Free Fall (Packaged Combination Product)		30	29	2	25	35	22 to 36	Pass
			32	3	27	38	24 to 40	Pass

Abbreviations: NLT = not less than; NMT = not more than.

6.3.1.6. *Actuation Force*

After several rounds of deficiencies regarding the acceptability of the actuation force specification of the device, the sponsor has confirmed that the final actuation force acceptance criteria is [redacted] kgF – [redacted] kgF at [redacted] and [redacted] kgF at [redacted] deg C. This was confirmed in response to an Agency IR (received

3/7/2019). The Agency requested that the Sponsor decrease the actuation force, as the original upper specification of (b) (4) kgF for actuation force was relatively high as compared to other emergency use products such as Epipen, which has an actuation force of (b) (4) kgF.

Reviewer Note:
The product labeling states that the product should be stored and administered at room temperature, therefore an actuation force specification at -20 deg C is not necessarily relevant. Additionally, the labeling mitigation to always store the device at room temperature appears to be an adequate mitigation to a user not being able to actuate the device at lower temps. Therefore, we did not request that the sponsor to lower the -20 deg C actuation force specification

They sponsor defined their actuation force specification as follows in Seq0030_1.11.1:

Table Q1-1 Proposed Actuation Force Specifications

EPR	Specification	Specification Applicability
Actuation Force	(b) (4)	

To justify the specifications, in table Q23-1 the sponsor provided pinch strength information for 10-19 year olds and 10- 75+ year olds and provided a Monte Carlo analysis based on literature strength data from the literature reference Mathiowetz et al 1986. Based on the data summarized in this table, the mean ± standard deviation pinch strenght for adolscents is 8.04 ± 2.25 kgF. Assuming a normal distribution, the data referenced implies that ~68% of the total data lies within one standard deviation; therefore 68% of users can exert the following maximum pinch strengths 5.79 – 10.29 kgF (for adolescents) and 6.41-11.47 kgF (for adults). See the summary data below:

Table Q23-1 Palmar Pinch Strength Force Monte Carlo Analysis Summary

User Population	Palmar Pinch Strength Force - Mean (kgf)	Palmar Pinch Strength Force - SD (kgf)	Palmar Pinch Lower 0.01% Content (kgf)	Palmar Pinch Upper 99.99% Content (kgf)
Persons aged 10 - 75+ years	8.94	2.53	3.04	14.83
Adolescents aged 10 - 19 years	8.04	2.25	2.81	13.27

Table Q23-2 Comparison of Actuation Force Limits to Palmar Pinch Strength

Use Condition	Proposed Actuation Force Specification Upper Limit @ 80 mm/sec (kgf)	Equivalent Actuation Force Specification Upper Limit @ 0.0125 mm/sec (kgf)	Palmar Pinch Force Mean (kgf)	Palmar Pinch Force SD (kgf)	Maximum Percentage of Users with Palmar Pinch Force Capability Exceeding the Upper Specification Limit
≥ Room Temperature	(b) (4)		8.94	2.53	95%
-20°C					87%

Reviewer Note:
The upper limit for actuation force at room temperature is (b)(4) kgF, (b)(4) for palmar pinch strength force of adolescents as young as 10 (b)(4) ears old. Additionally, the majority of devices tested for actuation force appear to be below (b)(4) kgF (mean of (b)(4) kgF)at room temperature. Therefore, assuming a palmar pinch strength of (b)(4) kgF and a normal distribution around that, if the mean device actuation force is (b)(4) kgF, nearly 85% of users should not have trouble actuating this device. Also the sponsor has provided actuation force with a displacement rate of 80 mm/s, which they state is rather fast relative to how the device may be used, therefore if the user displaces the plunger slower, the preceived force will be lower.

It also confirmed that the 80 mm/sec constant speed actuation used in automated bench-top testing is representative of the upper end of user actuation speeds; therefore, the current bench-top testing method measures the maximum forces that a user may experience during actuation. However, as discussed in previous responses, the user is able to reduce the actuation force they experience by reducing their actuation speed.

Additionally, the sponsor also provided information regarding the devices and actuation force data that were used in the human factors validation testing. The device version 2.1 was validated in the formative and summative HF study (included a max actuation force specfication of (b)(4) kgF) and there was no note of complaints in the summative HF study about patients stating that the device was difficult to actuate (youngest participant was 10 years old). See the summary device actuation force summary data (devices used in HF testing) below. Therefore, I believe that the sponsor has adequately validated the upper specfication for actuation force at room temperature.

Table Q2-1 Actuation Forces Experienced by Users in Clinical and/or Human Factors Studies

Device Configuration ID	Study Use	Representative Lot Tested	Actuation Force (kgf)				
			n	Mean	SD	Min	Max
1.0	• I8R-MC-IGBD • I8R-MC-IGBA • I8R-MC-IGBE • I8R-MC-IGBB • I8R-MC-IGBF • I8R-MC-IGBC • AMG107-001 (Human Factors)	F121220-001	10	3.8	0.28	3.4	4.2
2.0	• I8R-MC-IGBB • I8R-MC-IGBC • I8R-MC-B001 • I8R-MC-B002 • I8R-MC-IGBG • AMG107-002 (Human Factors) • AMG107-003 (Human Factors)	F140805-001	20	7.8	0.28	7.1	8.3
		F141016-001	40	7.9	0.55	6.5	9.3
		F141113-001	22	8.2	0.59	6.9	8.9
2.1	• I8R-MC-IGBI • AMG107-004 (Human Factors) • AMG107-005 (Human Factors) • AMG111 (Human Factors) • Formative Human Factors • Summative Human Factors	1623774	220	6.4	0.53	5.2	7.8
		1623775	220	6.4	0.42	5.5	7.5
		1623776/ 1623776CT	220	6.6	0.54	5.4	8.0
		1633276	50	5.6	0.17	5.1	6.0
		1624621	50	6.1	0.41	5.5	7.0
2.2	Planned Supplemental Human Factors	3418788	60	6.4	0.26	5.3	6.8
		3418786	60	6.5	0.34	5.3	7.1
		3418787	60	6.5	0.28	5.7	7.2

Below is the actuation force summary data provided by the sponsor to demonstrate that actuation force specification is met:

Table Q1-2 Actuation Force (@ (b) (4) mm/sec) Design Verification Testing Results

Test Description[a]	Design Specification (Actuation Force (kgf))	Sample Size	Mean $\bar{x}$ (kgf)	SD σ (kgf)	Minimum (kgf)	Maximum (kgf)	Tolerance Interval (kgf) $\bar{x} \pm$ Target $k*\sigma$	Pass/ Fail
In-Use Standard Conditions[b]	(b) (4)	101	6.8	0.3	5.9	7.4	6.1 - 7	Pass
Vibration		30	6.0	0.5	5.2	7.1	4.9 - 7	Pass
Free Fall (Combination Product)		25	6.6	0.3	6.0	7.2	5.8 - 7	Pass
In-Use Heat Exposure		49	5.1	0.4	4.2	5.9	4.1 - 6	Pass
In-Use Cold Exposure		52	9.2	0.6	7.5	10.4	7.6 - 10.8	Pass
Shipping		25	6.4	0.4	5.2	7.1	5.4 - 7	Pass
Free Fall (Packaged Combination Product)		49	5.1	0.4	4.2	5.9	4.2 - 6	Pass

Abbreviations: NLT = not less than; NMT = not more than; SD = standard deviation.
[a] Details of testing conditions are provided in Section 3.2.R.3.4.2, Table 3.2.R.3.4.2-2.
[b] Testing conducted at ambient laboratory temperature and humidity, with no pre-conditioning.

Amended 4/18/2019:

In addition to the testing described above, the sponsor has provided test results on 4/12/2019 of the subject EPR with preconditioning (at time = 0) to support the use of the product after the following preconditioning. All testing passed the acceptance criteria.

Table RF-3 Actuation Force Testing Results

Pre-Conditioning	Specification Limits (Actuation Force [kgf])	Sample Size	Mean $\bar{x}$ (kgf)	SD σ (kgf)	Minimum (kgf)	Maximum (kgf)	Tolerance Interval $\bar{x} \pm$ Target $k*\sigma$	Pass/Fail
Standard	(b) (4)	60	6.5	0.3	5.3	7	5.5 to 8	Pass
Vibration		60	6.0	0.3	5.4	6	5.3 to 7	Pass
In-Use Heat Exposure		60	4.7	0.3	4.0	5	4.1 to 5	Pass
In-Use Cold Exposure		60	8.3	0.4	7.0	9.5	7.1 to 9.4	Pass
Free Fall (Combination Product)		60	6.4	0.4	5.2	7	5.5 to 7	Pass
Free Fall (Packaged Combination Product)		60	6.0	0.3	5.4	6	5.2 to 7	Pass

Abbreviations: NLT = not less than; NMT = not more than.

6.3.2. *Stability Testing:*

The sponsor has stated that changes to the device components have been made since primary stability batches were produced:

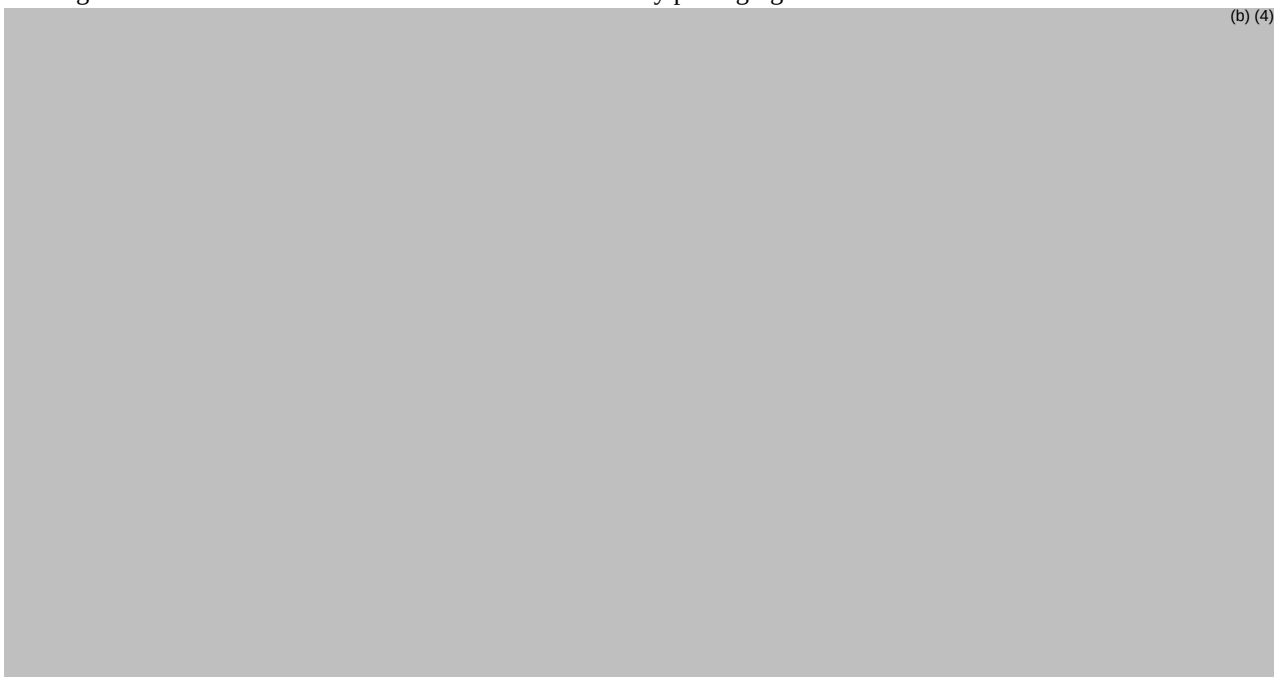
Device Delivery:

"Changes to the delivery device were made to enhance device robustness and assembly; however, features that impact patient interaction and dose delivery did not change. Changes include the following:

(b) (4)

Functional Secondary Packaging (Tube with Desiccant)

"Changes to the commercial form of the functional secondary packaging include:



(b) (4)

Reviewer Note:
While it is unlikely that the changes to the device from the primary stability lots would affect the performance requirements of the device, given that the internal assembly of the device are not changing, it is unclear if this would affect the drug stability or device performance requirements. A deficiency was sent to the sponsor and they responded with the following:

"Delivery performance of the device (i.e., Pump Delivery (spray/shot weight), Spray Pattern, Plume Geometry, and SCU) is dependent on only two factors:

(b) (4)

In contrast to solution-based nasal sprays, particle size distribution for nasal glucagon is not dependent on the device, but is an inherent property of the drug powder. Therefore, particle size distribution is not affected by this change. Device actuation force is a function of the (b) (4) generated during actuation. The primary constituents of actuation force are the (b) (4). As there were no changes to the primary container closure system, the changes have no effect on drug product compatibility.

The sponsor has provided an adequate response. I do not believe that the minor design changes listed above will change the device essential performance requirements,

Stability Results
The sponsor has only provided verification of EPRs to support up to a (b) (4) month shelf:

- Particle size distribution for (b) (4) months;
- Shot weight, actuation force, delivered dose uniformity (DDU), spray pattern, and plume geometry for (b) (4) months.

This is not up to the proposed expiry of (b) (4) months; however it is enough to support a (b) (4) month shelf life for the device constituent. The EPR stability verification testing is provided in document 0023(24)_1.11.1. There does not appear to be any negative trend as a result of aging, aside from DDU, which would be expected as a result of aging; CDER has stated that the DDU results provided is adequate to support a (b) (4) month shelf life.

Reviewer Note:
The sponsor is proposing a (b) (4) month shelf life, but has not verified the device EPRs up the (b) (4) month shelf life. The sponsor has provided verification testing to support (b) (4) month; therefore a (b) (4) month shelf life will be supported by CDRH. I have spoken to OND and OPQ and only a (b) (4) month shelf life will be granted if the product is approved. This is acceptable.

6.4. Simulated/Actual Shipping Validation

The sponsor provided a transportation study summary in 0000(1)_3.2.P.2. document container-closure and was supplemented in 0023(24)1.11.1. The summary testing is provided below. The sponsor appears to use ASTM D4169 as a reference for testing, this included vibration and dropping. This includes pass/fail testing for:

- Shot weight
- Actuation force
- Plume geometry
- Dose uniformity
- Spray Pattern
- Plume Geometry
- Particle Size

All results met acceptance criteria for each EPR. This is adequate.

Table RF2-1 (continued) Laboratory-Based Shipping Study Results (Batch 1624621)

Test Description	Specifications or Acceptance Criteria	Results	Control	Stressed
Particle Size (Mastersizer)	(b) (4)	Reported results (µm)	189.1	185.1
		Upper Tolerance Interval (µm)	297.2	346.1
		Pass/Fail	Pass	Pass
		Minimum (µm)	158.0	136.5
		Maximum (µm)	217.1	242.9
		Reported results (µm)	17.1	16.7
		Minimum (µm)	15.4	13.9
		Maximum (µm)	19.0	20.8
		Reported results (µm)	2.51	2.47
		Minimum (µm)	2.46	2.37
		Maximum (µm)	2.57	2.56

Plume Geometry	Plume Angle NLT (b) (4) and NMT (b) (4)	Reported results (deg)	34.3	35.8
		Tolerance Interval (deg)	23.0 to 45.6	26.9 to 44.8
		Pass/Fail	Pass	Pass
		Minimum (deg)	28.8	31.7
		Maximum (deg)	40.0	39.3
	Plume Width NLT (b) (4) and NMT (b) (4)	Reported results (mm)	37.2	38.9
		Tolerance Interval (deg)	24.4 to 50.0	28.5 to 49.3
		Pass/Fail	Pass	Pass
		Minimum (mm)	31.0	34.2
		Maximum (mm)	43.6	42.9
Spray Pattern	Dmin NLT (b) (4)	Reported results (mm)	17.4	17.4
		Lower Tolerance Interval (mm)	14.3	12.8
		Pass/Fail	Pass	Pass
		Minimum (mm)	15.2	13.4
		Maximum (mm)	21.3	21.9
	Ovality NMT (b) (4) Ratio	Reported results	1.4	1.5
		Upper Tolerance Interval	1.9	2.1
		Pass/Fail	Pass	Pass
		Minimum	1.2	1.2
		Maximum	2.1	2.3
	Dmax Report Results	Reported results (mm)	25.1	26.1
		Minimum (mm)	19.4	20.8
		Maximum (mm)	37.2	30.4

Table Q1-3 Laboratory-Based Shipping Study Results (Batch 1624621)

Test Description	Specifications or Acceptance Criteria	Results	Control	Stressed
Actuation Force	(b) (4)	Mean (kgf)	6.0	6.2
		Tolerance Interval (kgf)	4.8 - 7	4.8 - 8
		Pass/Fail	Pass	Pass
		Minimum (kgf)	5.5	5.5
		Maximum (kgf)	7.0	7.0

The shipping testing is adequate and the device EPRs meet their respective specification after shipping testing.

6.5. Device Reliability Review

The sponsor provided a summary report of the device reliability assessment that was completed in 3.2.R "medical device." The intended use of the nasal glucagon device is to deliver drug powder to the nasal mucosa of the patient for the treatment of severe hypoglycemia.

6.5.1. Reliability Requirements

Reliability comments were sent by John McMichael (CDRH) in a Type C meeting WRO (7/9/2016). Note, that these comments do not appear to include the 99.99% reliability specification with 95% confidence that has been recommended in the past for this type of device. Given the intended use your proposed product (i.e., emergency use) we expect you to establish a clinically-based reliability specification of at least 99.99% with 95% confidence (e.g., failure rate < 1/10,000) and verify this reliability through both design and manufacturing data analysis.

Reviewer Note:

In response to MC deficiencies. The sponsor has included all EPRs including and has stated that they meet the 99.99% reliability specification with 95% confidence:

- Shot weight
- Actuation force
- Plume geometry
- Dose uniformity
- Spray Pattern
- Plume Geometry
- Particle Size

However, the reliability analysis was not provided until the (b)(4) month shelf life, only 12 months. The sponsor states they used the results from stability testing to determine the reliability of the device:

"*All stability results meet the proposed specifications, and the results of the reliability analysis demonstrate the reliability requirement (≥99.99% reliability with 95% confidence) is met through* (b)(4) *months of shelf-life storage for the shot weight, actuation force, DDU, spray pattern, and plume geometry EPRs, and through* (b)(4) *months of shelf-life storage for the particle size distribution EPR.*"

The sponsor has provided this testing over 3 stability lots, however the sponsor provided reliability testing to 12 months. Shot weight was provided to (b)(4) months, the other device EPRs were provided to 12 months using stability lots (See section 6.5.4).

6.5.2. Safety Assurance Case (with regards to reliability)/Stack up Analysis:

Rather than a fault tree analysis, the sponsor provided a safety assurance case in a safety argument where they then estimate the total risk of failure of the device (system reliability) and individual EPR reliabilities. In this safety assurance case, the sponsor provided information regarding the predicated level of reliability of the device (system reliability). The sponsor has provide sources of failures that would affect the top level goals (as well as the EPRs of the device under these two sections of the SAC. These reference the device failure modes, including mitigations to failure modes that could cause failure of the individual device EPRs and that could affect the overall reliability. They then use a FMEA with the probability of occurrence to approximate the likelihood of failure of one of these attributes. While this is not a typical FTA that the Agency usually requests, I believe that if used correctly a SAC should be able to capture similar information and identify failure modes that would affect the top level failure modes as well as EPR failure modes. The top level argument case is provided below and an example of an EPR branch is shown below for shot weight:

Top Level Goal

3 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

While not an FTA, the SAC identifies the key parameters that would alter the reliabilty of the top level system reliability and the individual EPRs based on the component related failures. Although this is an alternative method that we find acceptable because it provides the same level of evidence that is gained from the requested FTA method. The sponsor then used a FMEA to approximate the probability of failure (with the mitigations included) based on these tolerances being out of specification. A tolerance interval analysis (TIA) (document 0023(24)_1.11.1) was used to analyze the likelihood of these failures. I believe that the sponsor has adequately demonstrate that a 99.99% reliability can be met for the top level system failure mode, which is based on the reliability of the individual device EPRs (as shown below).

Reliability Analysis Conclusions

The results of the reliability analysis are summarized in Table RF3-2.

Table RF3-2 Results of Reliability Analysis

Essential Performance Requirements	Unreliability	Reliability
EPR 1 - Shot Weight	0.0000665	0.99993
EPR 2 - Actuation Force	0.0000331	0.99997
EPR 3 - Spray Pattern	0.0000836	0.99992
EPR 4 - Plume Geometry	0.0000836	0.99992
EPR 5 - Particle Size	0.0000412	0.99996
EPR 6 - Delivered Dose Uniformity	0.0000665	0.99993

6.5.3. Reliability Test Sample Preconditioning

6.5.3.1. Preconditioning (FOR SHOT WEIGHT ONLY):

The sponsor provided verification with samples that were preconditioned in the following ways. **NOTE: this preconditioning protocol was only for shot weight verification testing (NOT ANY OTHER EPRS)**

- Shipping preconditioning:
  - Temperature/humiditiy: 25 deg C/ ambient RH
    Note: I don't believe that 25 deg C/ ambient RH is the worst case for shipping; however, if the devices were aged to the expiry with different storage conditions, this may not be an issue as EPR testing was done at hot/cold use.
  - Vibration based on ISTA 3A
  - Shipped with nozzle up orientation
- Customer handling preconditioning
  - Dropped one time in three different orientations
  - Vibration
- Storage preconditioning
  It appears that storage preconditioning of the product to the expiry ((b) (4) months), was not used as a preconditioning method. They state that their stability studies have not shown any differences between the performance requirements of the device. "Based on these data, no impact on device performance from shelf-life storage is expected, and storage conditioning was not conducted as a pre-conditioning activity."

The sponsor states that the devices were actuated within the reliability study at potentially worst case storage prior to actuation:

"Pre-conditioning to represent the reasonable worst-case environmental conditions for customer use included:

- 96 hours exposure at -20°C, followed by device actuation;
- 96 hours exposure at 50°C and 75% RH, followed by device actuation."

They also state that actuation orientation of the device was considered as well for reliability testing: "Actuation was conducted with the device in the nozzle-up orientation, which is considered to be worst-case due to the negative effect of gravity on the acceleration of the drug powder during expulsion."

This reliability protocol was used in the original reliability study; however this testing only demonstrated that delivered dose/shot weight met the 99.99% reliability with 95% confidence at (b) (4) months, not any of the other device EPRs. A deficiency was sent to the sponsor requesting that all EPRs be verified for reliability to the same specification.

6.5.3.2. Preconditioning (FOR ACTUATION FORCE, ETC.):

In the deficiency response after the midcycle referenced above, the sponsor provided testing with the remaining EPRs to support the device reliability but this testing only included testing with device stability lots (NOT including other preconditionings such as shipping/shock/vibration, etc.). **The following EPRs were tested for under these conditions (12 -18 months aging only):**

- Actuation force
- Plume geometry
- Dose uniformity
- Spray Pattern
- Plume Geometry
- Particle Size

The above preconditioning protocol does not appear to have been used for the reliability verification testing provided after midcycle for all device EPRs. Additionally **this testing was only provided up to 12 months and does not support a (b) (4) month expiry). We have discussed this with OND and OPQ and they agree that only a (b) (4) month shelf life should be granted.**

6.5.4. Reliability Study Results:

See below based on the device EPR:

6.5.4.1. Shot Weight/Delievered Dose Reliability Results:

The sponsor has provided summary results of the shot weight/dosage reliability testing that was completed up to (b) (4) months and with the multiple preconditioning steps outlined above. They state:

The test results demonstrated a k-value of 6.990, which exceeds the minimum k-value of (b) (4). The results support the capability of the nasal glucagon device to deliver the minimum required dose of (b) (4) mg glucagon with 99.99% reliability and > 95% confidence.

Based on the testing that was provided it appears that given the number of samples that were provided and confidence level the sponsor sought, shot weight/dose accuracy appears to be 99.99% reliable with 95% confidence up to (b) (4) months.

Table 3.2.R.3.5.7-1 Shot Weight Testing Results

Cond. Temp.	Sample Size	Shot Wt. Range (mg)	Mean Shot Weight (mg)	Mean Fill Weight (mg)	Shot Wt. (% of Mean Fill Weight)		
					Mean	Std. Dev.	Range
-20°C	50	31.4-33.5	32.4	33.2	97.5	1.65	94.3-101.4
50°C	50	31.1-34.0	32.6	33.2	98.0	1.66	94.2-101.8
Total	100	31.1-34.0	32.5	33.2	97.8	1.67	94.2-101.8

Delivered Dose Calculated Results

All of the 100 test samples delivered the minimum required dose of (b) (4)mg glucagon after being subjected to the cumulative stresses of shipping, various temperatures, humidity and pressure, vibration, and shock from dropping. Table 3.2.R.3.5.7-2 provides a summary of the study results.

Table 3.2.R.3.5.7-2 Delivered Dose Testing Results

Cond. Temp.	Sample Size	DD Range (mg)	Mean DD, x (mg)	SD, σ (mg)	Tolerance Limit (mg) x -Target k*σ	Specification Limit (mg)	Pass/Fail
-20°C	50	2.3-2.5	2.4	0.06	2.3	(b) (4)	Pass
50°C	50	2.3-2.5	2.4	0.04	2.3		Pass
Total	100	2.3-2.5	2.4	0.05	2.3		Pass

6.5.4.2. Actuation Force and Other Device EPR Reliability Results:

As stated above, the sponsor has only provided "reliability" results from devices from stability lots; i.e. no shipping, vibration, shock, etc. preconditionings. Additionally, this testing was only conducted up to 12 months (the proposed shelf life is (b) (4)months). The following EPRs were tested in this fashion:

- Actuation force
- Plume geometry
- Dose uniformity
- Spray Pattern
- Plume Geometry
- Particle Size

Reviewer Note:
I spoke with OPQ reviewer, Muthukumar Ramaswany and he stated that the shelf life of the product will be limited based on the information that is provided by April 2019 (submission action date), i.e. (b) (4) months.

The summary results are shown below:

Table RF1-22 Reliability Analysis of Stability Data

Test Description	Specifications or Acceptance Criteria	Sample Size	Mean	SD	Minimum	Maximum	99.99%/ 95% Tolerance Interval or Limit
Shot Weight	The minimum delivered dose calculated from the measured shot weight is NLT (b) (4) mg	630	2.4 mg	0.1 mg	2.1 mg	2.7 mg	2.1 mg
	Each individual shot weight is NLT (b) (4) % of the mean fill weight	630	98%	2%	89%	110%	90%
Actuation Force	Actuation force at (b) (4) mm/s actuation speed is NLT (b) (4) kgf and NMT (b) (4) kgf for devices and/or test environments greater than or equal to room temperature during actuation	660	6.4 kgf	0.5 kgf	5.2 kgf	8.0 kgf	4.4 kgf to 8.5 kgf
DDU	Dose delivered from device is NLT (b) (4) of LC	210	96%	3%	89%	105%	83%
Particle Size Distribution	X90 NMT (b) (4) µm	309	206 µm	28 µm	125 µm	312 µm	317 µm
Plume Geometry	Plume Angle NLT (b) (4) and NMT (b) (4)	270	30.1°	4.0°	14.5°	41.0°	13.2° to 47.1°
	Plume Width NLT (b) (4) mm and NMT (b) (4) mm	270	32.4 mm	4.6 mm	15.3 mm	45.7 mm	13.2 mm to 51.5 mm
Spray Pattern	Dmin NLT (b) (4)	315	17.8 mm	1.8 mm	13.7 mm	23.2 mm	10.5 mm
	Ovality NMT (b) (4) Ratio	315	1.5	0.2	1.1	2.4	2.2

Reviewer Note:
The actuation force reliability information was supplemented to include analysis with the reviesed upper specification of (b) (4) kgF.

Table Q1-4 Actuation Force Reliability Testing Results

Cond. Temp.	Sample Size	Actuation Force Range (kgf)	Mean Actuation Force, $\bar{x}$ (kgf)	SD, σ (mg)	Tolerance Interval (kgf) $\bar{x} \pm$Target k*σ	Specification Limit (kgf)	Pass/Fail
-20°C	52	7.5 - 10.4	9.2	0.6	7.8 - 10.6	(b) (4)	Pass
50°C	49	4.2 - 5.9	5.1	0.4	4.2 - 6		Pass

Abbreviation: NLT = not less than; NMT = not more than; SD = standard deviation.

Based on the sample size used the sponsor has defined the limits needed to achieve 99.99% with 95% confidence and demonstrate that the device can meet the current device EPR specifications with 99.99% reliability and a 95% confidence interval at 12 months, with no other preconditioning (aside from aging). The sponsor has provided a justification for why the current reliability information for all device EPRs are adequate to demonstrate reliability to 12 months below in Section 6.5.4.3.

6.5.4.3. Reliability Verification Conclusion:

(b) (4)

(b) (4)

CDRH sent an IR asking the sponsor to provide a justification of why the current reliability information is adequate for approval of the product, since it does not actually meet our initial request. since they have only provided shot weight/delivered dose after the sequential preconditionings referenced above (including 24 months aging) and actuation force, delivered dose uniformity, particle size, etc. with only 12 month aging as preconditioning. In response they have provided an argument for why the individual preconditionings; i.e. shipping, stability/aging, etc. are adequate to ensure reliablity of the device.

They state the following in a response to an IR dated 2/25/2019 (Seq0027_1.11.1):

Effects of other conditions and stresses on the product for the newly established EPRs were assessed during design verification testing. The testing procedures were done in conformance with ISO 20072 Aerosol drug delivery device design verification -- Requirements and test methods. This standard identifies conditioning and testing to be performed as part of design verification testing, but does not suggest to do cumulative conditioning. Devices were preconditioned and tested in accordance with the standard. Demonstrating that shelf-life storage does not result in degradation of device performance, and that combination product performance is not negatively affected by any of the individual preconditioning steps should provide the Agency with data necessary to approve and to support reasonable assurance that the device is safe and effective for its intended purpose.

*The data were collected from combination products that had been stored and testing according to the registration stability protocol described in Section 3.2.P.8.3, Stability Data – Primary Stability, and the results compared to the proposed specifications. All the EPRs met specifications. In addition, the data obtained from the stability samples were assessed using mean/SD/k-value to calculate and conduct a probability analysis whether the newly identified EPRs met reliability criteria established by FDA. Based on the calculation, the EPRs met the reliability specification of 99.99% reliability with 95% confidenc*e.

Lilly has provided the following to FDA in support of the reliability of the device:

- *Results from reliability testing of devices subjected to cumulative multiple preconditioning steps including shipment (vibration and shock from dropping), handling by the customer, and use by the customer for the shot weight EPR.*
- *Results from the assessment of the additional EPRs (actuation force, particle size distribution, delivered dose uniformity, spray pattern, plume geometry) from combination products that have not been cumulatively preconditioned, but have been stored for 12 - 18 months at the proposed label storage conditions demonstrating EPRs met specification at the aging time point tested.*
- *Calculated reliability of the device EPRs using the data from #2 above, which demonstrate that stability devices and design verification testing devices meet the reliability criteria of 99.99%.*

The totality of the evidence collected to date indicates that the device is reliable. (b) (4)

.

Reviewer Note:
The sponsor has provided a justification for why they believe that the currently level of reliability information is adequate for device approval. With regards to reliability verification of the device EPRs, the sponsor currently has provided the following:

- Delivered Dose/Shot Weight – up to 24 months with sequential preconditioning as requested
- Actuation Force – up to 12 months, stability only preconditioning
- Plume geometry – same as actuation force
- Dose uniformity – same as actuation force
- Spray Pattern – same as actuation force
- Plume Geometry – same as actuation force
- Particle Size – up to 18 months, stability only preconditioning

They have provided verification of the device EPRs (new devices) after simulated shipping testing, which includes vibration, drop, shock testing. Demonstrating that shock/dropping/and shipping do not result in shifting of the components. In all tested conditions, the testing met the respective EPR specifications. Additionally, in stability lots (up to 12 months), there does not appear to be any negative trend as a result of aging, aside from DDU, which would be expected as a result of aging; CDER has stated that the DDU results provided is adequate to support a (b) (4) month shelf life.

The SAC/FTA demonstrated 99.99% reliability of the device. Additionally, the sponsor provided verification to demonstrate reliability of 99.99% and 95% confidence up to 12 months (no additional verification) for all the device EPRs, excluding shot weight (delivered dose/shot weight was verified for 24 months with sequential preconditioning). Given that shot weight reliability was verified up to 24 months with multiple preconditioning (including shipping, drop/shock, temperature, etc.), this helps support the argument of reliability and that the stresses of shipping, aging, temperature cumulatively will not negatively affect use of the device and should not increase the likelihood of device related failure. (b) (4) .

In conclusion, the subject product will benefit its intended users by providing a more expedient way to administer glucagon in emergency situations, as compared to the current glucagon administration kits which make the user reconstitute the drug in solution prior to administration with a prefilled syringe. I believe that the likelihood of potential failure due to the product not being able to withstand shipping, aging, brief environmental storage changes is unlikely given the testing that was provided above and that stability testing of the EPRs up to 12 months did not show any deterioration of the EPRs (outside of DDU). **Therefore, I believe that the reliability testing is adequate to support approval for a (b) (4) month shelf life; however, if the sponsor wants to extend the shelf life to (b) (4) months, we recommend that the sponsor conduct full reliability testing with sequential preconditioning up to (b) (4) months as a supplement to the NDA .**

6.5.5. Incoming/In Process/Release Testing Used to Verify Reliability Specification:

The sponsor states:

Manufacturing process controls have been implemented to ensure proper function of each device and to achieve the reliability specification in the release product lots. For example:

(b) (4)

Section 3.2.P.2.3, Manufacturing Process Development, describes manufacturing controls that have been implemented. The controls will be confirmed during process validation which is discussed in Section 3.2.P.3.5, Process Validation and/or Evaluation.

A summary of risk management activities supporting the reliability of the delivery device are described in the Residual Risk Report (Appendix C).

6.5.6. Reliability Conclusion

In conclusion, the subject product will benefit its intended users by providing a more expedient way to administer glucagon in emergency situations, as compared to the current glucagon administration kits which make the user reconstitute the drug in solution prior to administration with a prefilled syringe. I believe that the likelihood of potential failure due to the product not being able to withstand shipping, aging, brief environmental storage changes is unlikely given the testing that was provided above and that stability testing of the EPRs up to 12 months did not show any deterioration of the EPRs (outside of DDU). Therefore, I believe that the reliability testing is adequate to support approval with a (b) (4) month shelf life; however, if the sponsor wants to extend the shelf life to (b) (4) months, we recommend that the sponsor conduct full reliability testing with sequential preconditioning u o 24 months as a supplement to the NDA .

Device Design Verification Recommendation:
The design verification is adequate to support a (b) (4) month shelf life.

7. DISCIPLINE SPECIFIC SUB-CONSULTED REVIEW

7.1. Biocompatibility

I spoke with CMC Muthukumar Ramaswamy (OPQ) regarding the necessity for a CDRH biocompatibility review. He stated:

"We do not need CDRH biocompatibility review for the fluid path components including primary container closure. CDER Office of Pharmaceutical quality review will complete product quality review of module 3 (drug substance and drug product sections including process and facilities associated with the application)."

Therefore, a biocompatibility review for the device constituent will not be conducted for the fluid path components. The mucosal/skin contacting devices were evaluated per ISO 10993-1 and the ISO 10993 FDA Guidance for biocomaptibilty testing for medical devices. Given the amount of contact that the patient will be using the device a contact duration of less than 24 hours was used. I believe that this is adequate, given that this is an emergency use product that will not be used regularly. Cytotoxicity, Sensitization, and Irritation testing was completed. Summary results are included below:

3.2.R.3.4.3.1 Cytotoxicity Testing Per ISO 10993-5

L929 Neutral Red Uptake

- Extraction liquid: Minimum Essential Medium with 10% fetal bovine serum
- Extraction condition: 37°C for 24 hours
- Cell line: Mouse fibroblast (L929) cell line
- Quantitative evaluation as defined in the standard

Results

All the patient contacting components of the delivery device met the acceptance criteria for cytotoxicity and are in compliance with the biocompatibility requirements of ISO 10993-5. The control extract confirmed the suitability of the test system. The (b) (4) desiccant component is part of the functional secondary packaging and is not intended to be a patient contacting material. The (b) (4) desiccant component is intended to remain inside the tube after the delivery device is removed. The desiccant material is formed by (b) (4) If the user were to stick their finger into the tube, it is possible to touch the (b) (4) desiccant (b) (4); so the (b) (4) was tested for biocompatibility. The desiccant (b) (4) demonstrated a cytotoxicity potential but met acceptance criteria for in vivo sensitization and irritation tests. Therefore, there is very low risk concerning the safety of the desiccant.

Reviewer Note:
Given that the desiccant is not meant to be used as the drug product or contacted by the user, I believe that the rationale and results above are adequate.

3.2.R.3.4.3.2 Irritation Test Per ISO 10993-10

Primary Skin Irritation

- Extraction liquids: 0.9% United States Pharmacopeia (USP) saline for injection (polar), cottonseed oil (CSO, non-polar)
- Extraction condition: 50°C for 72 hours
- Topical application of each extract medium to New Zealand White Rabbits for 4 hours
- Erythema and edema readings at 1, 24, 48, and 72 hours

Results

The USP 0.9% sodium chloride (NaCl) and CSO extracts of the test article were evaluated for their potential to produce primary skin irritation after a single topical 4-hour application to the skin of New Zealand White rabbits. No signs of erythema or edema (score of 0) were noted at any observation period for all components of the primary and secondary packaging. Based on the criteria of the protocol, a score of 0 for skin reactions to the test articles is not considered significant and the test article meets the requirements of ISO 10993-10 guidelines.

3.2.R.3.4.3.3 Sensitization Test Per ISO 10993-10

Kligman (Guinea Pig) Maximization Test

- Extraction liquids: 0.9% USP saline for injection (polar), CSO (non-polar)
- Extraction condition: 50°C for 72 hours
- Three pairs of intradermal injections made in Guinea pigs followed by topical applications described in standard

Results

The USP 0.9% NaCl and CSO extracts of the test article elicited no reaction (0% sensitization) at the challenge, following an induction and topical application phases. None of the treated or negative control animals exhibited any sensitization reaction (0% sensitized). The positive control article elicited discrete reactions in all animals (100% sensitized). Therefore, as defined by the Kligman scoring system, the components are classified as non-sensitizers. The tested components are in compliance with biocompatibility requirements of ISO 10993-10.

Device Biocompatibility Recommendation:
The biocompatibility information is adequate.

7.2. Quality Systems

The quality systems review was completed by Leslie Dorsey (CDRH/OC) prior to the midcycle reivew. Nikhil Thakur completed the review after midcycle. A summary of her review is shown below. Based on her review the following recommendations are provided:

Facilities Review:
See below:
Combination Product Applicant

Firm Name: Eli Lilly and Company

Address: Lilly Corporate Center, Indianapolis, IN 46285

FEI #1819470

Responsibility – Eli Lilly and Company is the applicant for this combination product and therefore, has overall responsibility for all manufacturing sites. In addition, it is responsible for the drug product packaging and labeling.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

Inspection Recommendation:

A pre-approval inspection is required because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
- A recent medical device inspection of the firm has not been performed.

Reviewer Note:
On 3/8/2019, OPQ reviewer Muthukumar Ramawamy, stated the following regarding the PAI:
"Device related PAI at Lilly corporate center is complete and received an acceptable recommendation."

Finished Combination Product Manufacturer

Firm Name: (b) (4)

(b) (4)

Responsibility – Manufacture of the dosage form and device assembly; primary and secondary packaging and labeling; quality control testing – visual/functional device inspection.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted (b) (4). The inspection covered drug CGMP and was classified NAI.

Inspection Recommendation:

A post-approval inspection is required because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
- A recent medical device inspection of the firm has been performed was conducted (b) (4). The inspection covered drug CGMP and was classified NAI.

Reviewer Note:
I spoke with Nikhil Thakur (DAGRID compliance lead) on 3/15/2019 and he stated that a post-approval inspection was recommend, rather than pre-approval, because a more recent inspection was conducted at this manufacturing facility.

Quality Systems Review:

Device Consituent Part Type: Nasal Inhaler or Spray

Device Consituent Part Class II

Combination Produc NDA 210134 Proposed Indication for Use: Severe Hypoglycemia

Was the last inspection of the finished combination product manufacturing site, (b) (4) OAI for drug or device observations?	YES ☐	NO ☒	NA ☐
Is the device constituent a PMA or class III device?	YES ☐	NO ☒	UNK ☐
Is the final combination product meant for emergency use?	YES ☒	NO ☐	UNK ☐
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	YES ☒	NO ☐	UNK ☐
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	YES ☐	NO ☒	UNK ☐
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	YES ☒	NO ☐	UNK ☐
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	YES ☐	NO ☒	UNK ☐

cGMP Risk: ☒ High Risk of cGMP issues.

The Quality System requirements applicable to a particular manufacturer may vary based upon the type of constituent parts being manufactured and the aspects of their manufacture that are being performed at that site. All manufacturers are responsible for ensuring compliance with all requirements applicable to the manufacturing activities at their facilities. Where multiple facilities bear responsibility for various aspects of the manufacturing process, only the holder of the application or clearance for the product is responsible for compliance with all aspects of the Quality System requirements applicable to the entire manufacturing process and across all facilities.

Applicant: Eli Lilly and Company

Lilly Corporate Center, Indianapolis, IN 46285

FEI: FEI #1819470

Finished Combination Product Manufacturer: (b) (4) (b) (4)

Several deficiencies were issued to the Sponsor at the Midcycle from Leslie Dorsey. See Section 12 for the deficiencies issued at Midcycle. Nikhil Thakur had taken over the review after midcycle and provide an assessment of the responses. He deemed the response were adequate to support approval. See responses in Section 12 for deficiency responses.

Quality Systems Recommendation:
The QS information is adequate.

Facilities Inspections Recommendation:
Facilities information is adequate. Inspection recommendations are below:

Combination Product Applicant

Firm Name: Eli Lilly and Company

Address: Lilly Corporate Center, Indianapolis, IN 46285

FEI #1819470

Inspection Recommendation:

A pre-approval inspection is required

Note: On 3/8/2019, OPQ reviewer Muthukumar Ramawamy, stated the following regarding the PAI: *"Device related PAI at Lilly corporate center is complete and received an acceptable recommendation."*

Finished Combination Product Manufacturer

Firm Name: (b) (4) (b) (4)

Inspection Recommendation:

A post-approval inspection is required

7.3. Human Factors

A human factors consult was completed CAPT. Mary Brooks (CDRH/ODE/DAGRID) for review of the Human factors study. Her review is provided below:

INTENDED USERS, USES, USE ENVIRONMENTS & TRAINING

Intended Use

Nasal glucagon is intended to deliver a single dose of glucagon to the nasal mucosa of a patient experiencing severe hypoglycemia.

Intended Users

The intended users of nasal glucagon include lay users and healthcare providers (HCPs).

Intended Use Environments

The product is intended for use in non-clinical environments (e.g., homes), as well as clinical environments such as an emergency department, long-term care facilities, assisted living communities, or an ambulance

Intended User Training

The standard of care for lay users directly responsible for the care of patients with diabetes (e.g., parents) would include training by a healthcare provider on the proper use of the product. Training would typically include a walkthrough of the IFU and demonstration of the use of the device, and may include the opportunity for the user to perform a simulated or real actuation to demonstrate understanding of proper use.

Lay users who do not normally provide care to patients (e.g., bystanders during a hypoglycemic event) may have no training at all.

Reviewer Analysis/Comments:
The sponsor provided the intended use of the combination product, the device constituent and principles of operation. This is a first of a kind combination product. The device was designed so it required few steps, no reconstitution and a needle-free option as opposed to the traditional glucagon IV/IM administration. Offering a mucosal nasal administration used would allow for a more rapid administration by healthcare providers, HCP, and lay users with limited to no training requirements prior to use. Labeling is provided on the primary container and a paper IFU included in the carton.

KNOWN USE PROBLEMS, FORMATIVE, IDENTIFICATION OF CRITICAL TASKS

Summary of Known Use Problems

Nasal glucagon uses a new technology, and is not a line extension of any other product. Additionally, because it is a single use device intended for emergency use, the user interface has little to no similarity to conventional nasal spray technologies. The current approved products used to treat patients experiencing a severe hypoglycemic event who cannot safely consume oral carbohydrates (outside of a hospital setting) is mainly limited to injectable glucagon.

Analysis of Use-Related Hazards and Risks

This section summarizes an excerpt of the program's comprehensive risk analysis that contains all the use related

hazards and risks, including those associated with potential use errors.

Risk analysis methods

With regard to use-related (i.e., human factors) risks, potential use errors were identified, analyzed, and documented through application Failure Mode and Effects Analysis (aFMEA). AFMEA methodology includes estimates of the probability and clinical severity of any associated potential harms. Each identified use error was analyzed in order to estimate severity of any resulting potential harm (see Table 2). Clinically significant harm is defined as a severity ranking of 4 or greater.

Table 1. Severity of Harm Ranking Table

SEV	Category	Description
5	Severe	Life Threatening or resulting in death
4	Major	State of Injury that is permanent OR requires major medical intervention.
3	Moderate	State of injury that is NOT permanent, BUT may require minor medical intervention.
2	Minor	Temporary AND non-debilitating state of pain/discomfort.
1	Negligible	State of dissatisfaction

Summary of use-related hazards and risks

Table 2 summarizes the use-related hazards, the potential harm that could result, the potential severity of the harm, all risk control measures implemented to eliminate or reduce the risk, and the source of evidence that each risk control measure was effective.

Use step	Potential use error	Potential Hazardous Situation	Potential harm	SEV	Risk controls	Evaluative method
User transports and stores product	User opens tube prior to emergency scenario requiring use	Degraded drug product	Continued SEVERE HYPOGLYCEMIA, may result in Death	5	Instructions on the tube state "Do not remove shrink wrap until ready to use. Do not open the tube until ready to use."	Knowledge assessment
	User drops device in tube, breaking seal	Degraded drug product	Continued SEVERE HYPOGLYCEMIA, may result in Death	5	Instructions on the tube state "Do not remove shrink wrap until ready to use. Do not open the tube until ready to use."	Knowledge assessment
	User carries a device that is expired	Degraded drug product	Continued SEVERE HYPOGLYCEMIA, may result in Death	5	Tube label states expiration date	Knowledge assessment
Opening the tube	User is unable to open the tube	No dose	Continued SEVERE HYPOGLYCEMIA, may result in Death	5	Tube is designed to be opened by intended users	Simulated Administration
Remove device from tube	User is unable to remove device from tube	No dose	Continued SEVERE HYPOGLYCEMIA, may result in Death	5	The tube and device are designed to afford removal	Simulated Administration
	User inadvertently actuates device	No dose	Continued SEVERE HYPOGLYCEMIA, may result in Death	5	Force to actuate device affords use by intended users while mitigating inadvertent actuation	Simulated Administration
	User exposes device to moisture	No dose	Continued SEVERE HYPOGLYCEMIA, may result in Death	5	Instructions state to not expose product to moisture	Knowledge assessment
Hold device between fingers and thumb	User actuates the device attempting to 'test' it prior to use	No dose	Continued SEVERE HYPOGLYCEMIA, may result in Death	5	Instructions on the tube state (b) (4)	Simulated Administration
Place nozzle in nostril	User places device in a location that is not the nostril	No dose or partial dose, depending on the location	Continued SEVERE HYPOGLYCEMIA, may result in Death	5	Instructions on the tube indicate to administer into the nostril	Simulated Administration
Depress plunger to administer a dose	User does not push the plunger far enough to administer a dose	No dose	Continued SEVERE HYPOGLYCEMIA, may result in Death	5	Instructions state to depress plunger until the green line at the bottom is no longer visible	Simulated Administration
	User is not able to depress plunger to administer a dose	No dose	Continued SEVERE HYPOGLYCEMIA, may result in Death	5	Force to actuate device affords use by intended users while mitigating inadvertent actuation	Simulated Administration
After giving a dose	User does not dispose of device and carries a used device with them	No dose	Continued SEVERE HYPOGLYCEMIA, may result in Death	5	Instructions state to discard the device after it has been used; After use the plunger is no longer visible	Knowledge Assessment

Section 7: Description and Categorization of Critical Tasks

Critical tasks are those that if performed incorrectly or not performed at all, would or could cause serious harm to the patient or user, where harm is defined to include compromised medical care (FDA, 2016). Table 3 lists the nasal glucagon critical tasks, potential use errors, harm, and how implemented mitigations have been evaluated.

Table 3. Critical Tasks for Nasal Glucagon

Task (use step)	Potential use error	Potential hazard	Potential harm	Mitigations	Evaluative method
User transport/stores product	User opens tube prior to emergency scenario requiring use	Degraded drug product	Continued SEVERE HYPOGLYCEMIA, may result in Death	Instructions on the tube state to not remove the shrink wrap until ready to use and to call for medical help right away after giving a dose.	Knowledge assessment
	User exposes device to moisture	Degraded drug product	Continued SEVERE HYPOGLYCEMIA, may result in Death	Instructions on the tube state to not remove the shrink wrap until ready to use and to call for medical help right away after giving a dose.	Knowledge assessment
	User carries a device that is expired	Degraded drug product	Continued SEVERE HYPOGLYCEMIA, may result in Death	Tube label states expiration date and to call for medical help right away after giving a dose.	Knowledge assessment
Open the tube	User is unable to open the tube	No dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	Tube is designed to be opened by intended users	Simulated Administration
Remove device from tube	User is unable to remove device from tube	No dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	The tube and device are designed to afford it to be removed by intended users	Simulated Administration
Hold device between fingers and thumb	User inadvertently actuates device	No dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	Force to actuate device affords use by intended users while mitigating inadvertent actuation, and instructions state to call for medical help right away after giving a dose.	Simulated Administration
	User actuates the device attempting to 'test' it prior to use	No dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	In the step "Hold device between fingers and thumb", the tube label instructions state "Do not press plunger", and to call for medical help right away after giving a dose.	Simulated Administration
Place nozzle in nostril	User places nozzle in a location that is not the nostril	No dose or partial dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	Instructions on the tube indicate to administer into the nostril, and to call for medical help right away after giving a dose.	Simulated Administration
	User does not push the nozzle far enough into the nostril	No dose or partial dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	Instructions state to insert the tip gently in one of the nostrils until finger(s) touch the outside of the nose, and to call for medical help right away after giving a dose.	Simulated Administration
Depress plunger to administer a dose	User does not fully depress plunger	No dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	Device designed for actuation force low enough for intended users, and high enough to prevent accidental actuation. Instructions state to depress plunger until the green line at the bottom is no longer visible, and to call for medical help right away after giving a dose.	Simulated Administration
After giving a dose	User does not dispose of device and carries a used device with them	No dose delivered	Continued SEVERE HYPOGLYCEMIA, may result in Death	Device is designed to visually indicate when it is used (plunger stays down, and green line is hidden when actuated). Tube label states nasal glucagon is a single use product, to throw away the used device.	Knowledge Assessment

Reviewer Analysis/Comments: <?>

A total of 6 formative HFE evaluations occurred between December 2013 – November 2016. In each iteration, test participants were untrained and most were caregivers with/without experience delivering IM glucagon and HCPs. These evaluations provided insight to the device design, use, labeling and knowledge about the device and nasal glucagon administration. All failures, observed difficulties, close-call and follow up feedback were evaluated and modifications were made accordingly to the device and labeling. Use related risk analysis was conducted which identified critical tasks, severity of harm, mitigations and methods of evaluation in the HFE summative study.

HF VALIDATION STUDY PROTOCOL & METHOD

Section 8: Details of Human Factors Validation Testing

In December 2017, a human factors validation study was conducted per PDS-PROTOCOLS-01225 in order to validate the safe and effective use of nasal glucagon by representative users in performing critical tasks for the intended use of the device in the intended use environment.

In this study, representative users completed a performance-based task (simulated use scenario in a stressful environment), and a knowledge-based task (IFU knowledge assessment). By simulating a time-critical, emergency-response situation representative of the expected use environment, a performance-based task allows an appropriate assessment of nasal glucagon use safety and effectiveness.

Test Environment

The study was conducted in a research facility configured to allow participants to complete tasks in a testing room while being monitored through a 1-way mirror from an adjacent observation room by sponsor and/or other study personnel.
To more closely simulate the expected use environment for nasal glucagon (i.e., time-critical, emergency-response situations), additional study stressors were used in the testing room during the session to artificially induce a stress response in the test participants.

Test Participants

The study included a total of 45 representative users, including:
[n=15] Adolescent lay users (10-17 years of age), including: **[n=7]** familiar with diabetes (e.g., living with someone with diabetes) **[n=8]** not familiar with diabetes

[n=15] Adult lay users (≥18 years of age), including: **[n=11]** familiar with diabetes (including **n=7** previously trained on injectable glucagon) **[n=4]** not familiar with diabetes

[n=15] Healthcare providers, including: **[n=3]** Emergency room physicians **[n=7]** Nurses **[n=5]** EMTs

Reviewer Analysis/Comments:
The study confirmed the test devices were production-equivalent nasal glucagon devices, tubes and labeling. The final drug name had not been finalized at the time of the study; a mock trade name "(b) (4)" was used. Test environment simulated as closely as possible to a time critical, emergency response scenarios with appropriate test distractions.

Participant Training

To reflect the worst case expected in actual use, all study participants were untrained.

Test Scenario 1: Simulated Use

To introduce the scenario, participants were positioned behind a screen blocking visibility of the test area, and told that a person with diabetes had suddenly become unresponsive in the next room and needed a dose of (b) (4) This included 4 tasks to be evaluated.

Test Scenario 2: IFU Knowledge Assessment

Participants were seated at a table with the moderator, provided with the tube and device, and asked a series of questions

Root Cause Investigation

After both tasks were complete, the moderator investigated root cause for any and all observed use problems by asking open-ended questions to determine the extent to which aspects of the design may have contributed to the problem.

Final Interview

At the end of the session, the moderator provided participants with an opportunity to provide any final thoughts related to the safety, usability, or testing of the product, then dismissed the participant.

HF Validation Study Results

Summary of Results

In the simulated use test, there were very few use errors, with 177 successful tasks out of a total of 180 tasks evaluated (45 participants, with 4 tasks per scenario). Three use errors associated with depressing the plunger (Task 4) were observed.

Root Cause Analysis of Observed Use-Related Issues

Table 4. Summary of Root Cause Analyses of Performance Failures in Validation Testing

Participant	Test Scenario	Observation	Participant comments	Root Cause	Clinical Consequence
Y03 [Female, Age 16, REALM- Teen 64, familiar with diabetes]	Test Scenario 1: Simulated Use	Did not fully depress the plunger – she pushed part way, but not far enough to actuate the device. Y03 opened and followed the IFU during the scenario. After the task (and before root cause investigation), when asked to give another dose, she was successful.	User said that the first time she used the device, she didn't know when to stop pushing the plunger.	User did not know to fully depress the plunger until the green line is no longer visible	Delay of therapy
Y06 [Male, Age 15, REALM- Teen 66, familiar with diabetes]	Test Scenario 1: Simulated Use	Did not fully depress the plunger – repeatedly went back and forth between the nostrils, partially depressing the plunger each time (similar to OTC nasal sprays). He opened and followed the IFU during the scenario. After the task (and before root cause investigation), when asked to follow the IFU to give another dose, he was successful.	User said that the first time he used the device, he didn't know that had to push down until the green line was not visible. He also said he expected it to work like a typical nasal spray, or syringe-like device (where repeatedly pressing it sprays medicine into the nostril).	User did not know to fully depress the plunger until the green line is no longer visible.	Delay of therapy
A10 [Male, Age 58, REALM 60, familiar with diabetes, prior training on injectable glucagon]	Test Scenario 1: Simulated Use	Placed the nozzle firmly into the nostril, but did not press the plunger. He then placed the device on the floor and stated he was finished. After the task (and before root cause investigation), when asked to follow the IFU to give another dose, he was successful.	User said he expected to push the device into the nose and it would actuate automatically like an EpiPen.	User did not know to fully depress the plunger until the green line is no longer visible.	Delay of therapy

Table 5. Summary of IFU Knowledge Assessment Failures in Validation Testing

Participant	Test Scenario	Observation	Participant comments	Root Cause	Clinical Consequence
Y09 [Female, Age 12, REALM-Teen 47, not familiar with diabetes]	IFU Knowledge assessment, Q2: According to the materials, when should you open the tube?	The participant could not locate the information on the tube.	The participant could not locate the answer to the question. She showed confusion over whether the yellow blocks of information on the label were separate instructions.	User was confused over the apparent redundancy of the "Do not remove shrink wrap" and "Do not open tube" lines.	Potential to deliver degraded drug if the user opened the tube and exposed the product to moisture before use.
Y10 [Male, Age 15, REALM- Teen 65, not familiar with diabetes]	IFU Knowledge assessment, Q3: According to the materials, what are you supposed to do after giving the dose?	The participant briefly looked at the tube, then abandoned the task. He did not peel back the label, so did not locate the information on the tube. After the task (and before root cause investigation), when asked what he would do in this situation, he said he would call 911.	User said he not see the "peel back" instructions, because his attention on that part of the label was focused on the "Do not remove shrink wrap" and "Do not open tube" lines.	User did not see the "Peel (b) (4) (b) (4) text on the label.	Little to no clinical consequence, as it did not prevent the participant from successfully delivering the drug.
A07 [Male, Age 31, REALM 55, familiar with diabetes]	IFU Knowledge assessment, Q3: According to the materials, what are you supposed to do after giving the dose?	The participant did not peel back the label, so did not locate the information on the tube. After the task (and before root cause investigation), when asked what he would do in this situation, he said he would call 911.	Participant did not peel back the label to read the information underneath. He did not pay attention to the "peel (b) (4) nstructions, saying that he felt like it was an anxious situation, and assumed that under the peel would be instructions he didn't need, such as drug or chemical information. He indicated that he would call 911 after giving a dose.	User assumed that the information in the "peel (b) (4) section label was nonessential or irrelevant to the task.	Little to no clinical consequence, as it did not prevent the participant from successfully delivering the drug.

Participant	Test Scenario	Observation	Participant comments	Root Cause	Clinical Consequence
A09 [Male, Age 55, REALM 51, familiar with diabetes, prior training for injectable glucagon]	IFU Knowledge assessment, Q3: According to the materials, what are you supposed to do after giving the dose?	The participant did not peel back the label, so did not locate the information on the tube. After the task (and before root cause investigation), when asked what he would do in this situation, he said he would call 911.	User said he expected instructions on what to do after giving a dose to be sequential with the steps on the tube, and was not expecting to find it under the peeled label.	User assumed that the information in the "peel (b) (4) section label was nonessential or irrelevant to the task.	Little to no clinical consequence, as it did not prevent the participant from successfully delivering the drug.
A15 [Female, Age 63, REALM 66, familiar with diabetes, prior training for injectable glucagon]	IFU Knowledge assessment, Q3: According to the materials, what are you supposed to do after giving the dose?	The participant did not peel back the label, so did not locate the information on the tube.	User said she would expect to be trained on this device by the doctor before even getting it.	User did not know to peel back the label to find what to do after giving a dose and assumed she would be trained to use it before getting it.	Little to no clinical consequence, as it did not prevent the participant from successfully delivering the drug.
Y08 [Female, Age 12, REALM-TEEN 52, familiar with diabetes]	IFU Knowledge assessment, Q5: According to the materials, how many times can a device be used?	The participant could not locate the information on the tube.	When directed to the phrase (b) (4) (b) (4) and asked to interpret, she said it was confusing and that she didn't know what it meant.	User did not understand the meaning of the phrase (b) (4) (b) (4)	Potential for delay of therapy if the user kept a used device thinking it could be used again.

Discussion and Assessment of Residual Use-Related Risks

The task failures shown in Table 4 reflect a risk of delay of therapy if users do not fully depress the plunger in actual use. The participants who experienced this task failure included 2 adolescents (16 year old female, and 15 year old male) and 1 adult (a 58 year old male) who did not know how far to depress the plunger. In the first case, the participant (a 16 year old female) did not see the instruction that the dose is complete when the green line is no longer visible. In the other 2 cases, the participants expected the device to work differently than described in the labeling (i.e., like nasal spray and an autoinjector, respectively). Before performing root cause investigation, these participants were asked to repeat the scenario while reading along with the IFU. In all three cases, the participants successfully administered a dose, indicating as expected that emergency situations contribute to lay user errors. Lilly intends for users to read the instructions, and the results show that the instructions serve as sufficient mitigation for the failure to activate the device. In light of the success of all participants in delivering a dose under conditions that they had read the instructions, Lilly concludes that no further mitigations are necessary.

Knowledge-Based Failures

One participant (a 12 year old female unfamiliar with diabetes) was confused when asked when to open the tube (question 2). However, she correctly answered question 1, "*According to the materials, when should you remove the shrink wrap*?" The failure would not have resulted in clinical consequence in actual use, and shows that the tube label provides sufficient mitigation for the failure. Lilly concludes that no further mitigations are necessary.

Four participants answered incorrectly to question 3, "*According to the materials, what are you supposed to do after giving the dose?*" which corresponds to a risk of users not calling for medical help after giving a dose. However, all 4 participants successfully administered the dose in simulated use (Test Scenario 1). Additionally, three of the four participants indicated that they would call 911 after giving the dose, and the fourth participant expected to be trained prior to use. As such, the results show that the tube label provides sufficient mitigation for the failure. Lilly concludes that no further
mitigations are necessary.

One participant (a 12 year old female) did not understand the meaning of the phrase (b) (4)." The risk of a potential delay of therapy (if the user kept a used device thinking it could be used again) is mitigated by the device

being designed to visually indicate when it is used (i.e., plunger stays down, and green line is hidden when actuated). Lilly concludes that no further mitigations are necessary.

Overall Acceptability of Residual Use-Related Risks

Residual risks may include use errors that could result in a missed dose or underdose. As nasal glucagon is intended for emergency treatment of a life-threatening condition, the clinical harm associated with significant delay of therapy due to use error is as significant as if a user did not have the therapy available (i.e., continued severe hypoglycemia).

- The current approved products used to treat unconscious patients experiencing a severe hypoglycemic event outside of a clinical setting have several steps to reconstitute glucagon with a prefilled syringe and a vial filled with powder. Nasal glucagon offers a treatment that requires fewer steps, no reconstitution, and needle-free delivery.
- The benefits of nasal glucagon in the areas of simplicity, usability, safety, and ease of training represent a significant improvement in the successful delivery of glucagon for the treatment of severe hypoglycemia outside of a clinical setting.

Lilly has mitigated known and foreseeable use-related risks through modifications of the user interface, and asserts that the mitigations have reduced use-related risks as far as possible given the limits of the nasal delivery technology. Residual use-related risks would not be further reduced by modifications of the design of the user interface, are not possible or practical, and are outweighed by the benefits that may be derived from use of the product as designed.

Summary of HF Validation

A human factors validation study (see Section 8) validated the safe and effective use of nasal glucagon by representative users (n=45) in performing critical tasks for the intended use of the device in the intended use environment. The validation test included 2 test scenarios, comprising a simulated use test and an IFU knowledge assessment.

- The results of the simulated dosing scenario showed a high rate of success in first-time use, in which there was no opportunity to learn about the product beforehand. There were 3 participants who did not know to fully depress the plunger to actuate the device. However, in all 3 cases the users were able to administer the dose after reading the IFU.
- The results of the knowledge assessments showed that the IFU is appropriately designed to allow users to understand the key elements of the IFU. Out of a total of 270 asked questions (45 participants × 6 questions each) there were a total of 6 incorrect answers given, for questions related to when to open the tube (n=1), what to do after giving a dose (n=4), and the meaning of the phrase "(b) (4)" (n=1). However, Lilly asserts that there are no design changes that would eliminate these kinds of cognitive errors.

Reviewer Analysis/Comments:

The sponsor provided a well-executed HFE/UE evaluation and followed CDRH's HF guidance document and provided the report as recommended in Appendix A. The sponsor adequately evaluated the appropriate users in a simulated emergency use environment to administer glucagon to the nasal mucosa in unresponsive diabetic patients suffering from life threating low glucose levels. The testing was done without prior training to represent the worst-case scenario. In scenario 1, medication administration, three participants failed to fully depress the plunger; however, they were successful after reading the IFU. All three were lay-users with previous experience with diabetic patients. In scenario 2, knowledge assessment, six failed to provide an adequate response. These six were lay users, four with and two without experience with diabetic patients. The root-cause analysis was conducted and it was concluded the residual risk of use errors could result in a missed dose or under dose. The sponsor states they have attempted to mitigated known and foreseeable use-related risks through modifications of

the user interface and labeling and claim the mitigations have reduced use-related risks as far as possible and the current medications available to HCP and lay-users are limited to injections that require reconstitution and/or knowledge to provide the injection. Given the emergency use of the drugs currently on the market, the clinical lifesaving benefit outweighs the residual risk.

Human Factors Validation Recommendation:
The human factors validation is adequate.

8. RISK ANALYSIS

8.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		

8.2. Summary of Risk Analysis

The sponsor provides a risk analysis in 3.2.R “medical-device-app-c-rrr”. They have provided the criteria for the grading of their risk analysis below:

Table 5.0-1 Severity of Harm

Category	Description	FMEA Ranking
Severe	Life Threatening or resulting in death	5
Major	State of Injury that is permanent OR requires major medical intervention.	4
Moderate	State of injury that is NOT permanent, BUT may require minor medical intervention.	3
Minor	Temporary AND non-debilitating state of pain/discomfort.	2
Negligible	State of dissatisfaction	1

Table 5.0-2 - Probability of Harm

Probability of Harm Level	Events per patient year of therapy*
5	> 1/100
4	≤1/100
3	≤1/1,000
2	≤1/100,000
1	≤ 1/10,000,000

* Expected use of device is once per year per patient

The sponsor did not provide the full risk analyses that were used for their risk analysis. They only provided what they deemed significant risks; i.e. risks with severity of a 4 or 5 and a probability that was greater than 1. Therefore, the full risk analysis was not provided.

Reviewer Note:
A deficiency was sent via interactive review on 9/25/2018. In response the sponsor provided a safety assurance case (SAC), which they state identifies “potential hazards, risk control measures, mitigation strategies with identification of the testing of these mitigations is provided with this response.” The SAC contains a claim that states that the “hazards related to drug product critical quality attributes are mitigated.” The review of the SAC device related risks are provided below:

SAC Device Related Risks Review:

The sponsor has provided their risk analysis in the context of a SAC. Therefore, they do not list ratings of harm/occurrence, but they do appear to address common hazardous situations that would potentially lead to patient risk and harm and reference their FMEA controls/mitigations. These include the following hazardous situations and appropriate mitigations including device design, verification/validation testing, lot release/manufacturing controls, labeling, etc.:

- Powder may not be expelled
- Product remains lodged in tube
- Device comes apart after assembly
- User cannot open tube
- (b) (4) will not move through entire stroke
- sticks on container
- Device may not remain intact during shipping
- Drug product exits before patient use
- No device is place in packaging container
- Incomplete device assembly
- Drug not in container closure
- Drug product not retained in container
- Device can't build pressure/no dose delivered
- Already actuated device in package
- Green strip on plunger is too low
- Button left with (b) (4) closed and unable to build sufficient pressure during dosing'
- (b) (4) (no powder dispensed)
- Biocompatibility
- Improper dose given

Device Risk Analysis Recommendation:
The risk analysis is adequate

9. LABELING

The following labeling images were taken from 1.14.1 Draft Labeling:

Instructions/Labeling on Nasal Spray Device:

(b) (4)

Instructions/Labeling on outer packaging magnified:

Folded IFU in carton:

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

Labeling Recommendation:
The labeling is adequate.

10.DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

The following release specifications are included for the device constituent in accordance with the approved specifications:

Device Performance Requirement	Specification	Lot Release Specification Included
Dose Accuracy	Each individual shot weight is NLT (b) (4)% of the mean fill weight The an shot weight is NLT (b) (4)% of the mean fill weight *	Yes
Delivered Dose Uniformity	NLT (b) (4)%	Yes
Spray Pattern Diameter/Shape	NLT (b) (4)mm and Ovality (Dmax/Dmin) NMT (b) (4)	No
Plume Geometry/Plume Angle	NLT (b) (4)deg NMT deg	No
Particle Size Distribution	X90 NMT (b) (4) microns	Yes
Actuation Force	<u>At Room Temperature:</u> NLT: (b) (4)kgF NMT: (b) (4)kgF <u>At -20 deg C</u>: NLT: (b) (4)kgF NMT: (b) (4)kgF	Yes

Reviewer Note:
OPQ Reviewer Muthukumar Ramaswamy has stated that CDER does not recommend that plume geometry and spray pattern be included as lot release specs/tests as this is a quality control test and does not need to be included. While, I do not agree with this decision to exclude these device performance requirements from lot release as it is important that the device is able to administer the drug product in the correct fashion to achieve the clinical affect, CDER is the lead center on this product; therefore I defer to CDER/OPQ. Additionally, the sponsor has included testing for these specific device EPRs in their reliability testing and has demonstrated that they can be met with 99.99% reliability, which supports the consistency of the delivery.

Device Lot Release Specifications Recommendation:
The lot release specification/testing is adequate.

11.INTERACTIVE REVIEW (PRE-MIDCYCLE)

11.1. IR#1: Written 8/24/2018; Returned from Sponsor on 10/23/2018 - RESOLVED

1. Please state if the to-be-marketed version of the device was used in the pivotal clinical study. Alternatively, if it was not used in these trials, please provide a comparison of the clinical use device and the to-be-marketed version of the device and how the clinical use device supports the safety and effectiveness of the to-be marketed version to bridge the two devices.

Sponsor Response
The devices used to deliver the drug powder during clinical trials employed the same fundamental scientific technology and used the same operating principles as the to-be-marketed device. All versions of the development device were used in clinical studies and are production equivalent to the to-be-marketed device. None of the changes during development affected the safe and effective use of the combination product.

A detailed description of changes made to the device during the development process is located in Section 3.2.P.2.4, Container Closure System. Similar information is provided in Table Q1-1 and a description of device operation is provided in Section 3.2.R.3.3.2.
The pivotal clinical studies, IGBB and IGBC, used Configuration ID 1.0 of the device. The studies were resupplied with product using device Configuration ID 2.0. Study IBGI was an adult confirmatory clinical study that used device Configuration ID 2.1. The only difference between the device Configuration ID 2.1 and the to-be-marketed device (Configuration ID 2.2) are minor changes to one component of the device to improve the molding and assembly processes (detailed in Section 3.2.R.3.3.1 and the response to Question 3).

The safe and effective use of device Configuration ID 2.1 was demonstrated in the 69 person clinical study IGBI. There were no unique safety findings in the confirmatory Study IGBI, and in general, the results were similar to adult pivotal Study IGBC. These findings show that the safety and efficacy profile of nasal glucagon was not altered by the implementation of manufacturing and device changes incorporated between the two studies (Section 2.7.4.2.5, Summary of Clinical Safety).

The to-be-marked device Configuration ID 2.2 incorporates a minor change made after study IGBI to several (b) (4) (b) (4) This change improves the manufacturability of the device, but does not impact the ability of the device to perform its intended use (to deliver drug powder). These (b) (4) changes are pictured in Section 3.2.R.3.3.1 and are discussed further in the response to Question 3, which also provides a risk-based assessment demonstrating how the changes do not affect device performance.

The production equivalent devices that have been used in clinical studies are representative of the to-be-marketed device; therefore, no further clinical studies are planned.

FDA Response
The sponsor states that there have been minor device changes to the device compared to what was used in the clinical study. They discuss the risks of these changes to the device performance in response to question 3. The sponsor has clarified the differences in the clinical use device and the to-be-marketed version of the device. These are also the same stability lots versions of the device.

While it is unlikely that the changes to the device from the primary stability lots would affect the performance requirements of the device, given that the internal assembly of the device are not changing, it is unclear if this would affect the drug stability or device performance requirements. A deficiency was sent to the sponsor and they responded with the following:

"Delivery performance of the device (i.e., Pump Delivery (spray/shot weight), Spray Pattern, Plume Geometry, and SCU) is dependent on only two factors:

(b) (4)

In contrast to solution-based nasal sprays, particle size distribution for nasal glucagon is not dependent on the device, but is an inherent property of the drug powder. Therefore, particle size distribution is not affected by this change. (b) (4)

As there were no changes to the primary container closure system, the changes have no effect on drug product compatibility.

The sponsor has provided an adequate response. I do not believe that the minor design changes listed above will change the device essential performance requirements and are adequate as far as clinically validating the device.

2. The CDER Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation states on page 11: "The following test parameters are recommended for nasal spray drug products. Appropriate acceptance criteria and validated test procedures should be established for each test parameter." This list includes: Pump Delivery, Spray Content Uniformity (SCU), Spray Pattern and Plume Geometry Shape, Droplet / Particle Size Distribution. The guidance also states on page 27: "specifications should include performance attributes of the pump (e.g.…minimum actuation force to achieve desired spray characteristics)."

   Given the intended use of your product as an emergency treatment of severe hypoglycemia, the performance characteristics of the device are vital to the administration of the drug product. While we note that you have completed some base level verification of these stated performance characteristics in your stability testing, you state in 3.2.R., document "medical-device", that only delivered dose is considered an essential performance requirement (EPRs). For nasal sprays, the Agency expects the EPRs to include, at a minimum, the following:

   - Pump Delivery (Spray Weight)
     - You have included pump delivery as an EPR.

   - Spray Pattern and Plume Geometry Shape
     - You state that both spray pattern and plume geometry do "not impact the ability of the device to deliver a dose." While it may not impact the shot weight, it may affect the delivery of the drug product through the nasal passage, resulting in a different clinical affect. Therefore, we recommend that spray pattern and plume geometry be evaluated after device actuation as an EPR.

- Spray Content Uniformity (SCU)
  - You state the drug product characteristic, uniformity of dosage units (UDU), is a replacement for spray content uniformity, however you do not plan to test for content uniformity after in use conditions; i.e. after device actuation. Therefore, UDU is not an adequate substitute for SCU and SCU after device actuation should be included as an EPR.

- Particle Size Distribution (PSD)
  - Although you have defined a specification for PSD, you state that PSD is not an EPR for the device component: "PSD of the delivered dose is determined and controlled by the drug powder manufacturing process….A failure of this performance function could result in severe hypoglycemia (Hazard severity = 4 or 5) if particles were large enough that they couldn't pass through the device following actuation, however, the delivered dose (Shot Weight) method would detect this failure.

    This rationale is not acceptable, as you have not provided the particle size that would be large enough to not be delivered with the device. Additionally, while the particle size may be determined by the manufacturing process, it is possible that the particles may agglomerate over time leading to a larger particle size distribution and a clinically different result. Therefore, we recommend that PSD after device actuation be included as an EPR.

- Actuation Force
  - You state that actuation force is not considered a EPR of your device because "An excessively high actuation force could result in the user having difficulty or being unable to actuate the delivery device in which case they could use two hands to deliver the dose. The most likely scenario is user dissatisfaction (Hazard severity = 1), and least likely scenarios include delay in therapy or no dose delivered with indication (Hazard severity = 5)." However, you do not support this statement with an appropriate specification and verification testing. Given that the actuation of the device is crucial to the administration of the drug product, the Agency recommends that this be included as an EPR

Therefore, you have not provided adequate design control documentation of the device constituent of the combination product. Provide the following documentation for your device, for all of the EPRs listed above:

a. Design Control Documentation

   i. Design Inputs/Outputs –A complete and detailed description of the device constituent design inputs and outputs per 21 CFR 820.30, specifically the design requirements/specifications documentation with objective acceptance criteria. Ensure that you clearly describe the acceptability of your design inputs and outputs within the context of the intended use of your combination product. The design inputs and outputs should be developed in accordance with the risk profile of the entire combination product and may vary depending on the indications for use, patient and/or user population, environment of use, etc. You have not provided clear design control documentation with the inputs/outputs, specifying the design requirements and justification for the specifications for all EPRs

   ii. Design Verification Documentation – Verification testing documentation should include summary test results of established test methods for the product (e.g. recognized consensus standards, FDA Guidance, etc.) or complete verification test reports for unique or unrecognized test methods. Test method validation should be provided for unrecognized test methods.

   All verification testing should be directly traced to the design inputs of the device constituent. Ensure that you utilize test methods and preconditioning that simulate the intended use of your product. You should use a statistically significant sample size for verification testing. Provide valid justifications for the acceptability of any test results that do not pass its acceptance criteria.

As part of design verification, you should verify the EPRs with the to-be-marketed version of the device constituent and the intended biologic/drug product. However, if you plan to rely on verification testing conducted with a surrogate be sure to provide a scientific rationale for the acceptability of the surrogate for the intended biologic/drug product (i.e. fluid characteristics, viscosity, etc.). If available, results of stability / shelf-life testing may be provided if the to-be-marketed version of the device constituent and intended drug/biologic product are used.

iii. Stability / shelf-life testing and shipping studies – We note that you are not including all the EPRs in your stability testing. Additionally, you have not provided verification of the device EPRs after actual/simulated shipping. You should provide documentation that ensures the to-be-marketed version of the combination product maintains all of the EPRs up to the labeled date of expiry and after actual and/or simulated shipping.

If you plan to use a test subject other than the to-be-marketed version, you should list the differences in the design and provide a risk-based assessment demonstrating how the differences do not significantly impact the product's EPRs. Stability/shelf-life testing and shipping studies may be incorporated into design verification testing.

iv. Lot release specifications – We note that you are not including all EPRs in your lot release specifications. In your lot release specifications include the EPRs. If you intend to propose alternative control strategies for the EPRs, we recommend requesting specific feedback regarding your strategy.

b. Traceability Documentation

It is recommended that a traceability matrix is provided to ensure 1) the design outputs are adequately verified to meet the design inputs and 2) the finished combination product is validated to meet the user needs. It is highly recommended that the EPRs are highlighted for ease of review. While a traceability matrix can take many forms, the Agency has provided a high-level example for reference:

Patient / User Needs	**Design Input(s)**	**Design Output(s)**	**Verification**	**Validation**	**Shelf Life / Stability (Y/N)***	**Shipping (Y/N)***	**Lot Release (Y/N)***

*These columns are applicable only for EPRs

3. You state that you have iplemented design changes since you have produced the primary stability batches and therefore you are not proposing to provide verification testing of the final finished version of your device. Provide a risk-based assessment demonstrating how the differences do not significantly impact the device essential performance requirements listed below:
    - Pump Delivery (Spray Weight)
    - Spray Pattern and Plume Geometry Shape
    - Spray Content Uniformity (SCU)
    - Particle Size Distribution
    - Actuation Force

Alternatively, provide stability testing with the final finished version of the device constituent.

Sponsor Response

As part of the change management process, the changes in the device design (see Section 3.2.P.2.4, Container Closure System, Table 3.2.P.2.4-2) between the primary stability batches (Design Configuration ID 2.1) and the final version of the device (Design Configuration ID 2.2) were assessed for impact to device performance, patient/user interaction with the device, and drug product compatibility. The differences between Design Configuration ID 2.1 and ID 2.2 do not affect device performance, patient/user interaction, or drug product compatibility, as described in the risk-based assessment provided below.

Delivery performance of the device (i.e., Pump Delivery (spray/shot weight), Spray Pattern, Plume Geometry, and SCU) is dependent on only two factors:

(b) (4)

Device actuation force is a function of the ΔP and the friction forces between the device components (i.e., (b) (4)) generated during actuation. The primary constituents of actuation force are the f (b) (4) .

As there were no changes to the primary container closure system, the changes have no effect on drug product compatibility.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Differences in the device design between the primary stability batches (Design Configuration ID 2.1) and the final version of the device (Design Configuration ID 2.2) do not affect the device performance, patient/user interaction, or drug product compatibility.

4. You have provided a reliability analysis in 3.2.R, "medical-device". However, this analysis is inadequate. See the following recommendations and provide the requested documentation:

    a. You state "the reliability requirement was established that at least 95% of the devices need to deliver a minimum dose of glucagon, with 95% confidence after the devices have been preconditioned with multiple,sequential, worst-case reasonably foreseeable stresses to simulate shipping, aging, vibration, shock from dropping in different orientations, and use in different environments." While, we acknowledge that you state you have demonstrated 99.99% reliability with a 95% confidence for the device to deliver the minimum dose of glucagon, in order to maintain the reliability of your device we expect that your reliability specification of your device component to deliver the minimum dose of glucagon be 99.99% with a 95% confidence interval. Please change your reliability specification to ensure that the reliability of the device component will maintained through the manufacturing and release of your product.

    In addition, while you have provided summary reliability testing of the device component to deliver the minimum dose of glucagon, you have not provided a reliability evaluation of the other device related EPRs, including, spray pattern, particle size distribution, actuation force, etc. You should provide additional verification testing that evaluates the reliability of the EPRs to the same reliability specification as well.

    Sponsor Response (Actuation force only):
    Lilly will implement a reliability design specification of 99.99% reliability with 95% confidence, as determined by the assessment of Cumulative Risk Probability (see Attachment Q4-1, Nasal Glucagon Residual Risk Grid) as part of our ongoing design control and risk management processes. Appropriate statistical requirements for controls implemented throughout the product lifecycle (e.g., design verification testing, cumulative pre-conditioning reliability evaluation, manufacturing and release of the product) have been established according to Lilly procedure CQP-161-2, Statistical Sampling for Medical Devices and Drug/Device Combination Products, to ensure the required reliability is maintained. The development and rationale for the manufacturing control strategy is described in Section 3.2.P.2.3, Manufacturing Process Development. The in-process controls and release testing controls are described in Section 3.2.P.3.3, Description of Manufacturing Process and Process Controls, Section 3.2.P.3.4, Control of Critical Steps and Intermediates, Section 3.2.P.5.1, Specifications, Section 3.2.P.5.6, Justification of Specifications, and the response to Question 2.a.iv. Actuation force data from the reliability study are summarized in Table Q4-1 and demonstrate that the device reliably actuates within the actuation force specification limits after being subjected to the cumulative stresses of shipping, various temperatures, humidity and pressure, vibration, and shock from dropping.

Table Q4-1 Actuation Force Reliability Testing Results

Cond. Temp.	Sample Size	Actuation Force Range (kgf)	Mean Actuation Force, $\bar{X}$ (kgf)	SD, σ (mg)	Tolerance Limit (kgf) $\bar{X} \pm$Target $k^*\sigma$	Specification Limit (kgf)	Pass/Fail
-20°C	52	7.47 to 10.37	9.2	0.59	7.80 to 10.60	NLT (b) (4) NMT	Pass
50°C	49	4.19 to 5.93	5.1	0.35	4.26 to 5.94	NLT NMT	Pass

Abbrevation = NLT = not less than; NMT = not more than; SD = standard deviation.

The test results at -20°C demonstrated a k-value of 5.6, which exceeds the minimum k-value of (b) (4) The test results at 50°C demonstrated a k-value of 10.3, which exceeds the minimum k-value of (b) (4). The results support the capability of the nasal glucagon device to be actuated within the specified force limits with 99.99% reliability and >95% confidence.

FDA Response:
The sponsor has provided summary testing of their actuation force reliability testing. However, there are outstanding deficiencies related to the actuation force specification and the FTA/stack up analysis. Please see Section 12 and 13 for follow-up deficiencies.

b. You provided a device safety assurance case that contains your summary FTA and your FMEA. However, under the reliabilty and risk analysis sections, I t does not appear that you have idenfied or quantified the probablility of the sources of device failure sources that would affect the reliabililty of the device to successfully delivery of the full intended dose of the emergency use product. You should include this evaluation for the EPRs of the device.

Per standard fault tree analysis quantification methods, the reliability of each basic event within the fault tree analysis should be assessed to determine, through a cumulative analysis, whether the reliability specification of the top-level failure mode is adequately supported. The statistical methods utilized to demonstrate the reliability of each basic event within the fault tree analysis should inform the test sample size necessary for reliability testing of the final finished combination product. We recommend utilizing a statistical tolerance interval method in which the limits of each individual component are analyzed (e.g., dimensions, geometry, material strength, etc.), both by itself and in conjunction with its associated components (i.e. stack-up analysis), to assess the potential for the component to result in a basic event failure mode of the device. To effectively use the tolerance interval method, the critical measurable elements of each component contributing to the basic event should be clearly stated and the statistical tolerance limit identified. Data to support the tolerance interval methodology should be provided and may include process validation data for individual components. The resultant k factor for each basic event should be used to calculate the necessary sample size of the reliability study based on the desired reliability specification and confidence interval.
Additionally, the basic events should be linked to appropriate design and/or manufacturing controls. Data linked to the fault tree basic events may be in the form of additional verification testing on finished products, verification testing on subcomponents/ subassemblies of the finished product, validation of manufacturing processes, etc. and should be conducted with a high degree of statistical confidence.

We recommend you use the statistical tolerance interval methodology. However, there are other methods that may also be utilized to support the fault tree analysis and overall reliability specifications. If you intend to use a

different method, we recommend that the manufacturer request a meeting with the review division to discuss the validity of the proposed approach for supporting the reliability specification.

Sponsor Response:
The probability of device failures that would affect reliability of the device to successfully deliver an acceptable dose of nasal glucagon and to be actuated within the specified force limits has been assessed as described in the Background Information, Section 1.2, Demonstration of Device Reliability, and the assessment is provided in Attachment Q4-1, Nasal Glucagon Residual Risk Grid. When available, actual data (e.g., statistical tolerance intervals) related to the controls were used to determine probabilities of failure. For those hazards associated with the essential performance requirement of the device (i.e., no dose, under dose, high actuation force, delay in therapy), >99.99% reliability has been demonstrated.

FDA Response:
The sponsor did not provide a FTA/stack up analysis that includes component related failures. A follow-up deficiency was issued to the sponsor requesteing they include component level failures. This was implemented and is adequate.

c. It appears that storage preconditioning of the product to the expiry ((b) (4) months), was not used as a preconditioning method. You state that their stability studies have not shown any differences between the performance requirements of the device. “Based on these data, no impact on device performance from shelf-life storage is expected, and storage conditioning was not conducted as a pre-conditioning activity.” While we acknowledge that you have completed shelf life studies, these studies were completed independently from other preconditioning methods and did not take into account cumulative preconditioning to address all reasonably foreseeable worst case risks that could impact the reliability of your product

In addition, the verfication testing of device reliability should be provided up to the (b) (4) month expiry of the combination product to support the shelf life of the product. Given the intended use of your proposed product (i.e. emergency use, life-saving), provide verification of the essential performance of your device to the reliability specification (99.99% reliability with a confidence of 95%) for the successful delivery of the full intended dose of the emergency use product.

In addition, you have not provided the full test methods for all preconditioniong methods, only a summary. Please provide the test methods that were used for all device preconditioning methods.

Sponsor Response:
As discussed in Section 3.2.R.3.5.6, Preconditioning, the delivery device is comprised of plastic parts (b) (4) . Real-time and accelerated storage of components and devices has demonstrated no changes to the plastic parts during room temperature storage. Real-time studies for the nasal glucagon combination product (24 months at room temperature) demonstrated the devices met performance criteria (including shot weight and activation force) at the end of their shelf life (see Section 3.2.P.8.3, Stability Data - Supporting Stability). In separate testing, devices (Configuration ID 2.0) were tested for shot weight (reported as a fraction of fill weight) following exposure to accelerated aging. Since the aging conditions were not appropriate for use with nasal glucagon drug powder, the devices were filled with lactose powder, a common pharmaceutical excipient, that is used by (b) (4) (the device design owner) as a suitable surrogate when testing device functionality. The devices met the requirement of ≥ (b) (4) % (fraction of fill weight) following exposure to the following conditions:

- Storage for 33 months at 40°C/75%RH, which is equivalent to 66 months at 30°C/65% RH according to the Arrhenius equation (using a conservative value for Q10 of 2.0)

- Storage for 33 months at room temperature
- Storage for 96 hours at 50°C and then for 19 months at room temperature

After exposures in all three scenarios above, the devices were tested and met shot weight requirements which would predict the devices to have a shelf life in excess of the anticipated (b) (4) months when stored below 30°C. Based on these data, the age of the device is not expected to have any effect on performance following exposure to the subsequently performed pre-conditioning activities (i.e., 96 hours exposure at -20°C, followed by device actuation, or 96 hours exposure at 50°C and 75% RH, followed by device actuation). Therefore, including storage as a pre-conditioning activity in the study is not necessary to demonstrate device reliability. As requested, we are providing the test methods that were used for all device preconditioning methods. The test methods for the following preconditioning activities conducted as part of the cumulative pre-conditioning reliability study are provided in Attachment Q4-2, Nasal Glucagon Delivery Device Reliability Protocol Appendices:

- The laboratory-based shipping profile that exposed the samples to atmospheric conditioning (temperature, humidity, and pressure), shock, and random vibration
- The shock hazard during handling, represented by free fall testing conducted based on the ISO 20072 standard
- Pre-conditioning to represent the reasonable worst-case environmental conditions for customer use, including 96 hours exposure at -20°C, followed by device actuation, and 96 hours exposure at 50°C and 75% RH, followed by device actuation.

FDA Response:
This is inadequate. It is unclear if the sponsor is not going to use devices aged to the expiry. Additionally, the devices tested were filled with lactose powder. The sponsor has not stated how this is adequate to use as a proxy for glucagon. The sponsor has completed follow-up testing with the to-be-marketed drug product and did not use lactose as a part of stability/reliablility lots. Follow-up deficiencies were provided in Sections 12 and 13 of the memo. The sponsor has used the drug product not lactose, in stability/reliability testing.

d. In the Type C Meeting written responses, dated 9/16/2018, we stated that:

"The Agency has conceived the following recommended circumstances of activation; however you should provide a rationale supporting the final circumstances of activation chosen.
i. Activation orientation
ii. Environmental temperature

While you provide verification testing for worst case environmental temperature to support the device reliability, you have not provided testing to support the activation orientation that you chose in your reliability testing. You state:

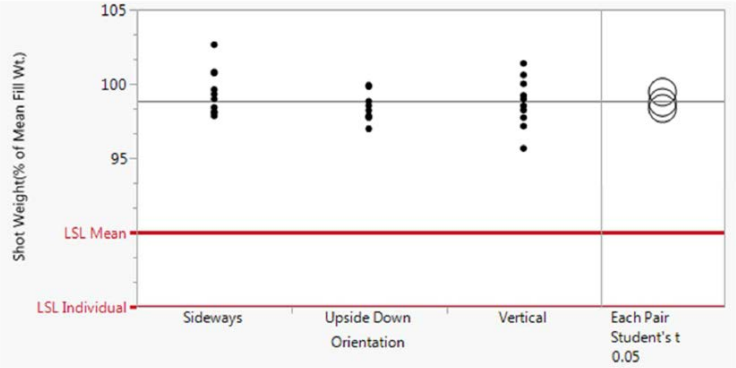
"Actuation was conducted with the device in the nozzle-up orientation, which is considered to be worst-case due to the negative effect of gravity on the acceleration of the drug powder during expulsion."

Given that the product may need to be administered in a variety of orientations, based on the patient position i.e. upright, lying down, etc., and use environments, please provide a strong rationale for why the activation orientation and environment temperature that you choose to use in your reliability study is the worst case scenario for the device reliability (i.e. autoinjector successful activation). To support your rationale, we

recommend that you provide performance testing of your top level essential performance goals with different combinations of activation orientation and environmental temperatures, with a limited sample size, to determine the combination of worst case use conditions (temperature and device orientation) for the device reliability. We recommend that these devices be tested under these conditions in your overall reliability analysis.'

Sponsor Response:
As discussed in Section 3.2.P.2.4.1.4.4 (Effect of User Actuation Technique, actuation at multiple orientations (nozzle tip up, nozzle tip down, and nozzle tip horizontal) has been demonstrated to have no meaningful effect on shot weight. In addition, the friction forces that are the primary constituent of the actuation force are not affected by device orientation. Therefore, actuation was conducted with the device in the nozzle tip up orientation, which is considered to be worst-case due to the negative effect of gravity on the acceleration of the drug powder during expulsion. In addition, clinical studies (IGBB, IGBC, IBGI, and IGBD) show that the device reliably delivers an effective dose of glucagon whether subjects are lying down or upright. The device orientation would be upright for a patient who is sitting and horizontal for a patient who is recumbent. In each of these studies, regardless of the orientation during use, Baqsimi produced a rapid increase in plasma glucagon to pharmacologic levels and also produced a glucose response similar to 1 mg injected glucagon (which serves as a common internal control across studies).

FDA Response:
The figure that is shown in Section 3.2.P.4.1.4.4 is the following:



While I would like to see more samples tested to demonstrate that the actuation orientation has no effect on actuation orientation, the upside down orientation lies within the shot weight percentage and the sideways acutation potentially has a higher shot weight %. Given that the top level failure mode is failure to dose. I believe the testing proposed (vertical dosing orientation) is adequate.

e. While we note that you provide manufacturing controls in place to mitigate the top level device failure of not delivering the full dose of glucagon; however, you are only proposing to maintain a reliability specification of 95% reliability specification with a 95% confidence interval. As we mentioned in part a of this deficiency, you should be maintained a reliability specification of 99.99% reliability with 95% confidence for the top level device failure of not delivering the full dose of glucagon. Provide altered or additional mitigations that will be necessary to maintain this reliability specification for the top level failure, as well as the other device EPRs. The reliability report should document the manufacturer's plan for maintaining device reliability throughout the product life cycle as part of good manufacturing practice requirements for combination products that a manufacturer has established per 21 CFR 4. The following should be addressed as part of this plan:

- The procedures must include requirements for analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources

of quality data to identify existing and potential causes of nonconforming product, or other quality problems.

- As part of defect and/or failure investigations, manufacturers should use the reliability data and fault tree analysis as part of the root cause analysis.
- The plan should include procedures for when, during a CAPA related activity, it is appropriate to image the device internally or physically open the device to inspect, measure and test assemblies or individual components and compare results with the specifications and data identified in the reliability analysis.
- The plan should include appropriate steps for linking the reliability data to the appropriate acceptance activities, including the specific product attributes that are evaluated, evaluation methods, and acceptability criteria that should be considered in the context of the product's reliability.
- In-process control and release test sampling plans should be described in detail to ensure that the reliability specification is maintained for each released lot.
- Action limits should be established for significant increases in rejections of the product and its components due to incoming inspection, in-process control, or release test failures.
- The activities triggered by exceeding an action limit should include, at a minimum, a root cause investigation and an associated risk analysis of the failure. The reliability data and fault tree analysis should be consulted as part of the root cause investigation.
- The plan should include procedures for updating the reliability data when new information is obtained (e.g., previously unidentified failure modes.)
- The plan should address disposition of non-released product pending analysis and mitigation of newly identified failures.

Sponsor Response:
As stated in the response to Question 4a, the device as designed and manufactured will meet a reliability level of 99.99% reliability with 95% confidence, as determined by the assessment of Cumulative Risk Probability as part of the design control and risk management processes throughout the product lifecycle. As demonstrated by the Background Information and the response to Question 4b, Lilly has demonstrated a robust control strategy to maintain this reliability specification for the essential performance requirements.

As discussed in the Background Information, the Lilly risk management process includes the use of risk management tools to develop and verify the effectiveness of the appropriate acceptance activities (product control strategy), including the specific product attributes that are evaluated, evaluation methods, and acceptability criteria, to ensure the reliability of the device design to meet the identified essential performance requirements. Appropriate statistical sampling plans for controls (e.g., in-process controls and lot release testing) have been established according to Lilly procedure CQP-161-2, Statistical Sampling for Medical Devices and Drug/Device Combination Products. The in-process controls and release testing controls are described in Section 3.2.P.3.3, Description of Manufacturing Process and Process Controls, Section 3.2.P.3.4, Control of Critical Steps and Intermediates, Section 3.2.P.5.1, Specifications, Section 3.2.P.5.6, Justification of Specifications, and the response to Question 2.a.iv.

The Post-Launch Risk Management (PLRM) process (conducted according to Lilly procedure PDS-SOP-00371, Post-Launch Risk Management) will be used after product launch to assure that the device reliability is maintained and that medical benefit continues to outweigh any residual risks.

In the PLRM process, information about the product is collected and reviewed throughout the post-launch phases of the product's lifecycle. The post-launch information is analyzed to identify:

- (b) (4)

- (b) (4)

(b) (4)

(b) (4)

FDA response:
I believe that this response is adequate. See Section 6.5 of the review that addresses the adequacy of the device reliability.

5. You provided a summary of your FMEA risk analyses in 3.2.R “medical-device-app-c-rrr” with only what you deemed as significant risks identified. However you did not provide the full device risk analyses for the device. Provide a risk analysis associated with the final finished combination product that is inclusive of risks associated with the device

constituent parts of the combination product. Your risk analysis should include all identified risks, potential hazards that are apparent to your device, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device. You should outline the methods in which you identified the risks of the product within your risk analysis documentation (e.g. DFMEA, UFMEA, Fault Tree Analysis, etc.). Refer to recognized consensus standard ISO 14971 “Medical devices - Application of risk management to medical devices” or device specific Guidance for more details.

Sponsor Response:
A complete Safety Assurance Case (SAC) including all identified risks, potential hazards, risk control measures, mitigation strategies with identification of the testing of these mitigations is provided with this response. The SAC is built in a stepwise manner as described below.

As discussed in Section 3.2.R.3, Appendix B (Safety Assurance Case (SAC) Introduction), a Preliminary Hazard Analysis (PHA) was used to identify hazards and potential causes of hazards and to identify circumstances in which users or patients are exposed to a potential source of harm. Potential hazards included no dose, under dose, or overdose delivered to the patient, contamination, lack of biocompatibility, difficult to use, patient dissatisfaction, incorrect route of administration, adulterated or wrong drug product, and physical trauma.

Risk management tools including Failure Modes and Effects Analyses (FMEA) were used to estimate the severity of the harms resulting from hazardous situations and the probability of harm. The Application FMEA focused on Human Factors and user interface with the device. The Design FMEA focused on hazards that could be addressed through the design of the device. The Process FMEA reviewed potential hazards affected by the manufacture and assembly of the device. Any unacceptable risks were mitigated and effectiveness of the controls was verified.

The SAC provides the traceability between the identified hazardous situation, the corresponding control, and the verification of the effectiveness of the control in the final device design. The SAC reconciles that the causes of these hazards have been adequately addressed for the nasal glucagon device and that residual risks are acceptably low when weighed against the benefit of the use of the device. Results from 11 clinical trials demonstrated that the device and IFU, as designed, met the identified intended use and user needs.

The SAC Graphic Report previously provided only included those risks related to the ability of the device to perform its primary function of delivering a dose of glucagon to a person experiencing severe hypoglycemia. Risks that are of low severity or not related to safety were identified and evaluated as part of the risk management process, but were not included in the previously provided SAC Graphic Report. The full SAC Graphic Report, which includes all identified risks, potential hazards, risk control measures/mitigations, and verification of risk control measures/mitigations is provided with this response. It is recommended that the Chrome web browser is used to view the SAC Graphic Report to reduce instances of illegible characters.

The Residual Risk Report (Section 3.2.R.3, Appendix C [Residual Risk Report]) previously provided includes summaries of the risk analysis methods utilized and the clinical acceptability of the residual risks. In addition, the report provides the analysis and conclusion that medical benefit of the therapy outweighs the cumulative risks (residual risks and risk control/mitigation effectiveness) associated with the design, manufacturing and use of the nasal glucagon combination product.

Refer to Section 3.2.R, Safety Assurance Case (medical-device-sac-full). It is recommended that the Chrome web browser is used to view the SAC Graphic Report to reduce instances of illegible characters.

FDA Response:

The sponsor has provided their risk analysis in the context of a SAC. Therefore, they do not list ratings of harm/occurrence, but they do appear to address common hazardous situations that would potentially lead to patient risk and harm and reference their FMEA controls/mitigations. These include the following hazardous situations and appropriate mitigations including device design, verification/validation testing, lot release/manufacturing controls, labeling, etc. See Section 8 of the review for the risk analysis review.

11.2. IR#2: Written 10/16/2018; Returned from Sponsor on 11/1/2019 - RESOLVED

CMC review for this NDA is in progress. At this time, we cannot provide any agreement on Lilly's proposed finished product specification or essential performance requirements with regards to the product spray pattern, plume geometry, spray content uniformity, and particle size distribution. We will finalize our CMC comments for finished product specification by midcycle.

However, in addition to shot weight, we recommend that you include device actuation force as an essential performance requirement. You should define both minimum and maximum force that is needed to actuate the device. Also we note that your current actuation force specification appears high given the emergency use nature of your product and intended users of your product. Justify the current maximum force specification of (b) (4) given the intended user groups and the emergency use nature of your product.

Sponsor Response:
Shot weight is the appropriate EPR for nasal glucagon, and unacceptable values of SCU, PSD, and actuation force would be detected by the shot weight test. In addition, available data from in vivo and in vitro evaluation of Baqsimi products demonstrate that spray pattern/plume geometry are not essential to the intended use of the product, since wide variations in these characteristics do not impact the ability of the device to perform its intended purpose of delivering a single dose of drug powder to the nasal mucosa of a patient. Although actuation force was not specifically identified as an EPR during development, it was tested as part of design verification and was incorporated into design control documentation, as shown in the responses to Questions 2 and 4. Since FDA recommended that actuation force be included as an EPR, the responses identify both shot weight and actuation force as EPRs.

FDA Response:
See design verification review section 6, where responses were analyzed. Follow-up deficiencies were issued in Sections 12 and 13. These were resolved interactively.

12.MIDCYCLE DEFICIENCIES: Issued 11/27/2018, Resolved 1/2/2019 – ADEQUATE

1) We previously stated in an email communication, dated 10/23/2018:
"CMC review for this NDA is in progress. At this time, we cannot provide any agreement on Lilly's proposed finished product specification or essential performance requirements with regards to the product spray pattern, plume geometry, spray content uniformity, and particle size distribution. We will finalize our CMC comments for finished product specification by midcycle. However, in addition to shot weight, we recommend that you include device actuation force as an essential performance requirement. You should define both minimum and maximum force that is needed to actuate the device. Also we note that your current actuation force specification appears high given the emergency use nature of your product and intended users of your product. Justify the current maximum force specification of (b) (4) given the intended user groups and the emergency use nature of your product."

In response to this, you provided responses to FDA quality related IRs #2 and 4, dated 9/25/2018, on 11/1/2018 regarding the device actuation force. However, after further review we recommend that your finished product specification and essential performance requirements of the device component include product spray pattern, plume geometry, dosage content uniformity, and particle size distribution. Please provide responses to the Agency's previous quality IRs #2, 4 (dated

9/25/2018) related to design verification/validation and device reliability for each of these product/device essential performance requirements. Please see deficiency #2 below which summarizes our previous deficiency #4 (dated 9/25/20180)

Sponsor Response:
The sponsor has provided a large amount of design control documentation. Please see Seq0016(21) Seq 1.11.1 Quality Info Ammendment.in GSR. The information has been summarized in Section 6 of this review memo.

FDA Response:
See design verification review section 6, where responses were analyzed. Follow-up deficiencies were issued in Sections 13. These were resolved interactively.

2) To clarify our previous deficiency #4 (dated 9/25/2018), given the intended use your proposed product (i.e. emergency use, life-saving) we expect you to establish a reliability specification of at least 99.99% with 95% confidence for the successful delivery of the full intended dose of the emergency use product and to verify this reliability through both design and manufacturing data analysis up to the proposed combination product's expiry. It is recommended that you utilize a fault tree analysis to identify all aspects of the design and manufacturing of the product that support the reliability specification and quantify the probability data to support the reliability specification. Previously conducted verification testing and/or validated manufacturing controls may be leveraged to support the reliability specification, if applicable. We recommend that you include other design input requirements into your reliability analysis to support your reliability specification, including: shot weight, actuation force, product spray pattern, plume geometry, dosage content uniformity, and particle size distribution.

Sponsor Response:
Lilly understands that FDA has recently established a reliability specification of 99.99% at 95% confidence for emergency use devices. During the development of the Baqsimi product, FDA feedback was to establish an appropriate reliability specification for our product. The rationale for the reliability specification selected (95% / 95%) was previously provided in Section 3.2.R.3.5.3, Clinical Acceptability of Requirements section. The Baqsimi product is used to treat severe hypoglycemia; but data on the incidence of death from severe hypoglycemic events suggest that no more than 1 in 10,000 severe hypoglycemia events results in death. Furthermore, successful treatment of a patient experiencing severe hypoglycemia remains possible, and even likely, in the event that a device does not function properly and no dose is delivered.

Severe hypoglycemia contrasts with anaphylaxis, a condition that can progress quickly to shock (Pumphrey. 2000), cardiorespiratory arrest, and death. Early treatment with epinephrine is the only intervention that clearly reduces these complications (Simons. 2011). Given that there is no real alternative method of delivery for epinephrine, device reliability expectations for EpiPen would theoretically be more rigorous than for emergency treatments where alternative delivery systems and treatments are available. Because there are alternate rescue treatments available to the patient suffering from severe hypoglycemia, the risk of harm from a nasal glucagon product failure may be lower than for other rescue therapy drug delivery devices.

Lilly established a reliability specification and performed testing. Results demonstrated the device performance was reliable. This data was previously communicated in Section 3.2.R.3, Medical Device. However, FDA has requested we include other design input requirements into the reliability analysis (including shot weight, actuation force, product spray pattern, plume geometry, dosage content uniformity, and particle size distribution) that will oblige Lilly to perform additional analyses for more parameters than previously included. For these reasons, Lilly needs additional time to update the fault tree analysis to include the evaluation of product reliability with respect to spray pattern, plume geometry, delivered dose uniformity, and particle size distribution. The updated fault tree analysis will be provided before the end of January 2019.

FDA Response:
The reliability information was reviewed and summarized in Section 6.5 of the review memo. Follow-up deficiencies were issued in Sections 13. These were resolved interactively.

3) You provided a residual risk grid in your device reliability analysis in your information request reponse on 11/1/2018. In Attachment Q4-1 , you provided a list of product related failures, including device related failure modes, that would "affect reliability of the device to successffuly deliver an accepable dose of nasal glucagon" However, these hazards are not traced to the component level assemblies and dimensional elements that could result in the top level failure mode of failing to deliver the full intended dose.

We recommend that you define tolerances of the device components, taking into account the individual components and their use in conjunction with associated components of the device which could affect the top level failure (failing to deliver the full intended dose) and establish a device reliability specification. Using this method you should provide an FTA that includes each failure mode under the top level failure mode, and trace the failure probability to the component assembly and dimensional elements that could result in activation failure.

Once you have completed the FTA, we recommend you utilize a statistical tolerance interval method in which the limits of each individual component are analyzed (e.g., dimensions, geometry, material strength, etc.), both by itself and in conjunction with its associated components (i.e. stack-up analysis), to assess the potential for the component to result in a basic event failure mode of the device. To effectively use the tolerance interval method, the critical measurable elements of each component contributing to the basic event should be clearly stated and the statistical tolerance limit identified. Data to support the tolerance interval methodology should be provided and may include process validation data for individual components. The resultant k factor for each basic event should be used to calculate the necessary sample size of the reliability study based on the desired reliability specification and confidence interval.

Please provide the full FTA (or other similar method) which demonstrates that you have accounted for all forseeable device related failure modes (including component and dimensional related failure modes) that would affect the reliability of the device. Additionally , please provide the results of your stack up analysis to support the sample size that you are using to verify the reliability of your device.

Sponsor Response:
For the reasons identified in the response to Question 20, Lilly will require additional time to update the fault tree analysis to include the evaluation of product reliability with respect to spray pattern, plume geometry, delivered dose uniformity, and particle size distribution. The updated fault tree analysis will show the traceability of the top level failure to the basic event, and will also provide data to support the cumulative probability assessment according to tolerance interval methodology. The updated analysis will be provided by the end of January 2019.

FDA Response:
The sponsor provided a response with the safety assurance case on January 28, 2019 on 0023(24)_1.11.1 Quality Information Amendment. This was reviewed in Section 6.5.2 of the review memo. Follow-up deficiencies were issued in Sections 13. These were resolved interactively.

4) You provided a response to deficiency 4c regarding device preconditioning prior to device reliability testing, in your information request reponse on 11/1/2018. However, this is inadequate. Please provide responses to the following:

a. It is unclear if you are not intending to use devices aged to the proposed shelf life of (b) (4) months to verify device reliabilty to 99.99% with a 95% confidence. In your response you conducted testing where the devices were aged past the (b) (4) month expiry with different storage conditions. You state: "*After exposures in all three scenarios above, the devices were tested and met shot weight requirements which would predict the devices to have a shelf life in excess of the anticipated* (b) (4) *months when stored below 30°C.…Based on these data, the age of the device is not expected to have any effect on performance following exposure to the subsequently performed pre-conditioning activities.…Therefore, including storage as a pre-conditioning activity in the study is not necessary to demonstrate device reliability.*" It is

unclear if this testing met the 99.99% reliability specification with 95% confidence for the ability to deliver the full intended dose or the individual device related EPRs.

Additionally you state: "*Real-time studies for the nasal glucagon combination product (24 months at room temperature) demonstrated the devices met performance criteria (including shot weight and activation force) at the end of their shelf life*". This testing does not appear to meet the 99.99% reliability specfication with 95% confidence.

To clarify our previous recommedation, we recommend that you provide testing to support the reliability specification of your device, which includes the indivdual device EPRs up to the expiry of your combination product. Please provide testing to support the reliability specification of the individual device EPRs up to the expiry of your combination product. This testing should take into account cumulative preconditioning to address all reasonably foreseeable worst case risks that could impact the reliability of your product.

b. In your response you state that devices tested under preconditioning methods were prefilled with lactose powder rather than the subject drug product. Please provide a thorough comparison of lactose powder to the subject drug product to support the testing that you provided. This should include a comparsion of drug particle size, density, dispersion, etc. Alternativley we recommend that you conduct this testing with the to-be marketed drug product.

Sponsor Response:
Samples of combination product from production equivalent batches were preconditioned and tested for shot weight and demonstrated reliability of 99.99% at 95% confidence. The Agency has requested testing from combination product that has been preconditioned and aged on-the-shelf for 24 months (end of expiration). It is not currently possible to provide data on samples that are 24 months old, as they will not achieve that age until Dec 2019. Lilly will agree to provide data from our current reliability study (using Device Configuration ID 2.1) following aging of samples to the proposed shelf-life of (b) (4) months when the data are available (b) (4). Refer to the response to Question 3 from the Information Request dated 25 September 2018 (submitted 23 October 2018 in Sequence No. 0008) for a detailed description of minor changes between Configuration ID 2.1 and Configuration ID 2.2 (the to-be-marketed version), and the risk-based assessment that the changes do not affect device performance. The following performance characteristics will be evaluated: shot weight, actuation force, spray pattern, plume geometry, delivered dose uniformity, and particle size distribution. (b) (4)

FDA Response:
The sponsor has stated that lactose was not used for this testing. This particular testing was reviewed in Section 6.5.4 of the review memo. Follow-up deficiencies were issued in Sections 13. These were resolved interactively.

5) In Sequence 0010(12) document "Quality-response-to- ep-2018, you provided a response to an Agency IR requesting that you include actuation force of the device at an essential performance requirement. However we have the following deficiencies regarding the information you provided.

a. You state that your actuation force specification is (b) (4)– (b) (4) kgF ((b) (4) N). The upper limit of the actuation force specification appears high for an emergency use device. You state: The upper specification limit for actuation force was determined based on correlation of results from palmar pinch strength data from representative user populations (Mathiowetz, et. al. 1985, 1986). The upper specification for actuation force appears high for the emergency use indication of your product. It is important that all of the intended users of your product are able to adequately actuation your products, including adolescents. The literature that you reference does not include any information regarding the actuation force capabilities of adolescents. Therefore, we recommend that you reduce your actuation force specification upper limit to a force that will all users of your product will be able to adequately actuation the device. Please provide the following:

i. Please evaluate all of your device verification testing for actuation force against the narrowed actuation force specification
ii. Please change your lot release specification for actuation force to reflect the updated actuation force specification
iii. Please provide a rationale for why all users can adequately actuate your device based on the actuation force specification

b. In Q2-4, you provide summary testing of actuation force (mean ± standard deviation and a tolerance interval) of your combination product in different use situations. Please provide a response to the following:

i. You did not provide minimum and maximum values of actuation force to demonstrate that all devices met your actuation force specification. Please provide summary results that include the minimum and maximum values for actuation force for each use situation. Please evaluate these results against your updated actuation force specification.
ii. The in-use cold exposure testing results in an actuation force that appears relatively high, especially for adolescent users. Please evaluate these results against your updated actuation force specification which accounts for all users of your device.

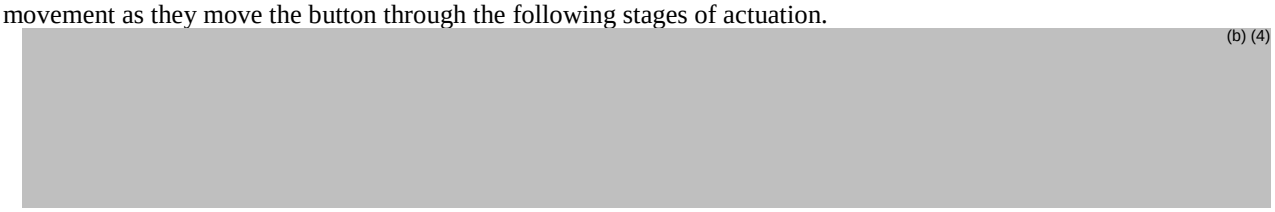
c. You provided actuation force testing in your stability testing in document: "primary-stab-data". Please evaluate this testing against your specification for actuation force to support the use of the device to the (b) (4) month expiry.

Sponsor Response:

In our prior response to the Agency's questions about actuation force, we provided two literature references by Mathiowetz; one for adults and one for adolescents. We refer the reviewer to the Mathiowetz reference entitled "Grip and Pinch Strength: Norms for 6-to-19 Year Olds" published in October 1986. This publication includes information regarding the grip and pinch strength capabilities of adolescents and has been considered as part of the actuation force specification.

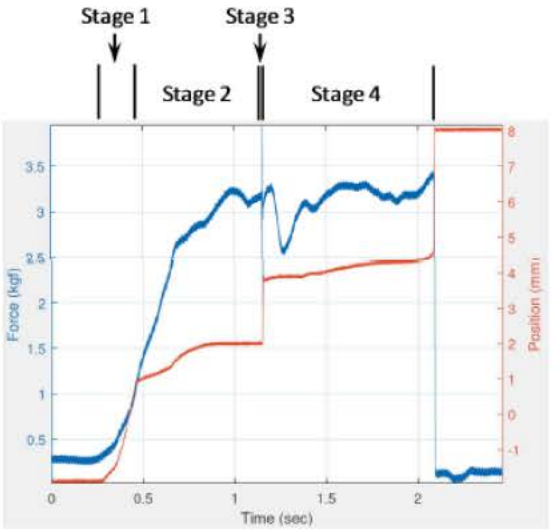
The actuation force specification upper limit of (b) (4) kgf for actuation when the device is greater than or equal to room temperature was originally established using bench-top testing data from combination product batches used in clinical or human factors studies and batches representative of those used in clinical or human factors studies. The clinical and human factors studies included actuation of the device by the full intended user population (persons aged 10 - 75+ years); therefore, an upper specification limit of (b) (4) kgf (with devices and/or test environments greater than or equal to room temperature) is considered to be acceptable to ensure that users are able to actuate the device. The actuation force data used to determine the specification was generated using the Sprayview test equipment, with actuation of the device conducted at a constant speed (80 mm/sec) that is intended to minimize testing variability and maximizes capability to detect issues with device function. While the bench-top testing is useful for characterizing the mechanical function of the device, it is not intended to simulate actuation by the user.

Device actuation force is significantly affected by two factors: actuation speed, and the temperature of the device and/or test environment. During manual actuation, the user is able to change the actuation force by varying the speed of button movement as they move the button through the following stages of actuation.



During stages 1 and 3 of actuation, the user will typically experience lower resistance to button movement, and will therefore perform those stages at a higher speed. During stages 2 and 4 of actuation, the user will typically experience higher resistance to button movement, and will therefore perform those stages at a lower speed. Refer to Figure Q23-1 for an example of the manual actuation profile. To provide additional information regarding the effect of actuation speed on actuation force, actuation force data has been generated where the speed was varied. The data shows a direct correlation between speed and

force required to actuate the device (see Figure Q23-2 and Figure Q23-3), confirming that users can significantly reduce the force experienced by pressing the button at a slower speed.



Example Manual Actuation Profile

Due to the properties of the materials selected for the device, the force to actuate at extremely cold temperatures (-20°C) is higher than the force to actuate at the expected storage and use temperatures (i.e., room temperature). While it is possible that someone may use Baqsimi at -20°C, it is considered to be an extreme use condition with a low probability of occurrence. Baqsimi was tested at extreme temperature conditions as part of design verification testing to demonstrate a high rate of successful actuation is possible, even when tested at this foreseeable extreme condition. The increase in actuation force due to exposure to extreme cold temperature is reversible (b) (4) , the actuation force will return to normally expected levels. This has been confirmed by the temperature cycling study data presented in Section 3.2.P.2.4.1.4.3, Effect of Storage, Handling, and Use Environment. Even though no direct correlation can be made between forces from bench-top testing and actual user actuation, palmar pinch strength data reported in literature may be used as a conservative approximation of the forces that could be applied during device actuation. The palmar pinch strength data is considered conservative because it was measured at a static condition, and the study participants were not subjected to relevant stressors intended to simulate the Baqsimi product use scenario. The literature reports that the actual force generated during performance of tasks can exceed static strength measures because of acceleration and inertial factors that are not reflected in static strength testing (Wiggerman, et. al. 2018). Therefore, the forces able to be generated by a user during actuation of Baqsimi are likely to exceed the static forces reported in literature for palmar pinch strength. As described in the response to Question 2 of 25 Sep 2018, a representative mean and standard deviation for palmar pinch strength of the intended user population (persons aged 10 - 75+ years) was calculated using a Monte Carlo analysis based on the literature strength data and population data from the 2015 US Census Bureau. Palmar pinch strength norms for 10 to 19 year old (i.e., adolescent) subjects used in this analysis were obtained from literature reference Mathiowetz, et. al. 1986. A summary of results from the Monte Carlo analysis for the entire intended user population and for the adolescent age sub-set of the intended user population is provided in Table Q23-1, and shows that the adolescent user population palmar pinch strength force range is similar to that calculated for the entire intended user population. Therefore, the distribution determined for the entire intended user population is utilized in comparisons with the actuation force limits described below.

Table Q23-1 Palmar Pinch Strength Force Monte Carlo Analysis Summary

User Population	Palmar Pinch Strength Force - Mean (kgf)	Palmar Pinch Strength Force - SD (kgf)	Palmar Pinch Lower 0.01% Content (kgf)	Palmar Pinch Upper 99.99% Content (kgf)
Persons aged 10 - 75+ years	8.94	2.53	3.04	14.83
Adolescents aged 10 - 19 years	8.04	2.25	2.81	13.27

To compare bench-top actuation force limits set using data collected at a speed of 80 mm/sec with the literature reported palmar pinch strength data that was collected statically, the equations shown in Figure Q23-2 and Figure Q23-3 were used to convert the 80 mm/sec bench-top actuation force limit to an equivalent force limit at a slower speed of 0.0125 mm/sec. The actuation force at this slower speed is considered to approximate the static condition under which the palmar pinch force data was collected. Given the conservative nature of the palmar pinch strength data, the comparison shown in Table Q23-2 provides confirmation that the proposed upper specification limits for actuation at 80 mm/sec will ensure a high probability of successful actuation with the intended user population of persons aged 10 - 75+ years.

Table Q23-2 Comparison of Actuation Force Limits to Palmar Pinch Strength

Use Condition	Proposed Actuation Force Specification Upper Limit @ 80 mm/sec (kgf)	Equivalent Actuation Force Specification Upper Limit @ 0.0125 mm/sec (kgf)	Palmar Pinch Force Mean (kgf)	Palmar Pinch Force SD (kgf)	Maximum Percentage of Users with Palmar Pinch Force Capability Exceeding the Upper Specification Limit
≥ Room Temperature	(b) (4)	(b) (4)	8.94	2.53	95%
-20°C					87%

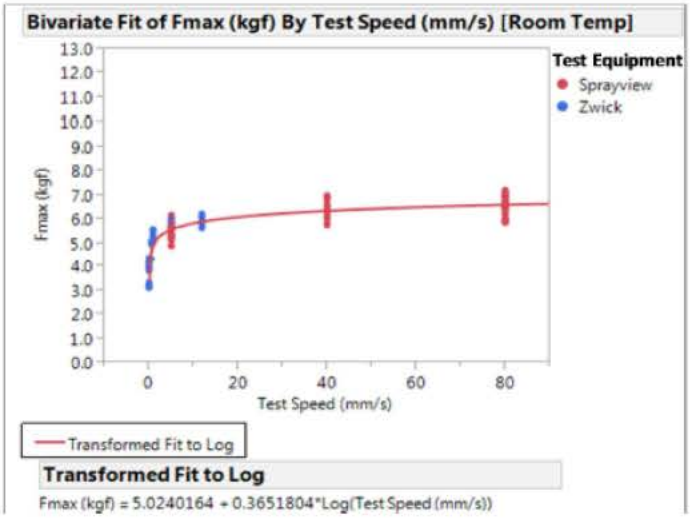
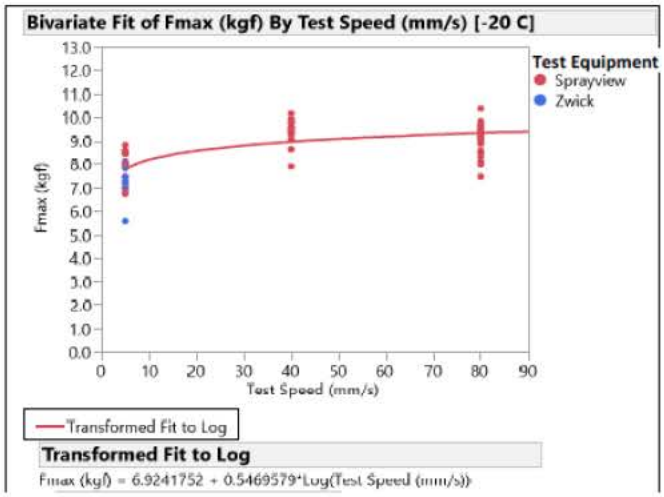


Figure Q23-2 **Actuation Force and Speed Correlation for Room Temperature Actuation**



I23-3 **Actuation Force and Speed Correlation for Extreme Cold Temperature Actuation**

Lilly Response to Question 23.c.i

Based on the justification provided above, Lilly proposes actuation force specifications shown in Table Q23-3.

Table Q23-3 Actuation Force Specifications

EPR	Specification	Specification Applicability
Actuation Force	Actuation force at 80 mm/s actuation speed is NLT (b) (4) kgf and NMT (b) (4) kgf for devices and/or test environments greater than or equal to room temperature during actuation	Lot Release; Stability; Design Verification/ Reliability (devices and/or test environments greater than or equal to room temperature during actuation)
	Actuation force at 80 mm/s actuation speed is NLT (b) (4) kgf and NMT (b) (4) kgf for devices and/or test environments at extreme cold temperature (-20°C) during actuation	Design Verification/ Reliability (devices and/or test environments at extreme cold temperature [-20°C] during actuation)

An evaluation of the design verification testing data against these specifications is provided in Table Q23-4. The data demonstrates that the specifications are met for all tests conducted.

FDA Response:

The sponsor provided verification to demonstrate that the device meets an actuation force upper limit specification of (b) (4) kgF. However this was not adequate validated. Please see Section 13 deficiencies which details to the sponsor that we recommend that they decrease the actuation force.

Quality Systems Deficiencies (Please see document 0016(21)_1.11.1. Quality Information Amendment for the full Sponsor responses: deficiencies 24-29):

The following deficiencies were identified while doing the documentation review of Application NDA 210134, original submission, glucagon nasal powder, in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

6) Your firm has inadequately addressed the requirement for 21 CFR 820.20, management responsibility. Please provide a summary of how your management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). Also, provide a description of the functions and responsibility of each facility involved in the manufacturing of the combination product.

Sponsor Response:
Please see document 0016(21)_1.11.1. Quality Information Amendment for the full Sponsor responses.

FDA Response (Nik Thakur):
The Applicant provided information to address 21 CFR 820.20 requirements in eCTD Module 1. 11.1(file titled "1111-quality-response-to-questions-27-nov-2018.pdf"). Table Q24.1 and the Applicant's response to Question 24 of the CR Letter appropriately describes the Applicant's adherence to this Quality System call out, including the responsibilities of the Application sponsor (Ely Lilly and Company), and Packaged Combination Product manufacturer contract facility ((b) (4) The Applicant's response is satisfactory.

7) Your firm has inadequately addressed the requirement for 21 CFR 820.30, design controls. Please explain how your firm utilized the design control process to develop the combination product under review and provide a description of your firm's design control procedures. The procedures description must include how requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are fulfilled. Provide a copy or a summary of the plan used to design the combination product. Explain how you utilized the design control process to develop the combination product under review.

Sponsor Response:
Please see document 0016(21)_1.11.1. Quality Information Amendment for the full Sponsor responses.

FDA Response (Nik Thakur):
The Applicant provided information to address 21 CFR 820.30 requirements in eCTD Module 1. 11.1 (file titled "1111-quality-response-to-questions-27-nov-2018.pdf"). The Applicant's response to Question 25 of the CR Letter provides an overview of the Design Control Framework established at the Applicant's facility. Subsequent sections describe the details of the design control process, as well lay out the framework to successfully implement design controls across their quality organization. Additionally, the relevant design control SOPs are included to further demonstrate a comprehensive knowledgebase. The Applicant's response is satisfactory.

8) Your firm has inadequately addressed the requirement for 21 CFR 820.50, purchasing controls. Please provide a summary of the procedure(s) for purchasing controls at your firm. The summary should:
   a. Describe your supplier evaluation process and describe how it will determine type and extent of control you will exercise over suppliers.
   b. Define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.
   c. Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

Sponsor Response:
Please see document 0016(21)_1.11.1. Quality Information Amendment for the full Sponsor responses.

FDA Response (Nik Thakur):
The Applicant provided information to address 21 CFR 820.50 requirements in eCTD Module 1. 11.1 (file titled "1111-quality-response-to-questions-27-nov-2018.pdf"). The Applicant's response to Question 26 of the CR Letter adequately describes the purchasing control oversight that Eli Lilly and its suppliers. Also, the Applicant's response describes supplier control at (b) (4). The response appears to be adequate.

9) Your firm has inadequately addressed the requirement for 21 CFR 820.100, corrective and preventive actions. Please summarize the procedure(s) for your firm's Corrective and Preventive Action (CAPA) System. The CAPA system should require:
   a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
   b. Investigation of nonconformities and their causes;
   c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and

d. Verification or validation of the actions taken.

Sponsor Response:
Please see document 0016(21)_1.11.1. Quality Information Amendment for the full Sponsor responses.

FDA Response (Nik Thakur):
The Applicant provided information to address 21 CFR 820.100 requirements in eCTD Module 1. 11.1 (file titled "1111-quality-response-to-questions-27-nov-2018.pdf"). The Applicant's response to Question 27 of the CR Letter appropriately describes how CAPAs are managed throughout their organization. The descriptions of the CAPA process appropriately identify an algorithm for identifying nonconforming practices and products, assessing nonconformities, how corrective and preventive actions are implemented, and how verification and validation activities are conducted to ensure that the CAPA addresses how current and future product will be appropriately remediated. Importantly, the CAPA process description identifies the feed back loop into the design control process. This feed back loop gives assurance that CAPAs are addressed at a design level, and feed back into the Design History File.

10) Please provide a summary of the procedure(s) for environmental and contamination controls of your firm or the facility where the final manufacturing of the finished combination product, if such conditions could adversely affect the combination product.

Sponsor Response:
Please see document 0016(21)_1.11.1. Quality Information Amendment for the full Sponsor responses.

FDA Response (Nik Thakur):
The Applicant provided information to address environmental and contamination controls in eCTD Module 1. 11.1 (file titled "1111-quality-response-to-questions-27-nov-2018.pdf"). The Applicant's response to Question 28 of the CR Letter appropriately addresses how environmental excursions will be mitigated. The response appropriately describes the approach to environmental monitoring at the Applican'ts manufacturuing site, and at relevant suppliers.

11) Please provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review. This information should display the important aspects of the production process.

Sponsor Response:
Please see document 0016(21)_1.11.1. Quality Information Amendment for the full Sponsor responses.

FDA Response (Nik Thakur):
The Applicant provided a detailed production flow diagram in eCTD Module 1. 11.1 (file titled "1111-quality-response-to-questions-27-nov-2018.pdf"). The Applicant's response to Question 29 of the CR Letter describes the production process. The response is adequate.

12) Please explain how your firm will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. You should specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. You should also provide the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product.

Sponsor Response:
Please see document 0016(21)_1.11.1. Quality Information Amendment for the full Sponsor responses.

FDA Response (Nik Thakur):
The Applicant provided information to address production and process control in eCTD Module 1. 11.1 (file titled "1111-quality-response-to-questions-27-nov-2018.pdf"). The Applicant's response to Question 30 of the CR Letter provides a detailed description of the Production and Process Controls implemented at the Applicant and (where appropriate) the Contract Manufacturer. The Applicant has satisfactorily addressed CDRH's original deficiency.

13.INTERACTIVE REVIEW (POST-MIDCYCLE)

13.1. IR#3: Written 2/8/2019; Returned from Sponsor on 2/25/2019 - RESOLVED

1. Your specification for dose accuracy is as follows:

"*Each individual shot weight is*
NLT (b)(4)% of the mean fill weight

The mean shot weight is
NLT (b)(4)% of the mean fill weight"

It is unclear why the specification for shot weight is based on the mean fill weight of the drug product rather than the specification for fill weight itself. With how your specification is written currently, shot weight specification could be affected if the fill weight for a particular lot/bath of product is at the low/higher end of the fill weight specification. Additionally, although we recognize your product is a (b) (4) nasal spray, the CDER nasal spray guidance states that pump delivery should be within: "15 percent of the target weight", not mean fill weight. We recommend that you revise your specification for shot weight to be:

"*Each individual shot weight is*
NLT (b)(4)% of the target weight (3 mg)

The mean shot weight is
NLT (b)(4)% of the target fill weight (3 mg)"

Alternatively, please justify what other receiving, in process, or release controls are in place to ensure that the mean fill weight of the device is held at approximately 3 mg, as there does not appear to be a fill weight specification in your specification sheet for stability or release.

Sponsor Response:
Lilly acknowledges that fill weight and shot weight are important attributes for nasal products. Given the unique nature of nasal glucagon, we would like to clarify why the specification for shot weight is based on the mean fill weight of the drug product rather than on the target fill weight. In addition, a brief discussion is provided for the in-process and release controls that are in place to ensure that the mean fill weight ((b) (4) mg glucagon nasal powder) of the device will deliver 3 mg of glucagon.

Manufacturing Process Description
During the manufacture of the drug product (Section 3.2.P.2.3.2.4, Primary Container Filling), the in-process (b) (4)
(b) (4)

(b) (4)

In-Process Control

(b) (4)

Shot Weight/Mean Fill Weight Rationale

(b) (4)

As outlined above, there is likely a difference between the (b) (4). For nasal glucagon, the use of (b) (4)

Release Controls

(b) (4)

Conclusion

Given the above clarification as to why the specification for shot weight is based on the mean fill weight of the drug product rather than target fill weight, as well as the explanation of the in-process and release controls that are in place to ensure that the mean fill weight of the device is held at a level to deliver 3 mg of glucagon, Lilly suggests that the current specification of "Each individual shot weight is NLT (b) (4)% of the mean fill weight and the mean shot weight is NLT (b) (4)% of the mean fill weight" is appropriate. Therefore, no changes to the shot weight or release specification are proposed, as an integrated control strategy consisting of shot weight, assay, UDU, DDU, and (b) (4) ensure delivery of an acceptable dose.

FDA Response:

The sponsor has described in process controls (b) (4)

(b) (4)
ate.

2. In the quality information ammendment provided on 1/2/2019, you provided a response to FDA question #23, which requested that you justify the adequcy of your actuation force specification and lower the specification to ensure that all intended users can actuation your device under an emergency use scenario. In response to this question, you provided two separate upper specifications for actuation force: (b) (4) kgF at room temperature and (b) (4) kgF at -20°C. To justify the specifications, in table Q23-1 you provided pinch strength information for 10-19 y lds and 10- 75+ year olds and provided a Monte Carlo analysis based on literature strength data from the literature reference Mathiowetz et al 1986. Based on the data summarized in this table, the mean ± standard deviation pinch strenght for adolscents is 8.04 ± 2.25 kgF. Assuming a normal distribution, the data referenced implies that ~68% of the total data lies within one standard deviation; therefore 68% of users can exert the following maximum pinch strengths 5.79 – 10.29 kgF (for adolescents) and 6.41-11.47 kgF (for adults). Based on this data and your upper specification for actuation force, (b) (4) kgF (room temp) and (b) (4) kgF (-20 degC), >50% of users would not be able to exert the pinch strength needed to actuate your device at room temperature. Additionally, we note that you have provided human factors and clinical validation of the device, it is unclear if the devices that were used in these studies had acutation forces at the higher limit of the acutation force specification : (b) (4) kgF (room temp) and (b) (4) kgF (-20 degC); therefore it is unclear if the upper end of the specification was validated in these studies.

   Given that the upper specification for actuation force is (b) (4) kgF (room temp) and (b) (4) kgF (-20 degC) and the data analysis that is referenced from Mathiowetz et al 1986, we do not believe that the literature adequately validates the upper specification for actuation force to ensure that all users could actuate your device. Provide validation of the higher end of the device acuation force specification to ensure that users of your device will be able actuate your device at room temperature and at cold temperature. If you have characterized the actuation force of the devices that were used in the human factors study and/or clinical studies and this information could support the current upper specification (at room temp and at cold temp), provide this information, with a justification for how it supports your current actuation force specification.

   Alternativley, reduce the upper limit of your actuation force specification to a force where you can adequately demonstrate that all intended users of your product will be able to actuate the device at the upper limit of the specification. If you choose to do this, update your specification document with the new actuation force specification and evaluate your device verification testing, including reliability testing, with the narrowed actuation force specification. Additionally, provide information, which validates the upper end of the new actuation force specification.

   Sponsor Response:
   Design Validation has been performed to ensure the device constituent parts of the combination product meet the intended use of the combination product. The Design Validation for device actuation force included clinical and human factors studies, simulated use actuation force testing, and literature review, as discussed below.

   Discussion of Clinical and Human Factors Studies
   A summary of actuation forces for lots of devices representative of those used in clinical validation and human factors studies is provided in Table Q2-1 and Figure Q2-1. As discussed in a prior response, the devices used to deliver the drug powder during clinical and human factors studies (Configuration IDs 1.0, 1.1, 2.0, and 2.1) employed the same fundamental scientific technology and used the same operating principles as the to-be-marketed device (Configuration ID 2.2).

   Of particular note with respect to the device actuation force are the Configuration ID 2.0 devices that were used in the pivotal clinical studies IGBB and IGBC, in the actual use clinical studies B001 and B002, and in two human factors studies. Users in these studies spanned the range of the intended user population of persons aged 10 - 75+ years. The maximum actuation force measured at a test speed of 80 mm/sec from this device configuration was 9.3 kgf, (b) (4) of the proposed specification for room temperature actuation. Given the pooled data from ID 2.0 devices is normally distributed, a

probable range of 6.5 kgf to 9.5 kgf (mean ± 3*SD) was experienced in the validation studies, (b) (4) There were no failures reported within these studies directly attributable to the inability of the user to actuate the device. These data provide confirmation that the proposed upper specification limit of (b) (4) kgf for room temperature actuation (tested at 80 mm/sec) will ensure a high probability of successful actuation with the intended user population of persons aged 10 - 75+ years.

Lilly asserts that the increased actuation force observed during actuation at -20°C is acceptable, based on the following points:

1. The majority of devices actuated at -20°C (~70%) will have forces within the validated upper specification limit of (b) (4) kgf for room temperature actuation (based on analysis of the data shown in Table Q2-2).
2. The below analysis of the literature strength data indicates that greater than 87% of users (see Table Q2-3) would be capable of actuating devices with bench-top actuation force values at the proposed (b) (4) kgf upper specification limit for the -20°C condition.
3. Actuation at -20°C is considered to be an extreme condition with low probability of occurrence. There is a very low probability that a user with low hand strength would be required to actuate a device with high actuation force at the -20°C condition.

While it is considered very unlikely that a user would experience an actuation force of (b) (4) kgf given the above provided rationale, the upper specification limit of (b) (4) kgf for actuation force at -20°C is necessary in order to meet the required reliability specification of 99.99% reliability with 95% confidence. As discussed above, the adequacy of the proposed actuation force upper specification limits (i.e., (b) (4) kgf for room temperature actuation, and (b) (4) kgf for -20°C actuation) to ensure that the intended users can actuate the device under an emergency use scenario is justified.

Table Q2-1 Actuation Forces Experienced by Users in Clinical and/or Human Factors Studies

Device Configuration ID	Study Use	Representative Lot Tested	Actuation Force (kgf)				
			n	Mean	SD	Min	Max
1.0	• I8R-MC-IGBD • I8R-MC-IGBA • I8R-MC-IGBE • I8R-MC-IGBB • I8R-MC-IGBF • I8R-MC-IGBC • AMG107-001 (Human Factors)	F121220-001	10	3.8	0.28	3.4	4.2
2.0	• I8R-MC-IGBB • I8R-MC-IGBC • I8R-MC-B001 • I8R-MC-B002 • I8R-MC-IGBG • AMG107-002 (Human Factors) • AMG107-003 (Human Factors)	F140805-001	20	7.8	0.28	7.1	8.3
		F141016-001	40	7.9	0.55	6.5	9.3
		F141113-001	22	8.2	0.59	6.9	8.9
2.1	• I8R-MC-IGBI • AMG107-004 (Human Factors) • AMG107-005 (Human Factors) • AMG111 (Human Factors) • Formative Human Factors • Summative Human Factors	1623774	220	6.4	0.53	5.2	7.8
		1623775	220	6.4	0.42	5.5	7.5
		1623776/ 1623776CT	220	6.6	0.54	5.4	8.0
		1633276	50	5.6	0.17	5.1	6.0
		1624621	50	6.1	0.41	5.5	7.0
2.2	Planned Supplemental Human Factors	3418788	60	6.4	0.26	5.3	6.8
		3418786	60	6.5	0.34	5.3	7.1
		3418787	60	6.5	0.28	5.7	7.2

Discussion of Simulated Use Actuation Force Testing

Empirical data from simulated use actuation force testing supports the conclusions from the literature review. Simulated use actuation force study data were generated by users actuating a device that had been placed into a piece of equipment designed to record the speed and force of device actuation, while minimizing interference of user interaction with the device. The study included 40 participants, divided approximately evenly between genders, and spread over a range of ages from 10 to 60+ years. After receiving instruction on device operation, each participant actuated one device at a speed of their choosing, and the speed and force of actuation were recorded.

The force profiles from automated bench-top testing were compared to data from the manual actuation simulated use study. This comparison confirmed the expected results that manual actuation typically results in lower measured forces compared to the forces obtained from bench-top testing at 80 mm/sec. It also confirmed that the 80 mm/sec constant speed actuation used in automated bench-top testing is representative of the upper end of user actuation speeds; therefore, the current bench-top testing method measures the maximum forces that a user may experience during actuation. However, as discussed in previous responses, the user is able to reduce the actuation force they experience by reducing their actuation speed.

The empirical data from simulated use actuation force testing supports the approach and conclusions from the analysis of literature data discussed in the following section.

Discussion of Literature Review

Lilly acknowledges the Agency directly compared the literature strength data to our proposed actuation force specification limit. However, Lilly contends that a correction factor must be applied to the proposed actuation force specification to account for differences in the methodology used to collect the palmar pinch data and the device actuation force data. The referenced literature data for palmar pinch strength provided a measure of the participants' capability to generate a static force, meaning that the strength values reported from the study do not include the acceleration or inertial factors present during device actuation. The actual force generated during performance of tasks, such as during the actuation of the device, can exceed static strength measures because of these acceleration and inertial factors that are not reflected in static strength testing (Wiggerman, et. al. 2018). Therefore, the palmar pinch strength data is considered conservative because it was measured at a static condition. In addition, the palmar pinch study participants were not subjected to relevant stressors intended to simulate the Baqsimi product use scenario. Thus, the forces able to be generated by a user during dynamic actuation of Baqsimi will exceed the static forces reported in literature for palmar pinch strength. To determine the correction factor to be applied to the proposed actuation force specification limit, a model was fit to actuation force data generated using actuation speeds ranging from 0.0125 mm/sec to 80 mm/sec, resulting in a logarithmic equation where the actuation force increases as actuation speed increases (as observed in the simulated use actuation force testing). The static condition of the palmar pinch data was approximated by using the slowest characterized actuation speed of 0.0125 mm/sec. Following application of the calculated correction factor, the proposed room temperature actuation force limit of (b) (4) kgf is equivalent to a static force limit of (b) (4) kgf, and the proposed -20°C bench-top force limit of (b) (4) kgf is equivalent to a static force limit of (b) (4) kgf. Comparison of the palmar pinch strength data to the calculated equivalent static force limits, as shown in Table Q2-3 and Figure Q2-2, provides confirmation that the proposed upper specification limits for actuation (tested at 80 mm/sec) will ensure a high probability of successful actuation with the intended user population of persons aged 10 - 75+ years.

Table Q2-3 Comparison of Actuation Force Limits to Palmar Pinch Strength

Use Condition	Proposed Actuation Force Upper Specification Limit @ 80 mm/sec (kgf)	Equivalent Static Force Upper Specification Limit After Correction Factor Applied (kgf)	Palmar Pinch Force Mean [SD] (kgf)	Maximum Percentage of Users with Palmar Pinch Force Capability Exceeding the Equivalent Static Force Upper Specification Limit
≥ Room Temperature	(b) (4)	(b) (4)	8.94 [2.53]	95%
-20°C				87%

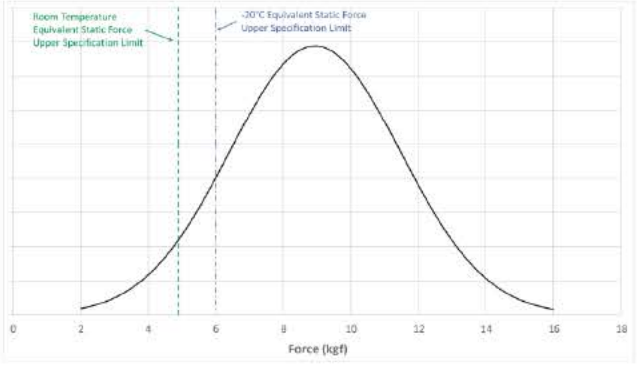


Figure Q2-2 **Palmar Pinch Force Distribution Compared to Calculated Equivalent Static Force Upper Specification Limits**

Conclusions:

Design Validation has been performed to ensure the device constituent parts of the combination product meet the intended use of the combination product. The proposed actuation force upper specification limits (i.e., (b) (4) kgf for room temperature actuation, and (b) (4) kgf for -20°C actuation) have been validated through clinical and human factors studies, simulated use actuation force testing, and literature review, as discussed above.

FDA Response:
The information that was provided above was analyzed. It is unclear if the argument that the sponsor is making is enirely valid for the following reasons:

- The sponsor states in response to this deficiency that the devices that were used in the human factors data were similar to what was shown in the verification testing for actuation force. See the table in the response. The majority of the lots tested in these studies showed that the mean actuation force is approximately 6.5 ± 0.5 kgF.
- They also state the following to support their actuation force spec:

  It also confirmed that the 80 mm/sec constant speed actuation used in automated bench-top testing is representative of the upper end of user actuation speeds; therefore, the current bench-top testing method measures the maximum forces that a user may experience during actuation. However, as discussed in previous responses, the user is able to reduce the actuation force they experience by reducing their actuation speed.

  While this is true that 80 mm/s is probably on the higher end of actuation speeds and that the user can lessen the speed so that a lower force can be used, the current upper specification allows for drift in the actuation force to a force that could potentially become unusable for users of the device at the speed you have chosen to test to simulate actual use of the device. Given that the actuation force verification testing and verification testing of human factors devices all were approximately within 6.5 kgF ± 0.5 kgF, we recommend that the sponsor lower the actuation force to [redacted] (b) (4) ([redacted] (b) (4) kgF) and reanalyze the data provided.

  Additionally, they state that given that the literature pinch strength data was taken as a static force (no movement), so they apply a "correction factor" to their specification so that they can approximate the equivalent specification at slow actuation speed to approximate a "static force". This is shown in the graph below and the sponsor used 0.0125 mm/s to approximate a static force. While, I understand that the device can be actuated with a low speed to decrease the force needed to actuate and 80 mm/s is a fast speed to actuate (<1 second actuation), however this is a reasonable speed to actuate and is similar to FDA recognized standard ISO 7886-1:2017, for syringes recommend the tested measure forces needed for break and glide force be tested with a rate of 100±5 mm/s. One follow-up deficiency was issued. See IR#4.

3. In 0023(24) 1.11. Quality information ammendment (1/28/2019), you state the following regarding your reliability study:

"*This response provides the evaluation of the data collected for batch release and stability test data from 3 lots of registration stability batches against the newly-identified EPRs. All results met proposed specifications. Data for actuation force were provided to the Agency previously. The results of the reliability analysis for the registration stability batch data demonstrate the reliability requirement (≥99.99% reliability with 95% confidence) is met for each Essential Performance Requirem*ent."

It is unclear if the devices tested in this version of your reliability study, were completed with multiple preconditioning steps including shipping, customer handling, storage etc. to simulate worst case use of the device. It appears that only stability lots of product was used aged to 12 or 18 months (depending on the EPR). We note that that in 0000(1) 3.2.R "medical-device", you previously conducted reliability testing for device shot weight, with devices that underwent multiple preconditionings such as the ones listed above. Additionally, in Type C written responses, issued 9/16/2016, we requested that reliability information be completed with multiple precondition steps including shipping, aging, storage orientation/conditions, vibration handling, shock handling. Please state if the reliability testing for the device EPRs submitted in the quality information amendment (1/28/2019) was completed with cumulative preconditionings as requested in Type C written response referenced above. Please note that we expect that the reliability of each EPR be verified up to the proposed shelf life that you claim.

If the devices tested in this reliability study did not include these cumulative preconditionings, please provide a justification with bridging information that references the reliability information gathered from device EPR verification testing with

individual preconditionings (i.e. shipping, only aging, only shock, etc. seperately) to justify how your your current level of verification testing meets the original reliability information that was requested in the 9/16/2016 comments. This justification should also explain how verification testing with individual preconditionings are adequate to represent the worst-case use of your device from a performance standpoint that could potentially occur with multiple cumulative precondition; i.e. shipping, storage, drop/shock, etc. Alternatively, you may provide updated reliability verification testing with the referenced preconditionings with devices aged to your proposed shelf life to demonstrate you meet your reliability specification.

Sponsor Response:
In response to Type C feedback received 9/16/2016, Lilly developed and executed a reliability protocol wherein devices were subjected to multiple cumulative preconditioning steps intended to simulate the reasonable worst-case conditions of shipment, handling by the customer, storage by the customer, and use by the customer, as deemed to be necessary based on available characterization data. The study was started in November 2017, once production-representative and qualified samples were available. The initial reliability testing data from this study (T0 timepoint) was submitted in Section 3.2.R, Device Reliability, and demonstrated that devices meet the reliability specification for the essential performance requirement of shot weight after cumulative preconditioning with the exception of full shelf life storage of (b) (4) months. Samples from this study that were exposed to the cumulative preconditioning were placed in storage to await the passage of (b) (4) months (i.e., the expected product shelf-life). These samples will be ready for testing after 24 months in storage (due 27 November 2019) with testing and (b) (4).

During review of the NDA, FDA informed Lilly that additional essential performance requirements (EPRs) would need to be tested and specifications established. Lilly maintains that shot weight can serve as a surrogate for many of the EPRs (e.g., if particle sizes are too large, they cannot exit the device and a low shot weight would result). However, FDA has recommended a total of 6 EPRs (shot weight, actuation force, particle size distribution, delivered dose uniformity, spray pattern and plume geometry). The five additional EPRs were not assessed on the T0 reliability samples due to the timing of FDA recommendation (Dec 2018), but will be assessed as part of the 24 month reliability testing. In order to provide FDA with data for the newly established EPRs, Lilly culled data from the registration stability testing samples (Configuration ID 2.1) that had been aged 12 - 18 month**s.**

Because Baqsimi is a single entity drug/device combination product, certain testing is performed in compliance with drug requirements and other testing is performed in accordance with device requirements. Registration stability testing was performed as outlined in ICH Q1A(R2) *Stability Testing of New Drug Substances and Products*, which does not require preconditioning of samples. Testing the EPRs using these samples identifies any degradation that may occur while the product ages. Data was provided from either the 12 month or 18 month time period, depending on the EPR. The data described in the follow-up response to Question 19 from the Information Request dated 27 November 2018 (submitted 28 January 2019, Sequence No. 0023) provided previously indicates that there were no changes in performance as a result of shelf storage, with the exception of DDU, which changes as a function of expected glucagon drug product degradation over time.

Effects of other conditions and stresses on the product for the newly established EPRs were assessed during design verification testing. The testing procedures were done in conformance with ISO 20072 *Aerosol drug delivery device design verification -- Requirements and test methods.* This standard identifies conditioning and testing to be performed as part of design verification testing, but does not suggest to do cumulative conditioning. Devices were preconditioned and tested in accordance with the standard. Demonstrating that shelf-life storage does not result in degradation of device performance, and that combination product performance is not negatively affected by any of the individual preconditioning steps should provide the Agency with data necessary to approve and to support reasonable assurance that the device is safe and effective for its intended purpose.
The EPR data provided in the 2 January 2019 response were gathered to support the design input/output DV elements of the new EPRs in response to Q19, not gathered per the reliability protocol, as described in Section 3.2.R.3.5, Device Reliability. The data were collected from combination products that had been stored and testing according to the registration stability protocol described in Section 3.2.P.8.3, Stability Data – Primary Stability, and the results compared to the proposed specifications. All the EPRs met specifications. In addition, the data obtained from the stability samples were assessed using mean/SD/k-value to calculate and
conduct a probability analysis whether the newly identified EPRs met reliability criteria established by FDA. Based on the calculation, the EPRs met the reliability specification of 99.99% reliability with 95% confidence.

Lilly has provided the following to FDA in support of the reliability of the device:

- Results from reliability testing of devices subjected to cumulative multiple preconditioning steps including shipment (vibration and shock from dropping), handling by the customer, and use by the customer for the shot weight EPR.
- Results from the assessment of the additional EPRs (actuation force, particle size distribution, delivered dose uniformity, spray pattern, plume geometry) from combination products that have not been cumulatively preconditioned, but have been stored for 12 - 18 months at the proposed label storage conditions demonstrating EPRs met specification at the aging time point tested.
- Calculated reliability of the device EPRs using the data from #2 above, which demonstrate that stability devices and design verification testing devices meet the reliability criteria of 99.99%.

The totality of the evidence collected to date indicates that the device is reliable (b) (4)

FDA Response:
Please see the reliability review section. The SAC/FTA demonstrated 99.99% reliability of the device. Additionally, the sponsor provided verification to demonstrate reliability of 99.99% and 95% confidence up to 12 months (no additional verification) for all the device EPRs, excluding shot weight (delivered dose/shot weight was verified for 24 months with sequential preconditioning). Given that shot weight reliability was verified up to 24 months with multiple preconditioning (including shipping, drop/shock, temperature, etc.), this helps support the argument of reliability and that the stresses of shipping, aging, temperature cumulatively will not negatively affect use of the device and should not increase the likelihood of device related failure. (b) (4)

In conclusion, the subject product will benefit its intended users by providing a more expedient way to administer glucagon in emergency situations, as compared to the current glucagon administration kits which make the user reconstitute the drug in solution prior to administration with a prefilled syringe. I believe that the likelihood of potential failure due to the product not being able to withstand shipping, aging, brief environmental storage changes is unlikely given the testing that was provided above and that stability testing of the EPRs up to 12 months did not show any deterioration of the EPRs (outside of DDU). **Therefore, I believe that the reliability testing is adequate to support approval with a (b) (4) month shelf life; however, we recommend that the sponsor conduct full reliability testing with sequential preconditioning up to 24 months as a PMR.**

4. It is unclear if you are including all device related essential performance requirements (EPRs) as lot release specifications. Please ensure that the device related EPRs (excluding spray pattern and plume geometry) are included in your lot release specifications to ensure that the device will continue to meet the EPR specifications at lot release. If you choose not to include all device related EPRs in your lot release specification, please provide a discussion of your control processes/strategy, including receiving and in-process controls, etc., that ensure that the device EPRs are met.

Sponsor Response:
Lilly agrees to establish device related essential performance requirements (EPRs) of shot weight, delivered dose uniformity, particle size distribution, and actuation force as lot release specifications. The proposed specifications will be updated to include the EPRs as shown in Table Q5-1, and added to Section 3.2.P.5.1, Specifications. The revised sections will be provided in a future information response.

FDA Response:

OPQ Reviewer Muthukumar Ramaswamy has stated that CDER does not recommend that plume geometry and spray pattern be included as lot release specs/tests as this is a quality control test and does not need to be included. While, I do not agree with this decision to exclude these device performance requirements from lot release as it is important that the device is able to administer the drug product in the correct fashion to achieve the clinical affect, CDER is the lead center on this product; therefore I defer to CDER/OPQ. Additionally, the sponsor has included testing for these specific device EPRs in their reliability testing and has demonstrated that they can be met with 99.99% reliability, which supports the consistency of the delivery.

13.2. IR#4: Written 2/28/2019; Returned from Sponsor on 3/1/2019 - RESOLVED

To justify your current upper actuation force specification of (b) (4) kgF (at room temp), you provided reference to the actuation force performance results from the devices used in clinical and/or human factors studies. The later versions of the devices used in your formative and summative human factors studies appear to be closer to an actuation force of ~5-7 kgF. Additionally, in your January 2, 2019 response to quality IRs, response 23.c.i, you provided verification results of the device actuation force; these devices also display an actuation force of ~5-7 kgF (outside of the cold exposure testing conditions). In summary, your results, outside of the cold exposure testing conditions, appear to be below the (b) (4) kgF upper specification for actuation force

You also state that the palmar pinch strength data referenced in Mathiowetz et al 1986, was a measure of static force, which you state may not be reflective of the "performance tasks" such as the force needed to actuate your device. Therefore, you reference actuation force testing that was measured at a slow displacement rate (0.0125 mm/s) to model and approximate the equivalent static force to the (b) (4) kgF upper specification limit for your device (displacement rate of 80 mm/s); however, it is unclear how this model that equates a dynamic force to a static force is validated. Additionally, your response does not discuss how a displacement speed of 0.0125 mm/s represents actual use of the product and how a slow displacement rate would affect the other product specifications, as the compressed air needs to be moved quickly through the device to properly deliver the drug to specification; therefore given this information a displacement rate of 80 mm/s appears to represent actual use of your product more closely than a displacement rate of 0.0125 mm/s.

Given the information listed above and that the risk of a patient being unable to actuate your device is not receiving their dose of an emergency use drug product, please adjust the upper limit of the actuation force specification of your device to (b) (4) kgF (b) (4)), to ensure that all users will be able to actuate your device. Please update your product specification sheet with this actuation force and reanalyze your actuation force performance data, including stability, shipping, reliability, etc. Please provide this updated documentation.

Sponsor Response:
While actuation forces measured by bench-top testing for the devices used in clinical trials and human factors studies have included distributions up to the (b) (4) kgf specification limit (see Figure Q2-1), Lilly acknowledges that the actuation force test results for the Configuration ID 2.1 (Primary Stability) and Configuration ID 2.2 (To-Be-Marketed) devices have been in the range of ~5 kgf to 8 kgf, as demonstrated by the data provided in Table Q2-3 through Table Q2-8. In order to reduce the risk of the user being unable to actuate the device and the patient not receiving their dose of an emergency use drug product, Lilly proposes the progressive upper limit acceptance criteria for actuation force shown in Table Q2-1, based on the observed distributions of actuation force data from commercially representative devices and the available data from validation studies and literature regarding user capability.

Table Q2-1 Proposed Actuation Force Specifications

EPR	Specification	Specification Applicability
Actuation Force	(b) (4)	Lot Release; Stability; Design Verification (For 80 mm/sec actuation speed with devices and/or test environments greater than or equal to room temperature during actuation)
		Reliability (For 80 mm/sec actuation speed with devices and/or test environments greater than or equal to room temperature during actuation)
		Design Verification/ Reliability (For 80 mm/sec actuation speed with devices and/or test environments at extreme cold temperature [-20°C] during actuation)

An upper specification limit of (b) (4) kgf is proposed for lot release testing, stability studies, and design verification testing. This upper limit is based on the following:

- The upper tolerance interval limit calculated for 99.99% reliability with 95% confidence on pooled data from the primary stability testing samples (Configuration ID 2.1) that had been aged up to 12 months (see Table Q2-2). Use of this upper tolerance interval limit allows for lot-to-lot variation which may result in infrequent individual values above the currently observed maximum value of 8.0 kgf.
- The (b) (4) kgf limit is within the range of actuation forces measured by bench-top testing for the devices used in clinical trials and human factors studies, which have included observed values up to 9.3 kgf (see Table Q2-1 from the response to Question 2 in the Information Request dated 21 February 2019, Seq. No 0027).
- In the palmar pinch study Monte Carlo analysis, estimates for the user force capability for the entire intended user population aged from 10-75+ years, and for the sub-group of adolescents aged from 10-19 years were calculated (see Table Q2-3). It is expected that adult caregivers will be the primary users of the device, with a lower probability of use by the adolescent population. Therefore, a specification limit of (b) (4) kgf, the average of the full population and adolescent sub-population, is justified.

An upper specification limit of (b) (4) kgf is proposed for reliability of the device. This upper limit is based on the following:

- An upper tolerance interval limit of (b) (4) kgf was calculated for 99.99% reliability with 95% confidence on pooled data from the primary stability testing samples (Configuration ID 2.1) that had been aged up to 12 months (see Table Q2-2). Assuming that the standard deviation calculated for this data set is representative of the true standard deviation for the to-be-marketed device design performance, an increase in the observed mean 0.1 kgf during reliability testing would result in failure of the product to meet the reliability specification; however, this minor change in mean actuation force does not represent a meaningful difference in device usability. Therefore, a limit of (b) (4) kgf is proposed for the reliability upper specification limit.
- The (b) (4) kgf limit is consistent with the upper end of the range of actuation forces measured by bench-top testing for the devices used in clinical trials and human factors studies, which have included observed values up to 9.3 kgf (see Table Q2-1 from the response to Question 2 in the Information Request dated 21 February 2019, Seq. No 0027).

As a point of clarification, the actuation speed of 80 mm/sec used for bench-top actuation force testing has been determined to be at the extreme upper end of expected range of actuation speeds based on our simulated use actuation force testing; therefore, this conservatively represents a speed that would generate the highest expected actuation forces. The flow rate of compressed air through the primary container to expel the powder is not dependent upon the speed at which the plunger is pressed. Unlike a syringe where the plunger movement speed determines the flow rate of product from the needle, the nasal glucagon device operates by compressing air during the actuation stroke, and then releasing this

compressed air once the button is pressed far enough to dislodge the centerpiece and ball (refer to Figure 3.2.R.3.3.2-1 and the linked video previously provided in Section 3.2.R.3.3.2, Description of Device Operation). The flow rate of the drug powder is determined by the pressure differential of the air between the inside and outside of the device at the time the ball is dislodged.

The results from reanalysis of the actuation force data from design verification, shipping, reliability study, and stability testing are provided in Table Q2-3 through Table Q2-8, demonstrating that the proposed specifications have been met.

FDA Response:
The sponsor has proposed the following actuation force specifications:

Table Q2-1 Proposed Actuation Force Specifications

EPR	Specification	Specification Applicability
Actuation Force	NLT (b) (4) kgf and NMT (b) (4) kgf	Lot Release; Stability; Design Verification (For 80 mm/sec actuation speed with devices and/or test environments greater than or equal to room temperature during actuation)
	NLT kgf and NMT kgf	Reliability (For 80 mm/sec actuation speed with devices and/or test environments greater than or equal to room temperature during actuation)
	NLT (b) (4) kgf and NMT (b) (4) kgf	Design Verification/ Reliability (For 80 mm/sec actuation speed with devices and/or test environments at extreme cold temperature [-20°C] during actuation)

The sponsor has proposed to move the upper limit of actuation force for lot release, stability, design vericiation testing from (b) (4) kgF to (b) (4) kgF. The state it is proposed for the following reasons:

- *The upper tolerance interval limit calculated for 99.99% reliability with 95% confidence on pooled data from the primary stability testing samples (Configuration ID 2.1) that had been aged up to 12 months (see Table Q2-2). Use of this upper tolerance interval limit allows for lot-to-lot variation which may result in infrequent individual values above the currently observed maximum value of 8.0 kgf.*
- *The (b) (4) kgf limit is within the range of actuation forces measured by bench-top testing for the devices used in clinical trials and human factors studies, which have included observed values up to 9.3 kgf (see Table Q2-1 from the response to Question 2 in the Information Request dated 21 February 2019, Seq. No 0027).*
- *In the palmar pinch study Monte Carlo analysis, estimates for the user force capability for the entire intended user population aged from 10-75+ years, and for the sub-group of adolescents aged from 10-19 years were calculated (see Table Q2-3). It is expected that adult caregivers will be the primary users of the device, with a lower probability of use by the adolescent population. Therefore, a specification limit of (b) (4) kgf, the average of the full population and adolescent sub-population, is justified.*

I do not agree with the sponsor's assessment for the selection of (b) (4) kgF as the upper limit for actuation force for verification testing and lot release testing. For the following reasons:

- They state the (b) (4) kgF, as compared to (b) (4) kgF, essentially allows for wiggle-room in terms of the actuation force needed for lot release because there highest actuation force observed in verification testing is (b) (4) kgF.

  Note: An extra (b) (4) kgF is not an adequate reason if the specification is not adequately validated.

- They state that (b) (4) kgF was validated in a very pre-formative human factors studies, however the trend of actuation forces drops between iterations of the device, with the lowest being the current iteration of the device.

Note: it is unclear if there was difficulty when these devices were used and the device was tuned to ensure that the actuation force of the device was lower. Additionally, the sponsor has not provided any information regarding the types of patients that were tested in this HF study.

- The sponsor states that (b) (4) kgF was chosen based on the palmar pinch data (see below) because the majority of users will be adult care givers rather than children or adolescents and (b) (4) kgF is the average between the two user groups.

Note: the indications for the product is for pediatric through adults, including elderly individuals; therefore, theres is a realistic possibility that the a pediatric and or elderly user could use this product. If the product is at (b) (4) kgF, based on the data below, it is potentailly forseeable that the product could be difficult to actuate or unable to actuate the device.

Based on the data submitted, and the reasons listed above, the sponsor has still not fully validated the proposed upper specficiation of (b) (4) kgF. See section 13.3 for Follow-up IR. This was resolved interactively.

13.3. IR#4: Written 2/28/2019; Returned from Sponsor on 3/1/2019- RESOLVED

In response to an Agency IR, which requested that adjust the upper limit of actuation force specfication to 8 kgF, you provided a justification to support an adjusted uper actuation force limit in your verification, stability, and lot release testing to (b) (4) kgF.

While you state that "*it is expected that adult caregivers will be the primary users of the device*", your product is also indicated for users that includes pediatrics and elderly users, who may have lower pinch strength capabilities than the 10-75+ average palmar pinch strength force of 8.9 (from Monte Carol Analysis Summary). Therefore, given that it is foreseeable that caregivers and/or adults will not be the only users of your device, the average between adolescents and the full population is not adequate. The upper specification for actuation force should be adjusted to a level that represents the pinch strength limit that of users that represent the worst case in terms of pinch strength capabilities, not the average of the full population.

You also state that you have validated a higher actuation force (up to (b) (4) kgF, (b) (4) kgf mean) in your previous human factors/clinical studies, but you have not provided any information on the user groups that were tested or if there were any complaints related to user difficulty actuating the device. Therefore, your current actuation force upper specification has not been adequately validated and it remains unclear if users, such as pediatrics or elderly, would have difficult or would be unable to administer your drug product at the upper limit of your actuation force specification. It is also noted that in Table Q2-1 from the Information Request dated 21 February 2019, Seq. No 0027, that the actuation force mean appears to have decreased based on the device configuration since device 2.0.

Given the information listed above and that the risk of a patient being unable to actuate your device is not receiving their dose of an emergency use drug product, please adjust the upper limit of the actuation force specification of your device to (b) (4) kgF (b) (4), to ensure that all users will be able to actuate your device. Please provide the following:

a) Please update your product specification sheet with (b) (4) kgF as your upper specification for actuation force and reanalyze your actuation force performance data, including stability, shipping, etc. based on the adjusted specification. Please provide this updated documentation.
b) We note that you are proposing to keep the upper limit of actuation force specification at (b) (4) kgF in your reliability testing, despite the change in the actuation force lot release specification. While you are demonstrating the reliability of the device to meet the actuation force specification at (b) (4) kgF, this may not adequately represent the reliability of the device to meet the actuation force specification at (b) (4) kgF (as requested in part a above); therefore, in lieu of revising the your 99.99%/95% tolerance interval, please provide a strong justification in support of your control

processes and strategy, including receiving, in-process, and lot release testing/controls, specific to actuation force that will ensure that the device constituent will consistently meet the upper limit actuation force of (b) (4)kgF.

Sponsor Response:
Lilly agrees to update the product specifications to implement an upper specification limit for actuation force of (b) (4)kgf, as shown in Table Q1-1. The results from reanalysis of the actuation force data from design verification, shippin reliability study, and stability testing are provided in Table Q1-2 through Table Q1-7, demonstrating that the proposed specifications have been met.

Table Q1-1 Proposed Actuation Force Specifications

EPR	Specification	Specification Applicability
Actuation Force	(b) (4)	

In addition to the data presented in the response to Question 1a), Table Q1-8 presents the tolerance interval calculated for 99.99% reliability with 95% confidence on pooled data from both the primary stability testing samples that had been aged up to 12 months (at either 25°C/60% RH or 30°C/75% RH) and the release testing of the process validation batches. This analysis demonstrates that the combined elements of the commercial manufacturing control strategy ensure that the device constituent will consistently meet the actuation force upper specification limit of (b) (4)kgF.

FDA Response:
The sponsor has changed the specification to (b) (4)kgF (including lot release) (b) (4) They have also reanalyzed their actuation force data for primary verification, stability, and shipping and demonstrate that they meet the specification. The response is adequate. No additional deficiencies regarding this are necessary.

14.RECOMMENDATION

CDHR/ODE Recommendation:
Device Constituents Parts of the Combination Product are Approvable with a (b) (4)month shelf life. If the sponsor would like to extend the shelf life to (b) (4)month, as originally proposed, we recommend that they submit a shelf-life extension protocol to propose the device performance testing that would be needed to extend the shelf life as a part of a supplement.

CDRH/OC Recommendation:
Quality Systems Recommendation:
The QS information is adequate to support approval.

Facilities Inspections Recommendation:
Facilities information is adequate. Inspection recommendations are below:

Combination Product Applicant

Firm Name: Eli Lilly and Company

A pre-approval inspection is required and was completed

Finished Combination Product Manufacturer

Firm Name: (b) (4)

A post-approval inspection is required

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/

MEGHNA M JAIRATH
04/23/2019 10:28:20 AM

Clinical Inspection Summary Addendum

Date	4/04/2019
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Min Lu, M.D., Acting Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Andreea (Ondina) Lungu, M.D., Clinical Reviewer Mitra Rauschecker, M.D., Clinical Team Leader Lisa B. Yanoff, M.D., Acting Division Director Meghna M. Jairath, Pharm.D., Regulatory Health Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA	210134
Applicant	Eli Lilly and Company
Drug	Glucagon Nasal Powder
NME	No
Therapeutic Classification	Glucose elevating agent
Proposed Indication	Treatment of severe hypoglycemia
Consultation Request Date	8/15/2018
Summary Goal Date	2/28/2019; addendum 4/04/2019
Action Goal Date	4/26/2019
PDUFA Date	4/26/2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this new drug application (NDA) consisted of two domestic clinical sites (representing three study sites) as well as the sponsor and contract research organization (CRO). The inspection of the sponsor, CRO and the clinical investigators revealed no regulatory violations.

Based on the inspections of the two clinical sites, the CRO and the sponsor, the inspectional findings support validity of data as reported by the sponsor under this NDA.

The classification for Drs. DiMeglio and Fox is No Action Indicated (NAI). Data from these sites is considered reliable based on the available information. The full Establishment Inspection Reports were submitted for review.

The classification for the contract research organization (b) (4) is NAI. Data from this CRO are considered reliable based on the available information. The full Establishment Inspection Report was submitted for review.

The classification for the sponsor Eli Lilly and Company is NAI. Data from this sponsor are considered reliable based on the available information. The full Establishment Inspection Report was submitted for review.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity.

II. BACKGROUND

Eli Lilly and Company (Lilly) submitted a new drug application (NDA) for glucagon nasal powder for the treatment of severe hypoglycemia. AMG504-1 is a novel, nasally-administered glucagon powder formulation containing synthetic human glucagon administered using a specially designed device that gently propels the powder into the nostril. Nasal glucagon was originally developed by A.M.G. Medical Inc. (AMG Medical) and later by Locemia Solutions ULC (Locemia) prior to acquisition by Eli Lilly and Company (Lilly) in 2015.

Inspections were requested for the two following studies:

- I8R-MC-IGBB / AMG103 Assessment of Intranasal Glucagon in Children and Adolescents with Type 1 Diabetes

Study IGBB (AMG103) was a multicenter, randomized, crossover study in pediatric patients (ages 4 years to <17 years) with type 1 diabetes mellitus (T1D) assessing the pharmacokinetics (PK), pharmacodynamics (PD), efficacy, and safety of glucagon administered via the nasal route (NG 2 mg or NG 3mg) compared to a marketed glucagon product administered intramuscularly (IMG 0.5 or 1 mg, weight based).

The study began December 18, 2013 and completed January 13, 2015. A total of 49 subjects were screened and 48 enrolled (36 subjects between the ages of 4 and <12 years and 12 subjects between the ages of 12 and <17 years). One subject in the 12 and <17 years age group was not randomized due to contraindicated concomitant drug use.

During insulin-induced hypoglycemia, once a plasma glucose level of <80 mg/dL was reached, the basal rate was returned to normal via the investigational product. A blood sample was collected for PK analysis (glucagon) and PD analysis (glucose). The primary outcome data for the study were the PK and PD results from the laboratories performing these analyses. Laboratory samples for PK/PD analyses were processed centrally and the results were sent electronically to the CRO (b) (4) .

- I8R-MC-IGBC/ AMG106 Efficacy and Safety of Intranasal Glucagon for Treatment of Insulin Induced Hypoglycemia in Adults with Diabetes

Study IGBC (AMG106) was a multicenter, randomized, open-label, crossover study in adult patients with T1D or type 2 diabetes mellitus (T2D) assessing the efficacy, safety, PK, and PD of glucagon administered via the nasal route (NG 3 mg) for reversing insulin-induced hypoglycemia compared to a marketed glucagon product (IMG 1 mg).

The study began December 19, 2013 and completed January 14, 2015. There were 95 subjects screened and 88 subjects enrolled; 83 subjects received at least one dose of the study drug (77 subjects with Type 1 Diabetes Mellitus, 6 subjects with Type 2 Diabetes Mellitus).

Induced hypoglycemia was followed by treatment with either IN or IM glucagon. Efficacy was assessed by the proportion of subjects who achieved one or both of the following efficacy endpoints:

1. Achievement of an increase in blood glucose to ≥70 mg/dL (3.9 mmol/L), within 30 minutes after receiving study glucagon, without receiving additional actions to increase the blood glucose level.
2. Achievement of an increase of ≥20 mg/dL from nadir within 30 minutes after receiving study glucagon, without receiving additional actions to increase the blood glucose level.

III. RESULTS (by Site):

Name of CI/ Address	**Protocol Site # # of Subjects Randomized**	**Inspection Date**	**Classification**
Linda A. DiMeglio, M.D. Indiana University Health Hospital and Clinical Research Center 550 N. University Boulevard Indianapolis, IN 46202-5109	I8R-MC-IGBB Site 39 14 subjects I8R-MC-IGBC Site 39 12 subjects	10/15 – 10/24/2018	No Action Indicated (NAI)
Larry Fox, M.D. Nemours Children's Clinic 807 Childrens Way Jacksonville, FL 32207-8426	I8R-MC-IGBB Site 8 13 subjects	11/05 – 11/08/2018	No Action Indicated (NAI)
(b) (4)			No Action Indicated (NAI)

Eli Lilly and Company Lilly Corporate Center 839 South Delaware Street Indianapolis, IN 46225-1782	N/A	01/21 – 01/25/2019	No Action Indicated (NAI)

Key to Compliance Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
*Pending = Preliminary classification based on information in 483 (if applicable) and preliminary communication with the field; final classification is pending letter to site.

NOTE: Site inspections focused on 100% review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

When inspections began, FDA inspectors were unable to verify the data line listing "Listing of Selected Individual Efficacy Measurements" for each subject in studies I8R-MC-IGBB and I8R-MC-IGBC as the laboratory results were not sent to the sites once the studies had ended. The sponsor was immediately contacted, and, on October 19, 2018, laboratory data were made available to all sites in studies I8R-MC-IGBB and I8R-MC-IGBC.

1. Linda DiMeglio/ Site 39 Study I8R-MC-IGBB/ Site 39 Study I8R-MC-IGBC

For Study I8R-MC-IGBB, there were 14 subjects screened and 14 subjects enrolled into the study; 14 subjects completed the study. There were 14 subject records reviewed.

For Study I8R-MC-IGBC, there were 13 subjects screened and 12 subjects enrolled into the study; 12 subjects completed the study. There were 12 subject records reviewed.

Dr. DiMeglio is the Assistant Director for Clinical and Translational Research, Pediatric Director Type 1 Diabetes Research Team, Division of the Pediatric Endocrinology, Indiana University School of Medicine.

The Institutional Review Board (IRB) of record for both studies was Indiana University Human Subjects Office of Research Administration.

Subjects' records were legible and filed in an organized manner in a three-ring binder. The site accessed the CRO's web-based electronic data capture system (EDC) to enter source data into the electronic case report forms for each subject. Source data was also entered in real time into an Excel spread sheet. The Excel spreadsheet did not provide a tracking

mechanism or audit trail. If the site made changes on the spreadsheet, each version of the spreadsheet would be revised and provided to the CRO. Also, changes were indicated in the combined EDC and Excel spreadsheet document prior to database lock in the "Investigator Review and Sign Off Packet" (Data Packet) for each subject. The FDA inspector confirmed that these Data Packets were maintained and that changes were being tracked for each subject.

After study closure, the CRO provided the site with a combined document containing both information entered into the EDC and Excel spreadsheet for each subject. The combined file also maintained audit trails to indicate changes to data.

The site followed protocol procedures for required time frames between Visit 1 and Visit 2. The glucose monitoring was performed for the required time points and documented in the source documents for each subject in both studies. The documents indicated that subjects arriving at the site had fasted for at least 8 hours prior to dosing.

The FDA inspector compared the sponsor data listings to source documents, electronic data capture and the Excel spreadsheet. There were no discrepancies noted. The primary efficacy endpoint data was verifiable.

There was no evidence of underreporting of adverse events. There were no serious adverse events (SAEs) for the two studies.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

2. Larry Fox/ Site 8 Study I8R-MC-IGBB

There were 13 subjects screened and 13 subjects enrolled into the study;13 subjects completed the study. There were 13 subject records reviewed.

Dr. Larry Fox is a Pediatric Endocrinologist and is the Medical Director of the Northeast Florida Pediatric Diabetes Center, Nemours Children's Clinic. Subjects recruited were patients seen by Dr. Fox and the other doctors at Nemours and at Baptist Medical Center, Wolfson's Children's Hospital.

The IRB of record was Baptist Medical Center IRB.

All records were well-organized, legible, and complete. The FDA inspector compared the sponsor data listings to source documents, electronic data capture and the Excel spreadsheet. There were no discrepancies noted. The primary efficacy endpoint data was verifiable.

There was no evidence of under-reporting of AEs. There was one SAE of hypoglycemia

(Subject 0010), which was caused by the time limit being exceeded for bringing the child out of hypoglycemia. This event was reported to the IRB December 12, 2014.

There were several reported protocol deviations. These were due to subjects who were randomized to the IM glucagon injection being given the product manufactured by Eli Lilly (Glucagon™) rather than GlucaGen® HypoKit® manufactured by Novo Nordisk per the protocol. (The sites had to order the marketed product as the IM glucagon was not supplied by the sponsor). This was not brought to the site's attention by the monitor during the study. This was reported to the IRB after site closure February 7, 2018.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

3. (b) (4)

The comprehensive inspection review included but was not limited to the following: standard operating procedures (SOPs), organizational charts, training records, device re-labeling, data security measures, audit trails, Excel spreadsheet validations, EDC system, randomization code protection, and blinding.

(b) (4) and the most responsible person at the firm. He was also the medical monitor for both studies

(b) (4) was established in 1993 as a nonprofit corporation and coordinating center for multi-centered clinical trials and epidemiologic research with a focus on projects involving eye diseases and diabetes (primarily type 1 diabetes).

Contracts were initially signed with AMG Medical and later Locemia Solutions ULC (Locemia) prior to contracting with Eli Lilly and Company.

(b) (4) was contracted for monitoring of the sites, data management, medical monitoring, statistical support and website development. Both on-site and remote monitoring were performed. No inspectional deficiencies were noted. There were no non-compliant clinical investigators in this trial and there were no sites where the study was terminated except due to lack of enrollment.

Monitoring comparisons of source documents against case report forms (CRFs) were made at the (b) (4) office as both documents were uploaded to the CRO's database. The monitoring records from monitoring visits, hospital records, office notes, workbooks and laboratory reports were also uploaded to the database and compared. The Excel spreadsheets were reviewed by (b) (4) staff for completeness and discrepancies. If changes were needed, the investigator site staff made the appropriate edits and provided a revised spreadsheet to (b) (4) All Excel spreadsheet were kept at the sites. All data changes were prior to database lock. No deficiencies were noted.

All database systems were password protected with limited entry. There were no issues noted with database management.

AMG504-1 was supplied to (b) (4) by Locemia Solutions. (b) (4) was then responsible for verifying device functionality and device re-labeling. The FDA inspector determined the device re-labeling and the necessary blinding took place with no unblinding of any subject. Randomization was performed with no discrepancies noted.

The central laboratory used for the studies was (b) (4) (b) (4) was involved with the quality control process by taking duplicate samples of glucose sent to the central lab and re-running the test to compare measurements. There were no data reliability concerns noted by the FDA inspector.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

4. Eli Lilly and Company/ Sponsor

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, investigational product accountability, the evaluation of the adequacy of monitoring and corrective actions taken by the sponsor/monitor/CRO, deviations related to key safety and efficacy endpoints, quality assurance and audits, adverse events evaluation and reporting, 1572s and investigator agreements, financial disclosures, standard operating procedures (SOPs), trial master file review, record retention, data management, escalation of issues, and clinical trial oversight.

This inspection was conducted jointly with European Union (EU) inspectors from the European Medicines Agency (EMA).

Eli Lilly and Company (Lilly) has operated for the past 140 years and employees approximately 38,000 individuals worldwide. Clinical research is conducted in more than 50 countries with 5,000 employees engaged in clinical development.

Lilly acquired the rights to Nasal Glucagon and accepted the ownership of IND 110674 in October of 2015; in December of 2015 there was a migration of SAEs to Lilly's Safety database. From 2016, Development Safety Update Reports (DSURs) have been prepared and submitted by Lilly to global regulatory authorities when required. There were no events submitted for Study IGBB or Study IGBC.

There were five protocol monitors assigned to monitor both studies that were selected from (b) (4) personnel; no contract monitors were utilized. Monitor qualification and training was reviewed, and no deficiencies were noted. There was adequate oversight of the

monitoring by Lilly.

The trial master file and records for sites are located in secured storage at the Lilly Corporate Headquarter. Upon receiving the data set from (b) (4) Lilly confirmed that the data collection system was designed, tested, developed, and executed per the protocol and the procedures that (b) (4) had in place. Data validation checks that were incorporated into the data collection tools were present. CRF audit trail was present for data changes, and Excel changes post-upload were captured in the database tables. The master datasets from (b) (4) were the equivalent to the raw data transferred to the Lilly secure data repository before being locked in the permanent storage system.

The firm maintained written procedures to assure the integrity of data collected as well as procedures for change control for data. The FDA inspector verified several data points (including adverse events and primary endpoints) provided to FDA with the (b) (4) database as well as the transferred Lilly database; no deficiencies were noted.

Study IGBB blinded study medication through an interactive web system. This information was provided by (b) (4) and the clinical sites were not provided with any unblinded reports during the study. Of note, there were different weights between the doses; the (b) (4) powder contained (b) (4) % by weight glucagon so the 2 mg and 3 mg devices had powder fill weights of (b) (4) mg and (b) (4) mg. There was no evidence that the site investigators or the subjects were aware of the weight difference.

The data capture that occurred during the two trials on Excel spreadsheets was discussed. Lilly agreed that capturing data in this way did not capture an audit trail and there was no way to ensure that the sheet had not been edited for bedside glucose measurements, although an audit trail record was developed.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

Data from this sponsor appear acceptable.

ADDENDUM:

(b) (4)

(b) (4)

(b) (4)

[redacted]

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm./ NDA 210134
DMEP/Division Director/ Lisa Yanoff
DMEP /Deputy Director/William Chong
DMEP/Team Lead/ Mitra Rauschecker
DMEP/Clinical Reviewer/ Andreea (Ondina) Lungu
DMEP /Regulatory Project Manager/ Meghna M. Jairath
OSI/DCCE/Division Director/Ni Aye Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Min Lu
OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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/

CYNTHIA F KLEPPINGER
04/04/2019 01:51:25 PM

MIN LU
04/04/2019 01:59:05 PM

KASSA AYALEW
04/04/2019 04:06:55 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 29, 2019

TO: Lisa Yanoff, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II
Office of New Drugs

Norman Stockbridge, M.D.
Director
Division of Cardiovascular and Renal Products (DCRP)
Office of Drug Evaluation I
Office of New Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
Staff Fellow
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles R. Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of (b) (4)

1. Inspection Summary

OSIS inspected the analytical portion of studies (b) (4)

I did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

Based on my review of the inspectional findings, I conclude the data from the audited studies are reliable.

2. Inspected Studies

(b) (4)

2.1. Studies not yet associated with an application

(b) (4)

3. Scope of Inspection

OSIS scientist Srinivas R. Chennamaneni, Ph.D. audited the bioanalytical portion of the above studies at (b) (4) from (b) (4).

The previous FDA inspection of (b) (4) was conducted in (b) (4) and classified as NAI. At the conclusion of the inspection, no deficiencies were observed, and no Form FDA 483 was issued.

The current inspection included a thorough examination of study records, facilities, laboratory equipment, method validation, and sample analysis, and interviews with the firm's management and staff. In addition, Standard Operating Procedures (SOPs), employee training records, laboratory notebooks, audit trails.

To assess the firm's current bioanalytical operations, I examined method validation and study sample analysis of ongoing (b) (4)

4. Inspectional Findings

At the conclusion of the inspection, I did not observe objectionable conditions and I did not issue Form FDA 483 to (b) (4)

(b) (4)

5. Conclusion

After review of the inspectional findings, I conclude that data from the audited studies are reliable. In addition, data from studies not audited but submitted to pending applications (**Attachment 1)** are reliable for Agency review.

Studies using similar methods conducted between the previous inspection (b) (4) and the end of the current surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI - (b) (4)

cc: OTS/OSIS/Kassim/Choe/Kadavil/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Chennamaneni
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au

Draft: SRC 3/18/2019, 3/21/2019, 3/27/2019
Edit: GB 3/18/2019, 3/20/2019; CRB 3/19/2019, 3/27/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/(b) (4) USA/FY18: First Day of Inspection/Post-Inspection Folder/EIR & EIR Review

OSIS File #: BE 8193 and BE 8333

FACTS: (b) (4)

Attachment 1
Studies not audited but submitted to pending applications

Application #	Study #	Study Type	Drug Name	Dates of conduct
NDA 200327/S022	P903-26	In Vivo	Ceftaroline Fosamil	1/29/2016 – 2/10/2018
NDA 210134	18R-MC-IGBI	In Vivo	Baqsimi® (Glucagon Nasal Powder)	11/24/2017 – 1/29/2018

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/

SRINIVAS RAO N CHENNAMANENI
03/29/2019 02:09:44 PM

GOPA BISWAS
03/29/2019 02:21:19 PM

CHARLES R BONAPACE
03/29/2019 02:50:42 PM

Clinical Inspection Summary

Date	2/21/2019
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Min Lu, M.D., Acting Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Mahtab Niyyati, M.D., Medical Officer Mitra Rauschecker, M.D., Clinical Team Leader Lisa B. Yanoff, M.D., Acting Division Director Meghna M. Jairath, Pharm.D., Regulatory Health Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA	210134
Applicant	Eli Lilly and Company
Drug	Glucagon Nasal Powder
NME	No
Therapeutic Classification	Glucose elevating agent
Proposed Indication	Treatment of severe hypoglycemia
Consultation Request Date	8/15/2018
Summary Goal Date	2/28/2019
Action Goal Date	4/26/2019
PDUFA Date	4/26/2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this new drug application (NDA) consisted of two domestic clinical sites (representing three study sites) as well as the sponsor and contract research organization (CRO). The inspection of the sponsor, CRO and the clinical investigators revealed no regulatory violations.

Based on the inspections of the two clinical sites, the CRO and the sponsor, the inspectional findings support validity of data as reported by the sponsor under this NDA.

The classification for Drs. DiMeglio and Fox is No Action Indicated (NAI). Data from these sites is considered reliable based on the available information. The full Establishment Inspection Reports were submitted for review.

The classification for the contract research organization (b) (4) is NAI. Data from this CRO are considered reliable based on the available information. The full Establishment Inspection Report was submitted for review.

The classification for the sponsor Eli Lilly and Company is NAI. Data from this sponsor are considered reliable based on the available information. The full Establishment Inspection Report was submitted for review.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity.

II. BACKGROUND

Eli Lilly and Company (Lilly) submitted a new drug application (NDA) for glucagon nasal powder for the treatment of severe hypoglycemia. AMG504-1 is a novel, nasally-administered glucagon powder formulation containing synthetic human glucagon administered using a specially designed device that gently propels the powder into the nostril. Nasal glucagon was originally developed by A.M.G. Medical Inc. (AMG Medical) and later by Locemia Solutions ULC (Locemia) prior to acquisition by Eli Lilly and Company (Lilly) in 2015.

Inspections were requested for the two following studies:

- I8R-MC-IGBB / AMG103 Assessment of Intranasal Glucagon in Children and Adolescents with Type 1 Diabetes

Study IGBB (AMG103) was a multicenter, randomized, crossover study in pediatric patients (ages 4 years to <17 years) with type 1 diabetes mellitus (T1D) assessing the pharmacokinetics (PK), pharmacodynamics (PD), efficacy, and safety of glucagon administered via the nasal route (NG 2 mg or NG 3mg) compared to a marketed glucagon product administered intramuscularly (IMG 0.5 or 1 mg, weight based).

The study began December 18, 2013 and completed January 13, 2015. A total of 49 subjects were screened and 48 enrolled (36 subjects between the ages of 4 and <12 years and 12 subjects between the ages of 12 and <17 years). One subject in the 12 and <17 years age group was not randomized due to contraindicated concomitant drug use.

During insulin-induced hypoglycemia, once a plasma glucose level of <80 mg/dL was reached, the basal rate was returned to normal via the investigational product. A blood sample was collected for PK analysis (glucagon) and PD analysis (glucose). The primary outcome data for the study were the PK and PD results from the laboratories performing these analyses. Laboratory samples for PK/PD analyses were processed centrally and the results were sent electronically to the CRO (b) (4)

- I8R-MC-IGBC/ AMG106 Efficacy and Safety of Intranasal Glucagon for Treatment of Insulin Induced Hypoglycemia in Adults with Diabetes

Study IGBC (AMG106) was a multicenter, randomized, open-label, crossover study in adult patients with T1D or type 2 diabetes mellitus (T2D) assessing the efficacy, safety, PK, and PD of glucagon administered via the nasal route (NG 3 mg) for reversing insulin-induced hypoglycemia compared to a marketed glucagon product (IMG 1 mg).

The study began December 19, 2013 and completed January 14, 2015. There were 95 subjects screened and 88 subjects enrolled; 83 subjects received at least one dose of the study drug (77 subjects with Type 1 Diabetes Mellitus, 6 subjects with Type 2 Diabetes Mellitus).

Induced hypoglycemia was followed by treatment with either IN or IM glucagon. Efficacy was assessed by the proportion of subjects who achieved one or both of the following efficacy endpoints:

1. Achievement of an increase in blood glucose to ≥70 mg/dL (3.9 mmol/L), within 30 minutes after receiving study glucagon, without receiving additional actions to increase the blood glucose level.
2. Achievement of an increase of ≥20 mg/dL from nadir within 30 minutes after receiving study glucagon, without receiving additional actions to increase the blood glucose level.

III. RESULTS (by Site):

Name of CI/ Address	**Protocol Site # # of Subjects Randomized**	**Inspection Date**	**Classification**
Linda A. DiMeglio, M.D. Indiana University Health Hospital and Clinical Research Center 550 N. University Boulevard Indianapolis, IN 46202-5109	I8R-MC-IGBB Site 39 14 subjects I8R-MC-IGBC Site 39 12 subjects	10/15 – 10/24/2018	No Action Indicated (NAI)
Larry Fox, M.D. Nemours Children's Clinic 807 Childrens Way Jacksonville, FL 32207-8426	I8R-MC-IGBB Site 8 13 subjects	11/05 – 11/08/2018	No Action Indicated (NAI)
(b) (4)			No Action Indicated (NAI)

Eli Lilly and Company Lilly Corporate Center 839 South Delaware Street Indianapolis, IN 46225-1782	N/A	01/21 – 01/25/2019	No Action Indicated (NAI)

Key to Compliance Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
*Pending = Preliminary classification based on information in 483 (if applicable) and preliminary communication with the field; final classification is pending letter to site.

NOTE: Site inspections focused on 100% review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

When inspections began, FDA inspectors were unable to verify the data line listing "Listing of Selected Individual Efficacy Measurements" for each subject in studies I8R-MC-IGBB and I8R-MC-IGBC as the laboratory results were not sent to the sites once the studies had ended. The sponsor was immediately contacted, and, on October 19, 2018, laboratory data were made available to all sites in studies I8R-MC-IGBB and I8R-MC-IGBC.

1. Linda DiMeglio/ Site 39 Study I8R-MC-IGBB/ Site 39 Study I8R-MC-IGBC

For Study I8R-MC-IGBB, there were 14 subjects screened and 14 subjects enrolled into the study; 14 subjects completed the study. There were 14 subject records reviewed.

For Study I8R-MC-IGBC, there were 13 subjects screened and 12 subjects enrolled into the study; 12 subjects completed the study. There were 12 subject records reviewed.

Dr. DiMeglio is the Assistant Director for Clinical and Translational Research, Pediatric Director Type 1 Diabetes Research Team, Division of the Pediatric Endocrinology, Indiana University School of Medicine.

The Institutional Review Board (IRB) of record for both studies was Indiana University Human Subjects Office of Research Administration.

Subjects' records were legible and filed in an organized manner in a three-ring binder. The site accessed the CRO's web-based electronic data capture system (EDC) to enter source data into the electronic case report forms for each subject. Source data was also entered in real time into an Excel spread sheet. The Excel spreadsheet did not provide a tracking

mechanism or audit trail. If the site made changes on the spreadsheet, each version of the spreadsheet would be revised and provided to the CRO. Also, changes were indicated in the combined EDC and Excel spreadsheet document prior to database lock in the "Investigator Review and Sign Off Packet" (Data Packet) for each subject. The FDA inspector confirmed that these Data Packets were maintained and that changes were being tracked for each subject.

After study closure, the CRO provided the site with a combined document containing both information entered into the EDC and Excel spreadsheet for each subject. The combined file also maintained audit trails to indicate changes to data.

The site followed protocol procedures for required time frames between Visit 1 and Visit 2. The glucose monitoring was performed for the required time points and documented in the source documents for each subject in both studies. The documents indicated that subjects arriving at the site had fasted for at least 8 hours prior to dosing.

The FDA inspector compared the sponsor data listings to source documents, electronic data capture and the Excel spreadsheet. There were no discrepancies noted. The primary efficacy endpoint data was verifiable.

There was no evidence of underreporting of adverse events. There were no serious adverse events (SAEs) for the two studies.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

2. Larry Fox/ Site 8 Study I8R-MC-IGBB

There were 13 subjects screened and 13 subjects enrolled into the study;13 subjects completed the study. There were 13 subject records reviewed.

Dr. Larry Fox is a Pediatric Endocrinologist and is the Medical Director of the Northeast Florida Pediatric Diabetes Center, Nemours Children's Clinic. Subjects recruited were patients seen by Dr. Fox and the other doctors at Nemours and at Baptist Medical Center, Wolfson's Children's Hospital.

The IRB of record was Baptist Medical Center IRB.

All records were well-organized, legible, and complete. The FDA inspector compared the sponsor data listings to source documents, electronic data capture and the Excel spreadsheet. There were no discrepancies noted. The primary efficacy endpoint data was verifiable.

There was no evidence of under-reporting of AEs. There was one SAE of hypoglycemia

(Subject [redacted]), which was caused by the time limit being exceeded for bringing the child out of hypoglycemia. This event was reported to the IRB December 12, 2014.

There were several reported protocol deviations. These were due to subjects who were randomized to the IM glucagon injection being given the product manufactured by Eli Lilly (Glucagon™) rather than GlucaGen® HypoKit® manufactured by Novo Nordisk per the protocol. (The sites had to order the marketed product as the IM glucagon was not supplied by the sponsor). This was not brought to the site's attention by the monitor during the study. This was reported to the IRB after site closure February 7, 2018.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

3. [redacted] CRO

The comprehensive inspection review included but was not limited to the following: standard operating procedures (SOPs), organizational charts, training records, device re-labeling, data security measures, audit trails, Excel spreadsheet validations, EDC system, randomization code protection, and blinding.

[redacted] and the most responsible person at the firm. He was also the medical monitor for both studies

[redacted]

Contracts were initially signed with AMG Medical and later Locemia Solutions ULC (Locemia) prior to contracting with Eli Lilly and Company.

[redacted] was contracted for monitoring of the sites, data management, medical monitoring, statistical support and website development. Both on-site and remote monitoring were performed. No inspectional deficiencies were noted. There were no non-compliant clinical investigators in this trial and there were no sites where the study was terminated except due to lack of enrollment.

Monitoring comparisons of source documents against case report forms (CRFs) were made at the [redacted] office as both documents were uploaded to the CRO's database. The monitoring records from monitoring visits, hospital records, office notes, workbooks and laboratory reports were also uploaded to the database and compared. The Excel spreadsheets were reviewed by [redacted] staff for completeness and discrepancies. If changes were needed, the investigator site staff made the appropriate edits and provided a revised spreadsheet to [redacted] All Excel spreadsheet were kept at the sites. All data changes were prior to database lock. No deficiencies were noted.

All database systems were password protected with limited entry. There were no issues noted with database management.

AMG504-1 was supplied to (b) (4) by Locemia Solutions. (b) (4) was then responsible for verifying device functionality and device re-labeling. The FDA inspector determined the device re-labeling and the necessary blinding took place with no unblinding of any subject. Randomization was performed with no discrepancies noted.

The central laboratory used for the studies was (b) (4) . (b) (4) was involved with the quality control process by taking duplicate samples of glucose sent to the central lab and re-running the test to compare measurements. There were no data reliability concerns noted by the FDA inspector.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

4. Eli Lilly and Company/ Sponsor

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, investigational product accountability, the evaluation of the adequacy of monitoring and corrective actions taken by the sponsor/monitor/CRO, deviations related to key safety and efficacy endpoints, quality assurance and audits, adverse events evaluation and reporting, 1572s and investigator agreements, financial disclosures, standard operating procedures (SOPs), trial master file review, record retention, data management, escalation of issues, and clinical trial oversight.

(b) (4)

Eli Lilly and Company (Lilly) has operated for the past 140 years and employees approximately 38,000 individuals worldwide. Clinical research is conducted in more than 50 countries with 5,000 employees engaged in clinical development.

Lilly acquired the rights to Nasal Glucagon and accepted the ownership of IND 110674 in October of 2015; in December of 2015 there was a migration of SAEs to Lilly's Safety database. From 2016, Development Safety Update Reports (DSURs) have been prepared and submitted by Lilly to global regulatory authorities when required. There were no events submitted for Study IGBB or Study IGBC.

There were five protocol monitors assigned to monitor both studies that were selected from (b) (4) personnel; no contract monitors were utilized. Monitor qualification and training was reviewed, and no deficiencies were noted. There was adequate oversight of the

monitoring by Lilly.

The trial master file and records for sites are located in secured storage at the Lilly Corporate Headquarter. Upon receiving the data set from (b) (4) Lilly confirmed that the data collection system was designed, tested, developed, and executed per the protocol and the procedures that (b) (4) had in place. Data validation checks that were incorporated into the data collection tools were present. CRF audit trail was present for data changes, and Excel changes post-upload were captured in the database tables. The master datasets from (b) (4) were the equivalent to the raw data transferred to the Lilly secure data repository before being locked in the permanent storage system.

The firm maintained written procedures to assure the integrity of data collected as well as procedures for change control for data. The FDA inspector verified several data points (including adverse events and primary endpoints) provided to FDA with the (b) (4) database as well as the transferred Lilly database; no deficiencies were noted.

Study IGBB blinded study medication through an interactive web system. This information was provided by (b) (4) and the clinical sites were not provided with any unblinded reports during the study. Of note, there were different weights between the doses; the (b) (4) powder contained (b) (4)% by weight glucagon so the 2 mg and 3 mg devices had powder fill weights of (b) (4) mg and (b) (4) mg. There was no evidence that the site investigators or the subjects were aware of the weight difference.

The data capture that occurred during the two trials on Excel spreadsheets was discussed. Lilly agreed that capturing data in this way did not capture an audit trail and there was no way to ensure that the sheet had not been edited for bedside glucose measurements, although an audit trail record was developed.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

Data from this sponsor appear acceptable.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Min Lu, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm./ NDA 210134
DMEP/Division Director/ Lisa Yanoff
DMEP /Deputy Director/William Chong
DMEP/Team Lead/ Mitra Rauschecker
DMEP/Clinical Reviewer/ Mahtab Niyyati
DMEP /Regulatory Project Manager/ Meghna M. Jairath
OSI/DCCE/Division Director/Ni Aye Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Min Lu
OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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/

CYNTHIA F KLEPPINGER
02/21/2019 11:23:49 AM

MIN LU
02/21/2019 11:49:44 AM

KASSA AYALEW
02/21/2019 11:53:02 AM

NDA:	210134
Subject:	Immunogenicity review memo – Nasal glucagon, LY900018-BAQSIMI (formerly AMG504-1, (b) (4) glucagon) for the treatmen of severe hypoglycemia in people with diabetes.
Review Date:	11/28/2018
PDUFA due Date:	04/26/2019
Primary Reviewer:	Mohanraj Manangeeswaran, Ph.D
Secondary Reviewer:	Daniela Verthelyi, M.D., Ph.D
Applicant:	Eli Lilly and company
Associated IND:	110674
Proposed Proprietary Name:	
Nonproprietary Name:	**BAQSIMI (Nasal Glucagon powder)**
Dosage form:	Powder for intranasal administration
Indication:	Treatment of severe hypoglycemia in diabetes patients
Clinical Division:	OND/ODEII/DMEP
RPM:	Meghna Jairath

1. Recommendation:

New drug application for BAQSIMI (Nasal Glucagon powder) from Eli Lilly and company is recommeded for approval from an immunogenicity standpoint. However, it is contingent upon the decision of product quality and pharm/tox that the commercial batch of DP is comparable to previous batches of DP.

2. Executive summary:

NON-NME/505b1 The sponsor conducted three clinical studies to assess the immunogenicity of Nasal Glucagon. The screening and confirmatory assays used in monitoring the ADA response and neutralizing activity were validated and found suitable for their intended purpose. Of the 124 patients tested, 6 showed ADA. The overall incidence of treatment emergent ADA was found to be 4.8%. The titers were low, with a maximum titer of 80. No samples tested positive for neutralizing antibodies. No impact on PK, PD, safety or efficacy was evident in the ADA positive patients. From an immunogenicity standpoint this application can be approved.

3. Review memorandum:

Background:

Diabetes patients (type I and type II) treated with insulin occasionally end up with complications of hypoglycemia. Depending on the severity of the episode, this can result in a range of physical problems from dizziness to seizures, coma and death. Glucagon is a 29 aa polypeptide hormone that counteracts the effects of insulin. Glucagon binds to glucagon receptor and aid in rapid conversion of glycogen to glucose. Glucagon is an effective therapeutic for severe hypoglycemia. The drug product and the native glucagon are not glycosylated. Nasal Glucagon is a drug/device combination product that delivers a single dose of (b) (4) mg white (b) (4) powder containing 3 mg glucagon using a single use intranasal powder delivery device. Each dose also contains betadex (β-cyclodextrin), (b) (4) and dodecylphosphocholine (DPC) (b) (4)

Glucagon:
Molecular Formula: $C_{153}H_{225}N_{43}O_{49}S$.
Molecular Weight: 3,483
The primary structure of Glucagon in humans:

NH_2-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-COOH.

The product and the native glucagon are not glycosylated. The sequence is highly conserved and identical across species, but immunogenicity was not assessed in the preclinical models.

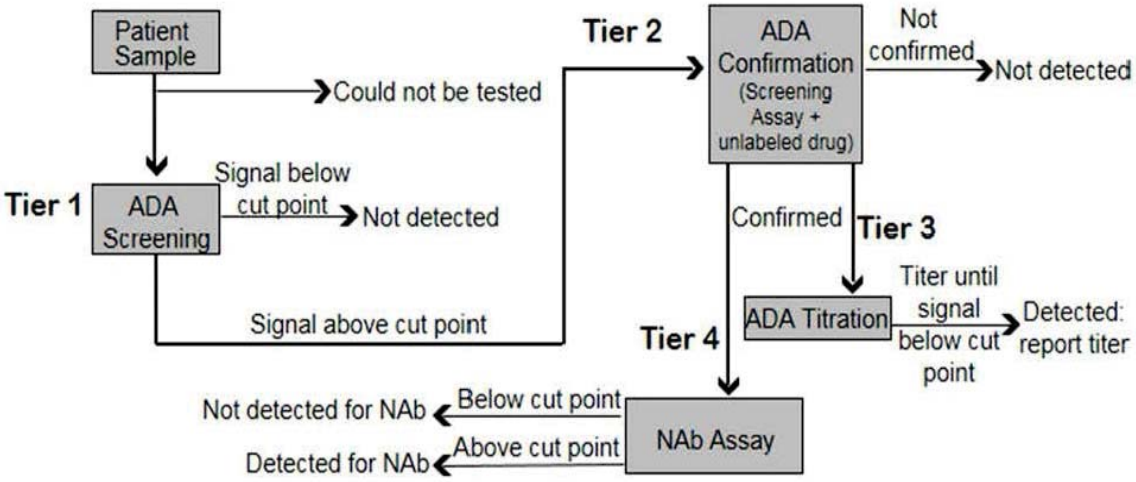
Risk assessment:

- This is the first intranasal (b) (4) (b) (4) nasal sparay) glucagon product. There are two glucagon products commercially available in the market to treat severe hypoglycemia in diabetes patients treated with insulin. The product inserts of approved products report that anti-drug antibodies are not developed against glucagon.

- The 29 amino acid peptide does not have disulphide bonds and is completely synthetic. A recombinant glucagon produced in E.coli is commercially used as an intra-muscular injection for treatment of severe hypoglycemia and has a relatively safe profile.
- The half- life of the drug is 8-18 minutes and the possibility of an effective recall immune response is very low.
- Mice where the gene responsible for the production of Glucagon and GLP-1 is knocked-out showed lower serum glucose levels but did not show any serious side effects indicating low risk associated with anti-drug antibodies neutralizing native glucagon.
- Hydrophobic residues Cys, Leu and Val, if they are exposed on the surface of a protein, could be part of an antigenic site. Assessment of the sequence using the "Antigenic" tool from EMBOSS showed a single hit with a low score of 1.073 at the position 20-26 (Gln-Asp-Phe-Val-Gln-Trp-Leu) of the polypeptide.

ADA assays:

The sponsor proposes a four tier anti-drug antibod assay strategy as outlined below.



Abbreviations: ADA = antidrug antibody; NAb = neutralizing antibody.

Method validation of screening, confirmatory, tittering and neutralizing antibody assays for LY9000018 and glucagon were previously reviewed by the agency (review memo dated 9/26/2017) and found suitable for the intended purpose. The memo is also attached at the end of this review. During analysis of the clinical trial samples, the rate of putative positives in the baseline samples were found to be significantly higher in both normal healthy volunteers and diabetes patient samples. Different rates of putative positives were attributed to differences in the clinical samples. Therefore, cut-points for tier 1 screening assay, tier 2 confirmatory assay, tier 3 titration assay and tier 4 neutralization assay were re-evaluated using in-study samples and new

cut points were established. So, addendum to the validation of the screening, confirmatory, tittering and neutralizing assays were performed.
All sera from treatment-naïve patients in studies 18-R-MC-IGBF, 18R-MC-IGBG and 18R-MC-B002 were combined and assessed for determination of in-study cut-point. A new screening cut point of 1.18 (Validation cut point was 1.06) was determined based on the 90% lower tolerance limit of the 95th percentile. The confirmatory cut point was determined to be 10.1% (validation cut point was 14.6%). The titration cut point was 1.21 (Validation cut point was 1.15). The cut point for neutralization established using 100 T1Dm and 50 T2DM treatment naïve in-study samples was 25.6% inhibition (Validation cut point was 13.9% inhibition).

Reviewers comments:
The addendum to the validation with new new cut points using in-study samples are acceptable.

Immunogenicity Vs Clinical Batch
Commercial batch of DP (IGBI) was different in terms of particle size compared to previous batches of DP. Immunogenicity studies were carried out with older batches of DP. Particle size can have an impact on immunogenicity based on the reach of the DP into interior regions of the airway and triggering an immune response. Product quality reviewer Dr. Muthukumar Ramaswamy was consulted on the exact differences in terms of particle size between the immunogenicity batch and commercial batch. Information provided by the sponsor in response to a query from the CMC reviewer regarding particle seize revealed that the commercial batch of DP (IGBI) did not have ?igher levels of fine particles compared to the immunogencity batches of DP (IGBF, IGBG, B002).

Reviewers comments:
Finer particles ((b) (4) uM) may fly deep into the respiratory system and midsize and coarse particles may be trapped in the nose. Particle size data provided by the sponsor revealed that the commercial batch of DP (IGBI) did not have more fine particles compared to the immunogenicity batches ((IGBF, IGBG, B002).

The particle size of the DP has shifted for the commercial batch. Comparability of commercial batch of DP to previous batches of DP is deffered to the product quality reviewer. If the commercial batch is comparable to previous batches, the immunogenicity data provided by the sponsor is acceptable.

Table Q1-1 Particle Size Distributions for Clinical and Commercial Scale Batches

Study	Purpose	Strength (mg bulk drug powder/device)	Batch	Particle size		
				X10 (µm)	X50 (µm)	X90 (µm)
IGBA	Dose Finding	(b) (4)	F120123-001	(b) (4)		
			F120123-002			
IGBE	Nasal Congestion		F121220-001			
IGBB	Pediatric PK/PD Pivotal		F130716-001			
			F130718-001			
			F140805-001			
			F140807-001			
IGBF	Immunogenicity		F130716-001			

Study	Purpose	Strength (mg bulk drug powder/device)	Batch	Particle size		
				X10 (µm)	X50 (µm)	X90 (µm)
IGBC	Adult PK/PD Pivotal	(b) (4)	F130716-001	(b) (4)		
			F140805-001			
B002	Actual Use Adults		F140327-001[a]			
			F141016-001			
B001	Actual Use Pediatrics		F141016-001			
IGBH	Repeat Dose - Terminated		F140423-001[a]			
IGBG	Repeat Dose		F141016-001			
N/A	Development Batch		1633276			
N/A	Development Batch		1624621			
N/A	Commercial Scale Batch		1623774			
N/A	Commercial Scale Batch		1623775			
IGBI	Clinical Comparability Commercial Scale Batch		1623776			

[a] These batches were intended for clinical trials but were withdrawn due to product performance issues attributed to a (b) (4) particle size distribution.

Immunogenicity data from clinical trials

Immunogenicity data from 3 clinical studies (IGBF, IGBG and B002) using Nasal Glucagon were included in the NDA package. Assessment of ADA using validated assays showed an incidence of 2% of treatment emergent ADA with a maximum titer of 1:80. No neutralizing antibodies were detected. Adverse events did not correlate with positive ADA results.

IGBF:

This was a Repeat single dose parallel design study (3 mg Nasal Glucagon Vs 1 mg Subcutaneous Glucagon) in 75 adult patients (59 Nasal Glucagon, 26 Subcutaneous Glucagon)

with Type 1 or Type II Diabetes. In each of the three study visits patients received a single dose of NG 3mg or Intramuscular Glucagon 1mg. Treatment visits were all 7 days apart. Blood samples for antibodies were drawn at baseline, 14 days post treatment and at end of study (43 days post first treatement). This study provided 146 immunogenicity samples (49 baseline and 97 post baseline) for patients treated with Nasal Glucagon and 77 immunogenicity samples (26 baseline and 51 post baseline) from 26 patients treated with IMG.

In this study, 4 out of 49 patients (8.2%) showed positive results for the ADA assay at baseline. The maximum titer observed at baseline was 1:40. None of the baseline samples were postive for the neutralization assay. Post-baseline samples showed 1 out of 49 patients (2%) with treatement emergent ADA. The maximum titer from this patient was 1:80. This patient was positive at 14 days post treatment and remained positive at the end of the study at 28 days post last treatment. None of the samples had neutralizing antibodies. All the immunogeniciy samples from IMG group were negative for ADA and neutralizing antibodies.

IGBG:
This was a single center, randomized study to evaluate the PK, PD and safety of single repeated 3mg doses of intranasal glucagon in adults with T1D and T2D patients. This study had 32 adults with T1D or T2D patients with 91 immunogenicity samples (32 at baseline and 59 post baseline) Of the immunogenicity samples from 32 patients, 1 patient (1%) was postivie for ADA at baseline. The maximum titer was 1:20. Of the post-baseline samples 2 out of 32 patients (6.3%) showed treatment emergent ADA. Both of these patients showed ADA 49 days post treatment which was the end of the study period. The maximum titer was 1:80. No samples showed neutralizing antibodies.

B002:
This was actual-use study for the effectiveness, ease of use and safety of Nasal Glucagon in 129 adults with Type 1 Diabetes. Samples for immunogenicity were taken at baseline and for patients who received at least one dose of Nasal Glucagon at the end of the study (approximately 6 months). This study produced 86 immunogenicity samples (43 at baseline and 43 at the end of the study) from 43 patients. None of the baseline samples were positive for ADA. None of the post-baseline samples showed ADA. None of the samples showed neutralizing antibodies.

Table 2.7.2.16. Immunogenicity Sampling Schedule for Nasal Glucagon Clinical Studies

Time Point	Study		
	IGBF N =75	IGBG N=32	B002[a] N=43
Samples at baseline	49 NG/26 IMG	32	43
Samples at 2 weeks postdose[b]	48 NG/25 IMG	27	-
Samples at end of study[c]	49 NG/26 IMG	32	43

Abbreviations: IMG = intramuscular glucagon; N = number of patients providing immunogenicity samples; NG = nasal glucagon.

a Only patients who received at least one dose of LY900018 provided an end-of-study sample for immunogenicity, from selective centers that had the capacity to process ADA samples.

b Approximate timing based on schedule in study protocol.

c End of study was approximately 43 days postdose for Study IGBF, 50 days postdose for Study IGBG, and up to 6 months postdose for Study B002.

Overall incidence of ADA: 11/124 (8.8%)
Baseline positives : 5/124
Overall incidence of treatment emergent ADA: 6/124 (4.8%)
The maximum titer observed in all the patient samples that were positive was 1:80.
None of the samples showed neutrazing activity.

Reviewers comments:
Rate of ADA seen in Nasal Glucagon treated patients is low (4.8%) after treatment with multiple doses. The proposed product is used in an emergency situtation and is only used sporadically. The benefit of using Nasal Glucagon to rescue patients with severe hypoglycemia far outweighs the risk of immunogenicity.

U.S. FOOD & DRUG ADMINISTRATION

Previous Review memo on the ADA assays

BB-IND:	IND 110674 (Immunogenicity consult)
SERIAL:	0084
DATE:	9/26/2017
FROM:	**Mohanraj Manangeeswaran, Ph.D.**
THROUGH:	Daniela Verthelyi, M.D. Ph.D.
PRODUCT:	LY900018 (formerly AMG504-1, (b) (4) (b) (4) Glucagon)
INDICATION:	Treatment of severe hypoglycemia in people with Diabetes
ROUTE OF ADMIN:	Intra nasal
DOSE REGIMEN:	(b) (4) mg LY900018
SPONSOR:	(b) (4)
IND PHASE:	pre-NDA

DATES FOR REVIEW PROCESS:
Received: 4/26/2017
Decision: 9/26/2017

Recommendation:
The approach to method validation is adequate and the assays appear suitable to their intended purpose. However, the cut point should be confirmed with samples from treatment-naive patients from the clinical trials for the proposed indication. Note that depending on the observed immunogenicity rate for your product an assay to quantitate IgA specific anti-drug antibodies may be needed.

Reason for the consult:
The sponsor has completed three immunogenicity trials to determine the rate of ADA in Type I (T1DM) and Type II (T2DM) Diabetes Mellitus patients treated with one or multiple doses of LY900018. The sponsor is planning to test the samples from the clinical trials using a three tiered ADA assay and has submitted the method validation studies to determine if the approach is acceptable.

Background:
Diabetes patients (type I and type II) treated with insulin occasionally develop hypoglycemia. Depending on the severity of the episode, this can result in a range of physical problems from dizziness to seizures, coma and death. Glucagon is a 29 aa polypeptide hormone that counteracts the effects of insulin. Glucagon binds to the glucagon receptor and aids in the rapid conversion of glycogen to glucose increasing the glucose levels. Glucagon is a highly effective therapeutic for severe hypoglycemia. LY900018 (formerly AMG504-1) is a completely synthetic product that has an amino acid sequence that is identical to human glucagon. LY900018 is a drug/device

combination product that delivers a single dose of (b) (4) mg white (b) (4) powder containing 3mg glucagon using a single use-intranasal powder delivery device. Each dose also contains betadex (β-cyclodextrin), (b) (4) and dodecylphosphocholine (DPC) (b) (4)

Sponsor material:

Composition of AMG-504-1

Name of Ingredient	Quality Standard	Function	Quantity/Unit Dose (mg)
			3 mg Strength
Glucagon	DMF	Active	3
Dodecylphosphocholine (DPC)	DMF	(b) (4)	
β-cyclodextrin	Ph. Eur./NF		
(b) (4)	USP		
	USP		

Glucagon:

Molecular Formula: C153H225N43O49S.
Molecular Weight: 3,483

The primary structure of Glucagon in humans:

NH_2-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-COOH.

The product and the native glucagon are not glycosylated. The sequence is highly conserved and identical across species.

Risk assessment:

- The 29 amino acid peptide does not have disulphide bonds and is completely synthetic. A recombinant glucagon produced in E.coli is commercially used as an intra-muscular injection for treatment of severe hypoglycemia and has a relatively safe profile.
- The half- life of the drug is 8-18 minutes and the possibility of an effective recall immune response is very low.
- Mice where the gene responsible for the production of Glucagon and GLP-1 is knocked-out showed lower serum glucose levels but did not show any serious side effects indicating low risk associated with anti-drug antibodies neutralizing native glucagon.

- Hydrophobic residues Cys, Leu and Val if they occur on the surface of a protein are more likely to be part of antigenic sites. “Antigenic” tool from EMBOSS is a semi –empirical method to predict antigenic determinants on proteins with use of physicochemical properties of amino acid residues and their freqencies of occurrence in experimentally known segmental epitopes developed by Kolaskar and Tongaonkar. Analysis of Glucagon polypeptide with this program reveals a single hit and a low score of 1.073 at the position 20-26 (Gln-Asp-Phe-Val-Gln-Trp-Leu) of the polypeptide.

Safety

There is increased concern of glucagon administered IN, because it is known to be a highly immunogenic route as the mucosa is lined with antigen presenting cells. However administration of high doses of LY900018 to rats and dogs for 28 consecutive days was well tolerated. Direct deposition of LY900018 into the lungs of rats did not result in any adverse findings suggesting that inadvertent pulmonary exposure would not cause direct toxicity on the lungs. The sponsors state that in prior human clinical studies (2 phase I and 1 phase II) with intra-nasal administration of LY900018 no adverse events linked to the product were observed. The sponsors also report that results in the literature where glucagon was administered IN resulted in limited side effects such as mild nasal irritation and occasional sneezing.The label for the commercial glucagon (intra muscular injection) has a warning for allergic reactions including breathing difficulties, and hypotension but there is no information on ADA on the label. Of note, glucagon has been used to treat patients with broncospasm suggesting that broncospasms resulting from direct stimulation of the bronchial mucosa are unlikely (Am J Emerg. Med. 1998 16(3) 272).

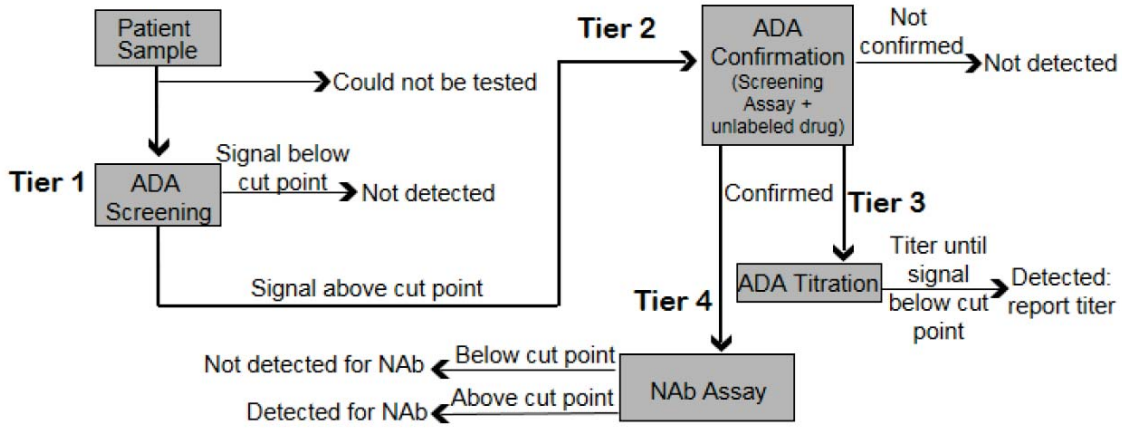
Anti- Glucagon antibodies

The sponsor has completed three immunogenicity trials and is planning to include the data from these trials in their NDA submission. This includes randomized, laboratory blinded, parallel safety study to evaluate the immunogenicity of a novel glucagon formulation compared with commercially available Glucagon administered by intramuscular injection in adults with type I and type II Diabetes (GlucaGen Hypokit for injection marketed by Novo Nordisk, Canada).

We send out comments to the sponsor at the end of phase II meeting on April 15, 2013, stating the sample size for the immunogenicity testing may not be enough. The sponsor has now amended the protocol and included additional patients in study. In addition, the sponsor is collecting samples from AMG 112 (n=32), a single center, randomized, four period, four way, crossover study evaluating different doses of glucagon nasal powder in patients with type I and type II diabetes to look for immunogenicity. The sponsor plans to submit immunogenicity data from three studies comprising an estimated 131 patients with type I or type II diabetes patients who received one to four doses of LY900018. In addition, we suggested the sponsor to submit

ADA assays for review before testing samples from pivotal trials. The sponsor has now submitted details of their ADA assays.

ADA assays to monitor anti-LY900018 antibodies



Abbreviations: ADA = antidrug antibody; NAb = neutralizing antibody.

A three-tiered approach is used to monitor anti-LY900018 antibodies in T1DM and T2DM patients treated with LY900018.

Screening ECL assay: Biotinylated LY900018 is allowed to bind onto strepatvidin coated plates. Samples were then incubated in this plate to capture ADA. After washing, captured ADA were eluted from biotinylated LY900018 with hydrochloric acid. Eluted ADA were neutralized with Tris-HCl and coated onto a second plate. ADA was then detected using biotinylated-LY900018 bound to sulfo-TAG streptavidin. After washing, a tripropylamine buffer ((b) (4)) was added to the plate. Ruthenium emits light at 620 nm when electrically stimulated and co-reacts with the tripropylamine buffer to enchance the electrochemiluminescent signal. The ECL units are directly proportional to the amount of LY900018 antibodies in the sample.

Confirmatory assay: Samples positive in the screening ECL assay are tested in a competitive inhibition assay using unlabelled LY900018. If the signal is reduced in the presence of unlabelled LY900018, the sample is considered confirmed positive.

Titer: Samples confirmed positive will be serially diluted to below the cut point value to determine the levels of ADA in the sample.

Reviewers comments:

Multi-tiered ADA testing approach is recommended and the three tier assay proposed by the sponsor is acceptable.

Method Validation

A test method was developed for the detection of anti-LY900018 antibodies in normal human serum samples. Screening and confirmatory cut points, precision, specificity, drug tolerance, sensitivity, ruggedness and robustness, interference and stability were assessed in the method validation study. Summary results from the validation studies are presented below.

Table 4.1. Validation Strategy Table

Validation Experiment		Tier 1	Tier 2	Tier 3		Tier 4
Potency						✓
MRD		✓ →	→			✓
Cut Point	Screening	✓				
	Confirmation		✓			
	Titration			✓		
	Neutralization					✓
Sensitivity		✓				✓
Drug Tolerance		✓ →	→	→		✓
Precision	Screening Assay (ECL)	✓ →	→	→		
	Confirmation (percent inhibition)		✓			
	Neutralization (percent inhibition)					✓
Robustness		✓ →	→	→		✓
Stability		✓ →	→	→		✓
Serum Factor Interference		✓ →	→	→		✓
Quality Control Levels[a]		✓ →	→	→		✓
Positive Specificity	Positive QCs ECL signal	✓				
	Positive QCs percent inhibition		✓			✓
Negative Specificity	Isotype-matched irrelevant antibody	✓				✓
	Rabbit polyclonal IgG antibody	✓				✓
	Non-neutralizing anti-glucagon antibody					✓

Abbreviations: ACE = affinity capture elution; ECL = electrochemiluminescence; Ig = immunoglobulin; MRD = minimal required dilution; QC = quality control; SD = standard deviation.

[a] For positive controls of both assays and the negative control of the ACE assay, QC ranges were set on limits of ±40% of the validated mean for each control. For the negative and noninhibitory control for the cell-based neutralization assay, QC ranges were set on limits of ±2SD of the validated mean for each control.

A tick mark represents tier where validation was directly performed and a solid arrow represents cases where validation of the ADA detection base method applies equally across the additional tiers.

Control Antibodies:

A human anti-LY900018 antibody is not available. The validation studies were conducted with affinity purified polyclonal antibodies from hyperimmunized rabbit serum or recombinant human/mouse chimeric monoclonal antibodies spiked into human serum. Due to the limited availability of purified polyclonal antibodies from rabbit sera, monoclonal antibodies were generated, tested for comparability to polyclonal antibodies and used during development and validation of the screening assay and as positive controls during sample analysis. Three anti-LY900018 monoclonal antibodies IBA 257 (targeting the N-terminal), IBA298 (targeting the mid domain) and IBA 297 (targeting the C terminus) were pooled in equal amounts to form the monoclonal antibody pool. These antibodies were purified similar affinity purification as the polyclonal antibodies.

Reviewers comments: The choice of control antibodies is acceptable. Hyperimmunized rabbit serum is not available in sufficient quantities and pool of monoclonal antibodies detecting N terminus, mid portion and C terminus portion of glucagon is acceptable. The method validation shows that the pool of three monoclonal antibodies shows similar sensitivity to detect anti-LY900018 antibodies.

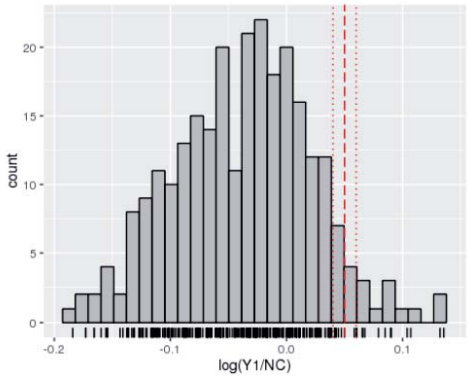
Minimum required dilution:
Sixteen individual normal human serum (NHS) lots were analyzed to select appropriate minimum required dilution (MRD). At least 10 single donor NHS samples were serially diluted in TBS. Dilutions of 1:2, 1;5, 1:10,1:20, 1:40 and 1:80 are tested in the presence of 100, 12.5 and 0.8 ng/mL of positive control antibody (monoclonal pool or polyclonal). These concentrations were chosen to span the linear range of the sensitivity curve of the assay and will approximate eventual low, mid and high positive control signals. The % difference between the individual NHS dilution result and the mean value of the assay buffer control was calculated for each level of spiked control antibody and each NHS donor. The optimal MRD was selected as **1:20**.
Reviewers comments:
This is acceptable. This dilution was selected as it minimized matrix interference when samples with and without positive control antibodies were compared to similarly prepared buffer samples. Further increase in MRD did not significantly improve the % difference from buffer with or without spikes.

Screening assay cut point:
Screening cut point will be used to differentiate between samples without detectable ADA and samples with potential ADA which may need confirmatory testing. Normal Human Serum (NHS) samples without LY900018 were used to determine the assay cut point. Fifty six individual NHS from adults were used for the analysis. Each sample was analyzed in duplicate in each analytical run. At least six analytical runs were performed over at least three days by at least two analysts.

The mean ECL signal, standard deviation and %CV of each sample was determined. NHS responses trended with the NC results due to the variability of the assay from each plate. When the total assay variability using either a fixed cut point or floating cut point was compared, fixed resulted in total assay variability (Coefficient of variation) of 11.4% while a floating cut point (normalization of sample results against the NC) resulted in total assay variability of 5.51%. A likelihood ratio test of the need of normalization was found to be significant ($p<0.05$). Additionaly, there was a high correlation of NHS and NC sample medians ona plate specific basis with a correlation of 0.88. Therefore, a floating cut point which controls for this variation was chosen. The cut point was calculated to result in approximately 5% false positive rate. The cut point estimation included removal of outlier analytical samples, outlier biological samples and appropriate use of parametric or nonparametric estimates based on normality tests. The floating screening cut point was estimated to be 1.06 (cut point factor relative to negative control plate mean) using parametric estimate (test of Normality pval=0.52) of the 95^{th} percentile (using a tolerence interval estimator). A boot strap estimate of the 95% confidence interval for the cut point is [1.04,1.07]. For the screening assay, a normalization factor (floating) cut point was calculated to be 1.06. The sponsor reports that the cut point for the screening and confirmatory assays were based on publised literature and established guidelines (Shankar et al., 2008; Zhang et al, 2013 and FDA guidance for industry: Assay development and validation for immunogenicity testing of therapeutic proteins, 2016.

Parameter	Value
Studentized residual threshold for outlier identification	2.58
Screening cut point method	floating
Screening cut point Percentile (%)	95
Confirmatory cut point Percentile (%)	99
Cut point Type	tolerance
Screening tolerance interval confidence level (%)	90
Confirmatory tolerance interval confidence level (%)	80
p-val threshold for Normality test	0.05
# Bootstrap samples	10000
Target probability LOW control well < fixed screening cut point (%)	1
Target probability NC control well > fixed screening cut point (%)	1
Failure to titer rate	1 in 10000

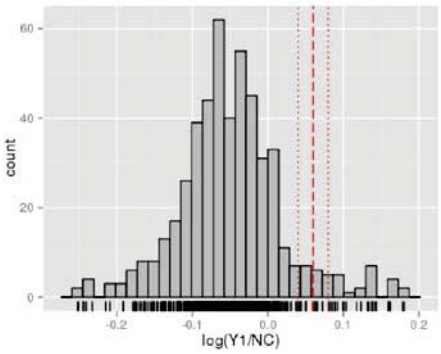
Histogram of floating screening assay values used to estimate the screening cut point



For T1DM serum

One hundred T1DM single–donor samples were used to determine the disease state assay screening cut point. Each sample was analyzed in duplicate in each analytical run. At least six analytical runs were performed over at least three days by at least two analysts. The mean ECL signal, standard deviation and %CV of each sample was determined. For the screening assay, a floating cut point was calculated to be 1.06. For sample analysis, T1DM cut point will be used for NHS, T1DM and T2Dm subjects undergoing immunogenicity analysis.

Histogram of floating screening assay values used to estimate the screening cut point in T1DM samples.

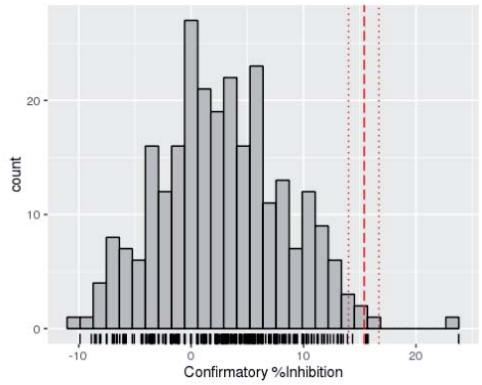


Confirmatory assay cut point:

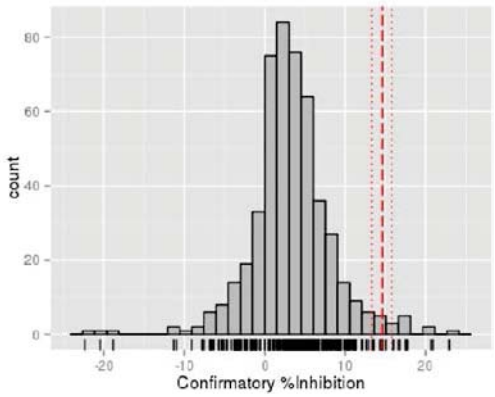
The tier 1 cut point determination was carried out in conjunction with the confirmatory cut point analysis. Confirmatory testing included the addition of excess LY900018 to show specificity of a positive signal through direct competition with excess unlabelled drug. During development of the assay, 1,2,5,10 and 20 µg/mL unlabelled LY900018 were shown to inhibit a positive signal. Sufficient inhibition was seen at concentrations greater than 2 ug/mL. Therefore, a concentration of 5ug/mL unlabelled LY900018 was chosen as it provided a 50 fold molar excess of the labelled API in the detection step of the assay. Samples were analyzed in the presence and absence of 5 µg/mL final concentration of LY900018. Samples without drug were used for determining screening cut point. The same NHS samples and T1DM samples will be used for confirmatory

assay cut point for NHS and T1DM. The monoclonal antibody pool will be used as the positive control material for this testing. The mean signal (ECL), change in ECL, and % inhibition for each naïve NHS sample, confirmatory NHS sample and positive assay control will be calculated. The confirmatory cut point was calculated to be 15.4 % for NHS and 14.6% for T1DM samples. For sample analysis, the T1DM confirmatory assay cut point (14.6%) will be utilized for NHS, T1DM and T2DM subjects undergoing immunogenicity analysis. Six screening biological outliers and 7 confirmatory biological outliers were eliminated from 100 total T1DM samples before determining the cut point.

Histogram of % inhibition values used to estimate the confirmatory cut point in NHS samples. The distribution appears normal.



Histogram of % inhibition values used to estimate the confirmatory cut point in T1DM samples



Reviewers comments:

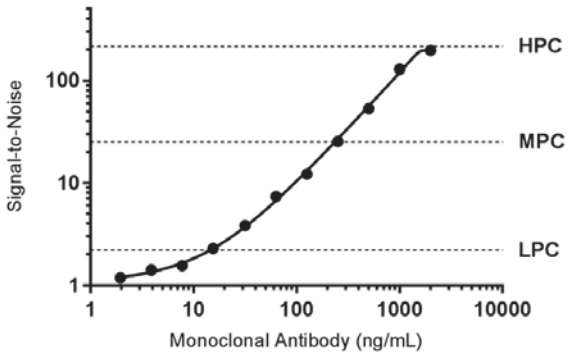
1. *Molar excess, inhibition of positive controls, acceptable confirmatory cut point and negative controls results support the selection of 5ug/mL unlabeled LY900018 to demonstrate specificity of a signal in the confirmatory step of the screening ADA assay.*
2. *Outliers were eliminated during tier1 and tier2 cut point analysis.*

3. *The assay variability was higher with a fixed cut point (11.4%) compared to a floating cut point (5.51%). Therefore, the use of floating cut point for the screening assay is acceptable.*
4. *When comparing the cut points of NHS and T1DM drug-naïve samples, the screening cut point was identical (1.06)*
5. *The tier 2 confirmatory cut point was different between NHS (15.4%) and T1Dm (14.6%). LY900018 treatment in intended for T1DM patients and so the use of T1DM cut point for the analysis is acceptable.*

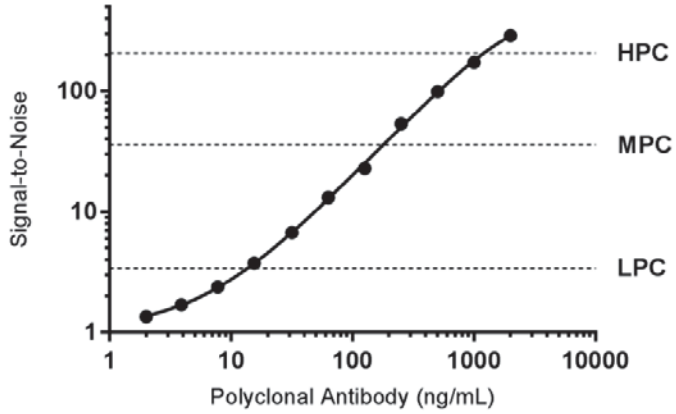
Assay controls:

High positive control (HPC), Medium positive control (MPC), Low positive control (LPC) and the negative controls were established at concentrations suitable to control the cut point and dynamic range levels by covering the upper and lower range of the linear portion of the sensitivity curve. The ranges were also set to correlate with clinically significant thresholds. Affinity purified anti-LY900018 rabbit polyclonal antibody diluted to 2000 ng/mL (HPC), 250 ng/mL(MPC), 16ng/mL (LPC) in normal human serum were used as assay controls. Unspiked pool was used as negative control. Four additional assay controls, anti-LY900018 monoclonal antibody pool diluted in NHS at 2000 ng/mL (HPC), 250 ng/mL(MPC), and 16 ng/mL (LPC) and unspiked pooled NHS(negative control) were used as assay controls. The monoclonal antibody pool is an equal molar mixture of recombinant mouse/human chimeric monoclonal antibodies IBA257, IBA297 and IBA 298 that target the N terminus, C terminus and Mid domain respectively of LY900018 respectively.

Quality control sample graph using monoclonal Anti-LY900018 antibodies



Quality control Sample graph using polyclonal anti-LY900018 antibodies.



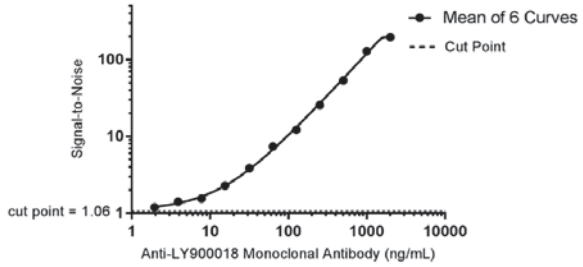
Reviewers comments:

The low positive control is well above the sensitivity of the assay. This may be adjusted to assess the consistency of sensitivity across runs.

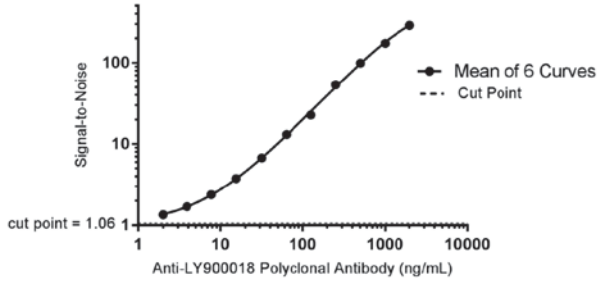
Sensitivity:

A pooled NHS sample was spiked with 4000 ng/mL anti-LY900018 rabbit polyclonal antibody or monoclonal antibody pool and then serially diluted twofold with pooled NHS starting from 2000 to 0 ng/mL. Independent curve preparations were performed over a period of 2 days by at least two analysts, with each analyst performing an equal number of assessments, so that at least six reportable results are generated. The mean signal was used to plot a dose response curve using a 5 parameter logarithmic algorithm. Two sensitivity determinations were made using interpolations of anti-LY900018 rabbit polyclonal antibody and monoclonal antibody pool concentration with cut point value. The sensitivity was determined to be **1.95 ng/mL for both monoclonal and polyclonal antibodies**.

Sensitivity using Monoclonal anti-LY900018 antibodies in human serum



Sensitivity using polyclonal anti-LY900018 antibodies in human serum



The screening assay cut point for T1DM serum was equal to the screening assay cut point for NHS. Therefore, the sensitivity will also be equal for both.

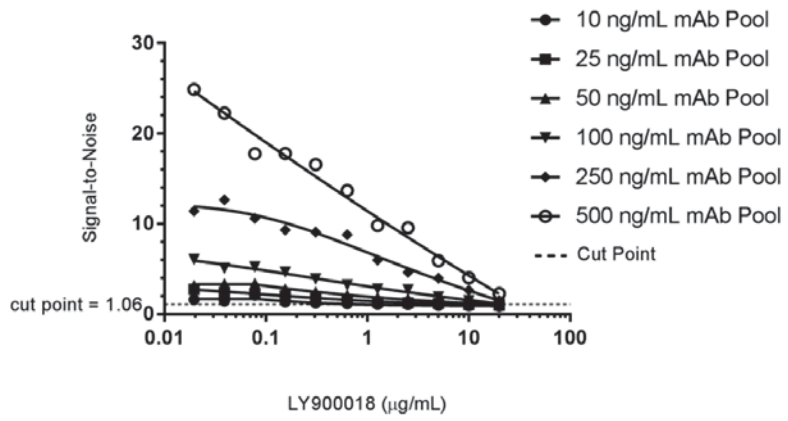
Reviewers comments:

1. *The recommended sensitivity for screening assay is ≤ 100 ng/mL. Sensitivity of 1.95ng/mL anti-LY900018 is acceptable.*
2. *Two fold dilution of the antibody was carried out in normal human serum (NHS) and so the matrix is undiluted. The final sensitivity is expressed as mass of antibody detectable/mL of undiluted matrix. This is acceptable.*

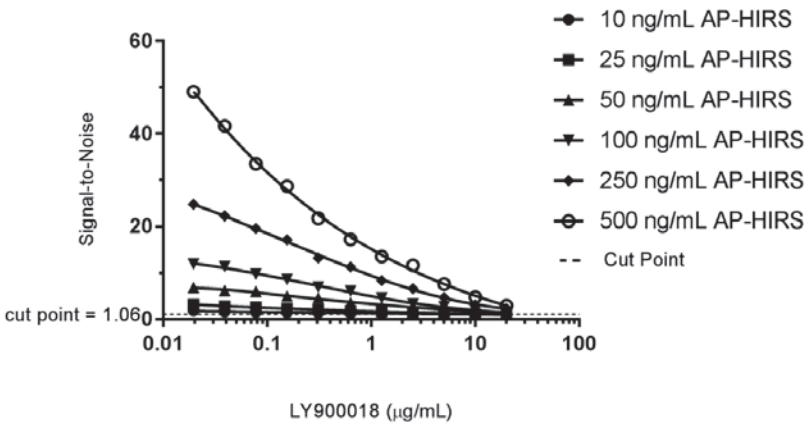
Drug Tolerance:

To mimic a patient sample that has been treated with LY900018, the drug will be added to the control antibody (polyclonal and monoclonal) at the sample dilution step. Final drug concentrations of 20, 10, 5, 2.5,1.25,0.625, 0.312, 0.156, 0.078, 0.039, 0.0195 and 0 ug/mL control antibodies with final concentrations 500, 250, 100, 50, 25 and 10 ng/mL were prepared in pooled human sera. Drug tolerance was determined to be more than 20ug/mL in the presence of 500 ng/mL of either polyclonal or monoclonal antibody pool.

Drug tolerance at different levels monoclonal anti-LY900018 antibody pool



Drug tolerance at different levels of polyclonal anti-LY900018 hyperimmunized rabbit serum



Reviewers comments:

1. *Affinity capture elution and neutralization is used to disrupt circulated ADA-Drug complexes. This is acceptable to increase drug tolerance of the assay.*
2. *The half-life of LY900018 is 15 minutes. The maximum anticipated concentration of LY900018 present in the serum during treatment is 1.45ng/mL. After administration of LY900018, the sampling time point for immunogenicity is days to weeks after treatment. Therefore the concentration is expected to be much lower and is not expected to interfere with the sensitivity of the screening assay.*

Titers:

The mid positive assay control anti-LY9000018 monoclonal antibody pool was serially diluted 1:2 using pooled NHS. Each dilution was analyzed in duplicate at a 1:10 MRD. The assay will demonstrate the ability to detect a positive sample to a level which falls below the assay cut point. The mid positive assay control was diluted to a titer of 1:128 to achieve a level that fell below the assay titer cut point of 1.08. T1DM serum samples had a titer cut point of 1.15. More data points were generated over longer time for the disease state cut point and the titer cut point for the T1DM samples were more representative of the variability. The T1DM cut point (1.15) was used for the sample analysis.

Dilution	1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512	1:1024	1:2048	1:4096
Mean of 6 curves	13.00	6.89	4.03	2.41	1.71	1.33	1.15	1.04	0.99	1.00	1.04	0.98

The anti-LY900018 antibody assay was able to titrate a positive sample to below the cut point for determination of titers.

Assay specificity:

Specificity was assessed using both monoclonal and polyclonal hyperimmunized rabbit serum. The controls were analyzed in the absence (naïve) and presence (confirmatory) of LY900018. In

all but one result, the inhibition of the negative control fell below 14.6% and the inhibition of all positive controls fell above 14.6%, indicating the suitability of this cut point to discriminate between positive and negative samples. The pooled NHS was also spiked with an irrelevant antibody at low (16ng/mL), mid (250ng/mL) and high (2000ng/mL) levels similar to the levels used for positive controls. The mean ECL signal for each concentration of irrelevant antibody was less than tier 1 cut point indicating the specificity of the assay. In addition, during assay development the ability of the ADA assay to sensitively detect IgA anti-glucagon antibodies was verified. Using the IgA anti-glucagon antibodies, the assay demonstrated a sensitivity of 1.7 ng/mL for tier 1 against a floating cut point of 1.06. Signal from IgA anti-glucagon ADA was also greatly inhibited by 5ug/mL glucagon, confirming the assay works for tier 2 confirmatory assay.

Reviewers comments:

1. *Specificity shown by the assay is acceptable.*
2. *Immune response for drugs administered through a mucosal route has the possibility of eliciting IgA response and testing the specificity of the assay to detect anti-LY900018 IgA antibody is useful.*
3. Note that depending on the observed immunogenicity rate for your product an assay to quantitate IgA specific anti-drug antibodies may be needed.
4. *The assay detects anti-LY900018 antibodies in normal human serum indicating the absence of interference from the matrix.*
5. *In the presence of an unrelated antibody the ECL signal was always below the cut point indicating the specificity of the assay.*

Interference:

The potential of icteric, lipemic and hemolyzed serum samples to interfere with the detection of anti LY900018 antibodies was analyzed by spiking bilirubin, cholesterol and hemoglobin in three different concentrations of anti-LY900018 antibodies. Interference was analyzed by spiking 80ug/mL of bilirubin, 10 mg/mL Intralipid and 2 mg/mL hemoglobin to represent the level under corresponding clinical conditions. The responses in all simulated samples indicated there was no interference by serum factors analyzed.

Stability:

Stability was demonstrated through 8 freeze/thaw cycles. The positive control antibody was also found to be stable for at least 48 hours at 2 to 8C or at 20 to 25 C.

Robustness:

Assay robustness was assessed using monoclonal assay controls along with 8 single donor NHS under predetermined, small but deliberate changes to the assay procedure as would be expected in day to day running of the assay. The following variables were assessed.

1. Instruments: Plates to be read on 2 different Meso Scale Discovery plate readers
2. Lot-to-lot variability: two combinations of pierce streptavidin and MSD plate lots
3. Slight shifts in incubation time +/-15% incubation time on all the assay steps, with the exception of the sample acidification step
4. Sample positional effects

When plate lots were compared with QC responses, variability was seen in streptavidin plates used in the assay. One lot was associated with assay failures. Streptavidin plates was therefore considered a critical reagent and a protocol to screen prior to use was established.

Assay precision:

The intra-assay (within run) and inter-assay (between run) precision of the anti-LY900018 assay were determined from results of each assay control prepared with monoclonal antibody pool, run at least 12 times. Each assay control was analyzed in duplicate wells in one run by a single analyst. The mean signal, SD, and % CV will be calculated. The inter-assay precision was determined from the results of each assay controls, both monoclonal and polyclonal pools run in at least 6 assays by at least two analysts over at least three days. The assay was run in the absence (naïve) and presence (confirmatory) of 5ug/mL final concentration of LY900018.

The intra-assay precision had a %CV less than 9% for all three levels of positive controls. The inter-assay had %CV of less than 18.7% for tier 1 and less than 9.2% for tier 2 for all three levels of positive controls.

Intra and inter assay precision from tier 1 and tier 2 assays using monoclonal pool and polyclonal antibodies

	AP-HIRS Monoclonal			AP-HIRS Polyclonal	
Control Level	Intra-Assay	Tier 1 Inter-Assay	Tier 2 Inter-Assay	Tier 1 Inter-Assay	Tier 2 Inter-Assay
Negative	7.9%	4.2%	55.8%	4.8%	81.7%
Low	5.1%	11.4%	9.2%	18.7%	8.8%
Mid	9.0%	10.6%	0.5%	10.3%	0.5%
High	6.1%	12.4%	0.4%	11.6%	0.3%

Reviewers comments:

1. *The tested conditions are commonly encountered clinical conditions known to interfere with the assessment of ADA. The strategy to test for interference from these factors is acceptable.*
2. *Stability, robustness and precision demonstrated by the validation are acceptable.*

Immunogenicity screening assay validation parameters

Assay Parameter	Result	Conclusion
MRD	1:20	A 1:20 MRD minimized serum interference relative to a buffer-only matrix, while also maintaining optimal sensitivity and drug tolerance.
Screening (Tier 1) Cut Point	Floating cut point was determined 1.06	Fifty-four commercial NHS samples and 100 T1DM baseline samples (12R-MC-BIAO) were investigated using the recommended experimental design and statistical analysis.[a] The cut point generated using NHS and T1DM samples was identical.
Confirmation (Tier 2) Cut Point	14.6% (Tier 2)	Fifty-four commercial NHS samples and 100 T1DM baseline samples (12R-MC-BIAO) were investigated using the recommended experimental design and statistical analysis.[a] The cut point generated using T1DM samples was chosen for analysis.
Outliers Eliminated During Tier 1 and 2 Cut Point Analysis	13/100 (13%)	Six screening biological outliers; 7 confirmatory biological outliers; based on 100 total T1DM samples.
Screening (Tier 1) Precision	Intra-assay: 5.1% to 9.0% CV Inter-assay: 10.3% to 18.7% CV	Intra- and inter-assay precision of the negative and 3 positive control Tier 1 signals were acceptable with %CV ≤20%.
Confirmation (Tier 2) Precision	Inter-assay: 0.3% to 9.2% CV	Inter-assay precision of the 3 positive control Tier 2 percent inhibitions was acceptable with %CV ≤20%.
Screening (Tier 1) and Confirmation (Tier 2) Positive Specificity	>55.8% inhibition for all positive controls	Positive controls demonstrated Tier 1 signal > screening cut point and Tier 2 inhibition >55.8% in the presence of 5-µg/mL API.
Screening (Tier 1) Negative Specificity	High S/N= 1.0; Mid S/N = 0.97; Low S/N = 0.96	Irrelevant antibody (polyclonal rabbit IgG) spiked into human serum at levels equivalent to the 3 positive controls resulted in a signal consistent with the negative control.

Assay Parameter	Result	Conclusion
Sensitivity	<1.95 ng/mL	Using both monoclonal antibodies and polyclonal AP-HIRS, the assay exceeds requirements of the 2016 FDA Guidance for sensitivity of 100 ng/mL to detect clinically relevant ADA.[b]
Drug Tolerance	>20 µg/mL at ADA concentrations of 100 ng/mL or higher	At a clinically relevant level of both monoclonal antibodies and polyclonal AP-HIRS, the assay demonstrated drug tolerance well above the maximum expected drug concentration (20 µg/mL).
Serum Factor Interference	Hemolysis: -2.4% to 8.3% difference Intralipid: 2.2% to 16.1% difference Bilirubin: -3.3% to 11.7% difference	Multiple serum factors evaluated did not significantly affect the ability of the assay to detect ADA.
Robustness	Robustness was acceptable. Streptavidin-coated plates will be considered a critical reagent	The assay was demonstrated to be robust with regard to incubation time, plate lots, and plate reader.
Stability	8 freeze–thaw cycles: -13.5% to 10.1% difference 4, 24, and 48 hours at ambient temperature (20°C to 25°C) and 2°C to 8°C: -3.9% to 14.5% difference	Samples are stable across 8 freeze–thaw cycles and at ambient temperature (20°C to 25°C) and 2°C to 8°C up to 48 hours, with all samples falling within a range of ±20% from reference values.
Titration	Mid-positive control titrates to a mean below the S/N of 1.15 at a 1:128 dilution. (Overall Titration including the MRD = 1:1280).	Demonstrated the ability of the assay to titrate a positive signal below the titer cut point of 1.15.

Neutralizing antibody assay:

The assay utilizes Human Embryonic Kidney (HEK) 293 cells stably transfected with the glucagon receptor and a cAMP responsive element-luciferase reporter (GRCRE cells). LY900018 binds to glucagon receptor resulting in induction of cAMP and thereby increase in luciferase reporter. Increasing concentration of LY900018 resulted in increase in luciferase expression by the cells. By maintaining a constant concentration of the drug and cell density in the assay system, Nabs are detected by a decrease in the luciferase expression as they inhibit LY900018 from binding to the glucagon receptor. When compared with the assay maximum control, a pool of NHS without NAb and stimulated with LY900018, the percent inhibition for a sample is calculated using the following formula

$$\%.. \ hibition = 100\ X \left(1 - \frac{(Sample\ Signal - Background\ Signal)}{(Assay\ Maximum\ Control - Background\ Signal)}\right)$$

Neutralization activity of ADAs relies on the inhibition of drug generated signal. The concentration of drug used for stimulation should be on the linear range of the potency curve and sensitive to low concentration of Nab. Multiple concentrations of drug ranging from the half maximal effective concentration to EC90 were tested for sensitivity, drug tolerance and approximated cut points. The concentration of 135 pg/mL LY900018 was chosen for stimulation of cells as it maintained sensitivity at low concentrations of Nab and resided in the linear portion of the curve.

Serum samples confirmed positive in tier 2 are analyzed for neutralizing activity. Samples are diluted 1:10 MRD using assay media containing LY900018. To capture the background of the assay, a NHS base pool is diluted 1:10 using assay media without LY900018. NHS samples (n=56) and 100 baseline serum samples from patients with T1DM from the clinical study were used to assess the cut point. ADA's are allowed to bind to drug in the assay media. After incubation, samples are transferred to a plate containing HEK293 GRCRE cells. The plate is incubated for four hours and exposed to Bright-Glo to measure luciferase activity. Samples containing neutralizing ADA inhibit the production of luciferase and thus luminescence.

Reviewers comments:
Use of a cell-based bioassay depending on the mechanism of action is recommended. The proposed strategy is a modification of the potency assay to assess the presence of neutralizing antibodies. This is acceptable.

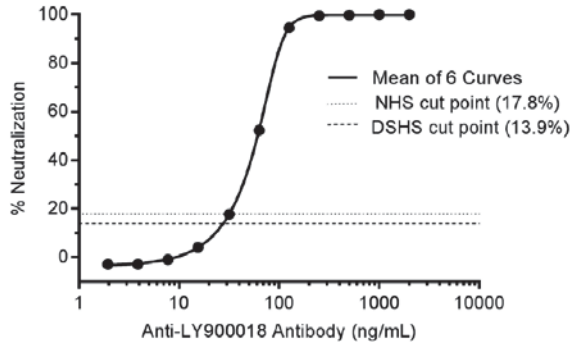
Cut point:
NHS samples (60 normal adults) were analyzed in the presence of 135 pg/mL LY900018 to determine the assay neutralizing cut point. The neutralization cut point is the level of response above which samples are classified as positive for neutralizing antibody. The resulting data was analyzed to calculate a cut point that would be expected to result in a false positive rate of approximately 1%. Cut point was calculated with 95 individual human serum samples from adults with T1DM to reflect the disease state. The neutralizing cut point for NHS was determined to be 17.8% and for T1DM was 13.9% (both calculated at the 99th percentile). The treatment is primarily aimed at T1DM patients and so the T1Dm cut point was used for the analysis of samples. All samples yielding a percent inhibition below the tier 4 cut point (13.9% inhibition) are reported as "not detected" for neutralizing antibodies. Outliers were eliminated before calculation of cut point.

Reviewers comments:

The neutralization cut point determined in the validation study is acceptable.

Sensitivity:

Positive controls consisted of IBA 297 and IBA 298 mAbs, diluted into the negative control base pool. Pooled NHS sample was spiked with 2000 ng/mL anti-LY900018 monoclonal antibody pool and then serially diluted with pooled NHS from 2000 to 0 ng/mL. The sensitivity of the method was determined to be **28.19 ng/mL** for anti-LY900018 monoclonal antibody pool using the T1DM cut point. The disease cut point was used for all the production runs.



Reviewers comments:

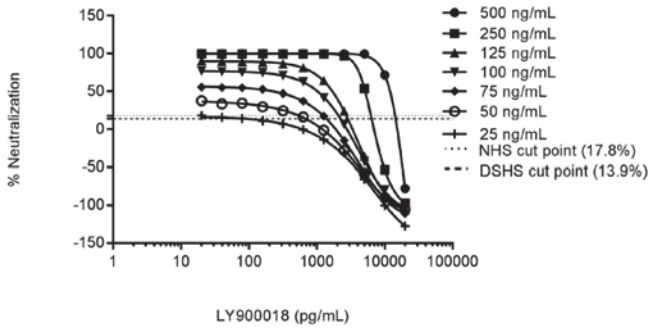
The sensitivity of the assay is 28.19 ng/mL. This meets the recommendation of less than 100 ng/mL and is acceptable.

Drug tolerance:

LY900018 was added to the control antibody pool at the sample dilution step to best approximate a sample from a patient treated with the drug. Assay tolerance to LY900018 was assessed. At 500, 250, 125 and 100 ng/mL of Nab, drug tolerance exceeded 2 ng/ mL. For 75 and 50 ng/mL Nab, the assay was tolerant to 1.4 and 0.7 ng of LY900018 respectively.

Reviewers comments:

The half-life of LY900018 is 15 minutes. The maximum anticipated concentration of LY900018 present in the serum during treatment is 1.45ng/mL. After administraton of LY900018, the sampling time point for immunogenicity is days to weeks after treatment. Therefore the concentration is expected to be much lower and is not expected to interfere with the sensitivity of the Nab assay.



Specificity:

Among the three anti-LY900018 monoclonal antibodies that formed the monoclonal antibody pool for the screening assay, IBA257 that binds to the n-terminal histidine residue of LY900018 was not a neutralizing antibody. This antibody was used as the specificity control for the neutralization assay. Serum factor interference was assessed by spiking bilirubin, intralipid and hemoglobin to mimic hyperbilirubinemia, lipemia and hemolyzed plasma. These factors did not interfere with the sensitivity and specificity of the assay.

Precision:

The intra assay precision was assessed from more than 12 reportable results for each assay control in 1 run by one analyst. The inter assay precision was calculated from all acceptable plates.

	%CV	
Control Level	Intra-Assay	Inter-Assay
Low	5.5	10.0
Mid	2.5	6.4
High	0.9	3.6

Neutralizing Immunogenicity assay validation parameters

Assay Parameter	Result	Conclusion
Potency	135 pg/mL API	135 pg/mL of API resided on the linear range of the potency curve and was sensitive to low concentrations of NAb.
MRD	1:10	A 1:10 MRD minimized serum interference relative to a buffer-only matrix, while also maintaining optimal sensitivity and drug tolerance.
Neutralizing (Tier 4) Cut Point	13.9% (Tier 4)	Sixty commercial NHS samples and 95 disease state (T1DM) baseline samples (12R-MC-BIAO) were investigated using the recommended experimental design and statistical analysis.[a] A statistically significant difference in cut point was identified between the 2 sample populations. The cut point generated using T1DM was chosen for analysis due to the intended patient population for LY900018.
Neutralizing (Tier 4) Precision	Inter-assay: 3.5% to 9.4% CV	Inter-assay precision of the 3 positive control Tier 4 percent inhibitions was acceptable with %CV ≤20%.
Neutralizing (Tier 4) Positive Specificity	67.8% to 84.4% inhibition at MPC and HPC, respectively. LPC inhibited 45.6%	MPCs and HPC generated >50% inhibition. The LPC also generated inhibition greater than the determined cut point of the assay (13.9%).
Neutralizing (Tier 4) Negative Specificity Binding	Tier 4 signal = -3.4% to 0.2% inhibition	The non-neutralizing anti-glucagon antibody control, IBA 257 spiked into buffer at levels equivalent to all 3 positive controls gave a Tier 4 signal ≤ Tier 4 cut point.
Neutralizing (Tier 4) Negative Specificity Non-binding	Tier 4 signal = 0.2% to 4.5% inhibition	The nonbinding isotype-matched antibody 4H9 spiked into buffer at levels equivalent to all 3 positive controls gave a Tier 4 signal ≤ Tier 4 cut point.
Sensitivity	28.19 ng/mL	The assay exceeds requirements of the 2016 FDA Guidance for sensitivity of 100 ng/mL to detect clinically relevant ADA.[b]
Drug Tolerance	2.22 ng/mL	At a clinically relevant level of anti-glucagon neutralizing monoclonal antibodies IBA 297 and IBA 298 (100 ng/mL), the assay demonstrated drug tolerance above expected drug concentrations at the time of immunogenicity sampling.

Assay Parameter	Result	Conclusion
Serum Factor Interference	Hemolysis: 0.5% to 18.3% difference Intralipid: -1.9% to 3.7% difference Bilirubin: -2.4% to 10.0% difference	Multiple serum factors evaluated did not significantly affect the ability of the assay to detect ADA.
Robustness	Robustness was deemed to be acceptable	The assay was demonstrated to be robust with regard to instrument (plate readers), plate lots, and incubation times (±10% on all assay steps, shifts in API concentration: ±10%, variation in cell plating density: ±10%, variation in cell passage: passage 5 to 20).
Stability	9 freeze–thaw cycles: -3.8% to 8.2% difference 4 and 24 hours at ambient temperature (20°C to 25°C): -12.6% to 0.7% difference 4, 24, and 48 at 2°C to 8°C: -6.0% to -1.0% difference	Samples are stable across 9 freeze–thaw cycles and at ambient temperature (20°C to 25°C) for up to 24 hours and 2°C to 8°C up to 48 hours, with all samples falling within a range of ±25% from reference values.

Abbreviations: ADA = antidrug antibody; API = active pharmaceutical ingredient in LY900018, which is synthetic glucagon; CV = coefficient of variation; FDA = Food and Drug Administration; HPC = high positive control; LPC = low positive control; MPC = mid-positive control; MRD = minimal required dilution; NAb = neutralizing antibody; NHS = normal human serum; T1DM = type 1 diabetes mellitus.

[a] The cut point estimation method is based on a consensus reading of the published literature and regulatory guidelines (Shankar et al. 2008; Hoffman and Berger 2011; Gupta et al. 2011; Zhang et al. 2013; FDA 2016). Key components of this calculation include removal of outlier analytical values, outlier biological samples, and appropriate use of parametric or nonparametric estimates based on normality tests.

[b] FDA 2016.

Source: Validation Report 16-189-121.

Reviewers comments:

Overall, the sensitivity, drug tolerance, precision, specificity, robustness of the neutralizing antibody assay is acceptable for the detection of neutralizing anti-LY900018 antibodies.

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/

MOHANRAJ MANANGEESWARAN
02/21/2019 12:19:42 PM

DANIELA I VERTHELYI
02/21/2019 12:22:32 PM

LABEL AND LABELING AND HUMAN FACTORS RESULTS REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
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:	January 30, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 210134
Product Name and Strength:	Baqsimi (glucagon) nasal powder, 3 mg
Product Type:	Combination Product (Drug-Device), Single Ingredient
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly and Company
FDA Received Date:	June 28, 2018 and September 27, 2018
OSE RCM #:	2018-1387 and 2018-1416
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD
Associate Director for Human Factors:	Quynh Nhu Nguyen, MS
Associate Director	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

The Division of Metabolic and Endocrinology Products (DMEP) requested that DMEPA review the human factors (HF) validation study report and proposed labels and labeling submitted under NDA 210134 for glucagon nasal powder, submitted on June 28, 2018.

2 PRODUCT INFORMATION

Lilly submitted NDA 210134 for Baqsimi (glucagon), which will be supplied as a nasal powder, for the emergency treatment of severe hypoglycemia in adult and pediatric patients. The proposed nasal delivery device is a prefilled, single-dose device that is intended to deliver one dose of glucagon to the nasal mucosa of a patient experiencing a severe hypoglycemic episode. Each device contains 3 mg of glucagon and will be supplied in a carton containing one device inside a shrink-wrapped sealed tube with printed instructions. Of note, users are expected to carry the sealed tube containing the nasal delivery device without the carton, so instructions are included on the outside of the device and tube when the printed IFU may be unavailable.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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
Human Factors Study	C
ISMP Newsletters	n/a
FDA Adverse Event Reporting System (FAERS)*	n/a
Review of Product Sample	D
Information Requests	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the human factors validation study results and we performed a risk assessment of the proposed labeling to identify areas of vulnerability that may lead to medication errors and other areas of improvement.

4.1 HUMAN FACTORS VALIDATION STUDY RESULTS

The sections below provide a summary of the study design, errors observed with the critical tasks (Table 2), and our analysis of the HF validation study results.

4.1.1 SUMMARY OF STUDY DESIGN

Lilly conducted a Human Factors validation study designed to provide data to support that the intended users could use the Baqsimi nasal powder device to administer doses and comprehend the product instructions in an emergency.

The usability study was conducted with 45 representative users: 15 adolescents aged 10-17 years (7 familiar with diabetes and 8 unfamiliar with diabetes), 15 adults ≥18 years of age (11 familiar with diabetes and 4 unfamiliar with diabetes), and 15 healthcare providers (3 emergency room physicians, 7 nurses, 5 emergency medical technicians). All study participants were untrained, and they were not shown the product prior to completing the study tasks; however, they were provided a general overview of the study's purpose.

Each participant was asked to simulate administering a dose of glucagon nasal powder after being presented with a manikin either lying on the floor or seated in an upright position with the tube containing the product, which included instructions on the tube label and device label, and the paper IFU on a table nearby. In addition, a sound machine was used to create beeping sounds, which increased in pitch, frequency, and intensity for the duration of the task to simulate a stressful environment. After the administration tasks were completed, participants were asked knowledge questions related to information provided in the product labeling.

We note that study participants having access to the paper IFU may not be representative of real-world use of the product. We expect that some users discard ancillary packaging materials when storing products; therefore, they may only have access to the instructions on the nasal device and tube label when administering the product. We determined that the study methodology may not reflect the most vulnerable scenarios with users who would need to rely on the device and tube labeling only. Thus, we have provided recommendations to the sponsor regarding their study methodology.

4.1.2 STUDY RESULTS AND ANALYSIS

Table 2 below summarizes and focuses on the results observed with the critical task, including knowledge tasks, which were evaluated in the HF validation study along with the root cause analysis that Lilly provided for each failure. The table also includes our assessment of the critical task failures. Of note, Lilly did not propose any further mitigation strategies to address the failures identified in the study.

Table 2: Human Factors Validation Study Results				
Tasks[a]	Use Errors	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Usability Task 4: Depress plunger to administer the dose	<u>3 errors:</u> -2 adolescents familiar with diabetes -1 adult familiar with diabetes and glucagon injections The adolescent participants failed to push the plunger far enough to actuate the device (i.e., until the green line was no longer visible). The adult participant placed the device in the nostril without pressing the plunger and indicated that he expected it to automatically actuate like an EpiPen. Of note, each of these participants were able to successfully complete this	The sponsor attributed these errors to the participants' failure to read the instructions prior to attempting to administer the dose. In addition, the adolescents' errors were attributed to a lack of familiarity with the device and the expectation that the nasal device would work similarly to OTC nasal sprays which require repeated sprays into the nostril vs. one forceful spray.	The sponsor expects that caregivers will be familiar with the device prior to use, unlike in this simulated study, and will have either read the IFU or received counseling from the prescribing physician or pharmacist prior to use. In addition, they expect that the first instruction in the paper IFU, which provides the recommendation to show family and friends the product and instructions before they are needed, is sufficient to ensure that participants are familiarized with the product before an emergency arises. The sponsor concludes that the device design and instructions are sufficient to mitigate for the failure to	Our assessment indicated that there is a risk for patient harm associated with this error. As noted with these failures, caregivers may not realize that they did not administer the full dose of glucagon. In addition, patients requiring glucagon therapy are typically unconscious and would not be able to communicate to the caregiver whether they received the dose. Per the sponsor's December 20, 2018 response to our information request (see Appendix E), one adolescent participant used the images in the paper IFU and the other used the

[a] All study tasks were classified as critical.

Table 2: Human Factors Validation Study Results				
Tasks[a]	Use Errors	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	task after they were asked to refer to the instructions in the paper IFU.		fully actuate the device; thus, they determined that no further mitigation is required.	instructions on the nasal device to complete the task the first time, while the adult participant was noted as using the instructions on the tube. For the second attempt, they were able to successfully complete the task when referred to the paper IFU. As noted previously, we expect that users may only have access to the instructions on the nasal deice and tube label in actual use, so we are concerned that users had the option to also refer to the paper IFU. In addition, we note that the device must be fully actuated to administer the dose and it is not designed to provide partial doses. Therefore, if the plunger is not fully depressed, the patient will

Table 2: Human Factors Validation Study Results				
Tasks[a]	Use Errors	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				not receive the intended therapy. We acknowledge that the sponsor has included multiple statements in the labeling (nasal device label, tube label, and IFU) to indicate that the plunger must be pressed until the green line is no longer showing to administer the full dose. However, we determined that additional clarity is needed to highlight that information on the nasal device label and tube label. Please see our recommendations in Section 5.2 (bullets B1 and C4).
Knowledge Assessment Question 2: "What do the instructions	<u>1 error:</u> -1 adolescent unfamiliar with diabetes	The sponsor attributed these errors to the participant's apparent confusion over the statements (b) (4)	The sponsor indicated that this failure would not result in clinical consequences in actual use because this error would not prevent delivery of the dose and	Our assessment indicated that there is risk for patient harm associated with this error considering that product degradation may occur if the product is

Table 2: Human Factors Validation Study Results				
Tasks[a]	Use Errors	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
say about when to open the tube?"	This adolescent participant was unable to find the information to answer this question on the label and indicated confusion with the use of yellow blocks to separate the instructions.	(b) (4) on the outside of the sealed tube. This participant correctly answered the prior question about leaving the shrink wrap on the tube until it is ready to be used.	determined that the current warnings on the tube label are sufficient. Thus, they determined that no further mitigation is required.	removed from the tube and stored improperly. Therefore, we would expect that patients may not receive the full therapeutic effect from the glucagon dose administered. We note that sponsor has included multiple statements in the labeling (nasal device label, tube label, and IFU) to indicate that tube containing the device should remain sealed until the dose is to be administered. However, we note that the location of the warnings "Do not remove the shrink wrap until ready to use." and "Do not open the tube until ready to use." are located on the side panel and, as noted through subjective feedback provided after these failures, users may

Table 2: Human Factors Validation Study Results				
Tasks[a]	Use Errors	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				over look this important information. (b) (4) [redacted] Therefore, we determined that that the labeling on the tube could be revised to increase the visibility of these warnings. Please see our recommendations in Section 5.2 (bullet C3).
Knowledge Assessment Question 3: "According to the materials, what are you supposed to do after giving the dose?"	<u>4 errors:</u> -1 adolescent unfamiliar with diabetes -2 adults familiar with diabetes and glucagon injections -1 adult familiar with diabetes but unfamiliar with glucagon injections	The sponsor attributed these errors to the participants' failure to notice the "Peel (b) (4) [redacted] statement on the tube label and the assumption that the information on the flap was not important for use of the product.	The sponsor indicated that this failure would not result in clinical consequences in actual use because this error would not prevent delivery of the dose and determined that the current warnings on the tube label are sufficient. Thus, they determined that no further mitigation is required.	Our assessment indicated that there is risk for patient harm associated with this error considering that the product is to be administered in an emergency that may require further medical attention, as noted through subjective feedback provided after these failures, users may over

Table 2: Human Factors Validation Study Results				
Tasks[a]	Use Errors	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
	Each of these participants failed to identify the warning on the tube label that provided instructions to call for medical help after giving the dose. Of note, the participants had to pull back a tab on the tube label, per instructions to "Pee (b) (4) to access these instructions and each participant overlooked those instructions. However, 3 of the 4 participants did state that they would call 911 for assistance after giving the dose in actual use.			look this important information. We note that sponsor has included the statement "Call for medical help right away." as the third bullet located inside the flap of a peel apart label on the tube label. However, as evidenced by the HF study results, users may not pull back the tab to reveal this information. In addition, we reason that it is important for the instructions to reflect that medical help would be needed after administering the dose to ensure consistency with the prescribing information. Therefore, we determined that that the labeling on the tube could be revised by increasing the visibility of this warning. Please see

Table 2: Human Factors Validation Study Results				
Tasks[a]	Use Errors	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				our recommendations in Section 5.1 (bullet B5) and Section 5.2 (bullet C5).
Knowledge Assessment Question 5: "According to the materials, how many times can a device be used?"	1 error: -1 adolescent familiar with diabetes This participant was unable to locate the information on the tube label which indicates that the device should only be used once.	The sponsor attributed these errors to the participant's apparent confusion over the statement (b) (4) on the outside of the sealed tube and an inability to understand the meaning of the phrase (b) (4)	The sponsor indicated that this failure does have the potential to result in a delay of therapy if the user were to keep a used device with the belief that it could be used again. The sponsor determined that the risk for this error is adequately mitigated by the design of the device (i.e., the plunger stays down, the green line is hidden after actuation). In addition, they have included statements on the labeling to indicate that the device is for a single use. Thus, they determined that no further mitigation is required.	Our assessment indicated that there is risk for patient harm associated with this error considering the product is to be administered in an emergency. We note that sponsor has included multiple statements in the labeling (nasal device label, tube label, and IFU) to indicate that the nasal device only contains a single dose, including a statement located inside the flap of a peel apart label on the tube label. However, we determined that additional clarity could be provided to highlight that information on the carton and device labels.

Table 2: Human Factors Validation Study Results				
Tasks[a]	Use Errors	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				Please see our recommendations in Section 5.1 (bullet B4) and Section 5.2 (bullets C1 and E1).

4.2 LABELS AND LABELING

In addition to the human factors study evaluation, DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We noted that additional modifications are needed to improve the clarity and readability of important information on the proposed labeling and we provide recommendations in Section 5.1 for the Prescribing Information (PI) and Instructions for Use (IFU) and in Section 5.2 for the container labels and carton labeling.

5 CONCLUSION & RECOMMENDATIONS

Our review determined that the study results do not support that users can use the Baqsimi nasal powder device and associated labeling to administer doses correctly because there were failures performing the critical task of depressing the plunger to administer the dose. In addition, we identified several areas of improvement and we provide recommendations to the product labeling, based on the study results, safety concerns, and post-market experience with other glucagon products.

In addition to the recommendations provided, we recommend that Lilly implement any other changes that they consider to be necessary, finalize the proposed to-be-marketed product, and conduct a supplemental usability study to demonstrate safe and effective use of the product by the intended users for its intended uses and use environments. We also have recommendations regarding the study methodology which Lilly should incorporate for the supplemental study.

Our recommendations for the prescribing information and Instructions for Use are provided in Section 5.1 and the carton and container labeling recommendations provided in Section 5.2.

5.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Highlights of Prescribing Information
    a. Under the Dosage and Administration heading, we recommend adding the following bulleted statements:
        - "Baqsimi is for intranasal use only.
        - Seek emergency medical care immediately after use.
        - Administer a single 3 mg dose into one nostril."
    b. Under the Dosage Forms and Strengths heading, we recommend revising the statement to read as follows: "Nasal powder: 3 mg of glucagon per device"

2. Dosage and Administration Section 2
    a. Consider moving the dosing information to Section 2.2 and making Important Administration Instructions Section 2.1.
    b. Under Important Administration Instructions, we recommend revising the section to read as follows:

"Baqsimi is for intranasal use only [redacted]

Because treatment of severe hypoglycemia must be performed by someone other than the patient, instruct the prescription recipient to inform those around them about Baqsimi and Instructions for Use.

Instruct the patient or caregiver to read the Instructions for Use at the time they receive a prescription for BAQSIMI. Emphasize the following instructions to the patient or caregiver:
[redacted]

- Do not attempt to reuse Baqsimi. Each Baqsimi device contains a single dose of glucagon and cannot be reused.
- Administer Baqsimi according to the printed instructions on the [redacted] the Instructions for Use.
- Do not [redacted] or test the device prior to administration.
- To administer the dose, [redacted] until the green line is no longer showing.
- Call for emergency medical [redacted] immediately after administering the dose."

c. Under Dosing in Adults and Pediatric Patients, we recommend revising the statement to read as follows: [redacted]

3. How Supplied/Storage and Handling Section 16
   a. Under How Supplied Section 16.1, we recommend revising the section to read as follows:

      "Baqsimi is supplied as a [redacted] intranasal device containing 3 mg of glucagon [redacted] as a preservative free white powder.

      - Baqsimi [redacted] pack: carton containing one (1) intranasal device (NDA 0002-6145-11)
      - Baqsimi two pack: carton containing two (2) intranasal devices (NDA 0002-6145-27)

      [redacted]

B. Instructions for Use
   1. We recommend adding an image of the device that identifies the parts. Consider also including an image of the labeled product in the tube in addition to the image of the nasal device.

2. Under the Important Points to Know heading, we recommend revising the bulleted statement [redacted] as follows: "Do not remove the shrink wrap or test the Baqsimi device until ready to use."
3. Under the Important Points to Know heading, we recommend adding the following as a bulleted statement: [redacted]
4. Due to the knowledge assessment error associated with failure to understand that the device is for a single use observed in the HF study, we recommend moving the statement [redacted] From the "[redacted]" section to Step 3 as the part of the step.
5. Due to the knowledge assessment errors associated with contacting medical help after administering the dose observed in the HF study, we provide the following recommendations regarding the "After Giving [redacted]" section of the IFU.
    a. We recommend that this information is designated as a fourth step and revise the order as follows:

        "Step 4:

        - Call for medical help right away.
        - Encourage the person to eat as soon as possible.
        - If the person is unconscious, turn the person on their side [redacted]"

5.2 RECOMMENDATIONS FOR ELI LILLY

We note that the results of your Human Factors (HF) validation study showed that multiple study participants failed to administer a dose of the Baqsimi nasal powder device correctly. Our review of the instructions for use (IFU), carton labeling, and container label identified several areas that should be modified. Please see our recommendations below.

In addition to the recommendations provided, we recommend that you implement any other changes that you consider to be necessary to further address the failures noted in your HF validation study, finalize your proposed to-be-marketed product, and conduct a supplemental human factors validation study to demonstrate safe and effective use of the product by the intended users for its intended uses and use environments.

Of note, your validation study protocol submitted on October 25, 2018 stated that the paper IFU would not be provided during the validation study. However, your November 13, 2018 response clarified that you decided to include the paper IFU during the simulation to be more realistic. We note that in actual use, some users may discard ancillary packaging materials when storing products. Therefore, as you conduct your supplemental HF validation study, we recommend that participants only have access to the nasal device label and the sealed tube labeling to represent a real-world use scenario.

A. General Comments (container labels and carton labeling)

1. We recommend revising the statement "(b) (4)" to read "For Nasal Use Only". In addition, we recommend increasing the prominence of this statement for improved readability.
2. We note that the container label (attached to inhaler) uses a different NDC than the carton and container (attached to sealed outer tube) of 1 unit. The NDC for each should be the same; therefore, please revise the NDC numbers so that the device, tube, and carton labels use the same NDC.
3. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the 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 a space be used to separate the portions of the expiration date.

B. Container Label (attached to inhaler)
1. Under step 1, we recommend updating the image to bring more attention to the green line on the plunger to ensure consistency across the different labeling components for the proposed product. For example, consider incorporating the following cutout from the image used in "Step 1: Giving the Dose" of the proposed IFU.

C. Container Labeling (attached to sealed outer tube)
1. We recommend revising the statement (b) (4) as follows for improved clarity: "1 (b) (4) dose (b) (4)".
2. We recommend that you consider moving and unbolding the "Rx only" statement below the net contents statement on the PDP as this information appears more prominent than the other information on the label.
3. We recommend removing the statements "Do not remove shrink wrap until ready to use. Do not open the Tube until ready to use." from the label because they may be easily overlooked in the current location, as noted in the HF study. We recommend adding the following statement to the shrink wrap on the tube instead: "Do not open or remove wrap until ready to use."

4. Under step 1, we recommend updating the image to bring more attention to the green line on the plunger and to ensure consistency across the different labeling components for the proposed product. For example, consider incorporating the following cutout from the image used in "Step 1: Giving the Dose" of the proposed IFU.

5. We recommend adding the following information as step 4 on the label: "Call for medical help right away." This important step may be easily overlooked in its current location (b) (4) as we noted that multiple study participants overlooked the recommendation to (b) (4)
6. Consider reorienting the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to the curvature of the tube.

D. Carton Labeling

1. On the principle display panel (PDP), we recommend revising the statement (b) (4) to read as follows: "Contains 1 (or 2) (b) (4) nasal device(s). Keep tube sealed until ready to use."
2. On the side panel, we recommend adding the following statement after "Keep Baqsimi in the shrink-wrapped tube until ready to use.": (b) (4)
3. We recommend adding the use instructions to the side panel of the carton labeling for improved readability of the summary instructions included on the tube and device labels.
4. As dose is constant and does not vary, we recommend removing the statement "see accompanying (b) (4)" and providing the specific dose information on the side panel per 21 CFR 201.55.
5. The placement of the graphic right before the proprietary name competes with the readability of the proprietary name which may lead to misinterpretation of the proprietary name. We recommend moving or decreasing the prominence of the graphic before the proprietary name.

In addition to the labeling comments, our evaluation of the product sample determined that the green line on the device should be more prominent as it is a critical visual indicator for

complete product administration. Therefore, we recommend that you consider making the green line on the plunger wider so that it is more visible to users.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Baqsimi received on June 28, 2018 from Eli Lilly.

Table 2. Relevant Product Information for Baqsimi	
Initial Approval Date	n/a
Active Ingredient	glucagon
Indication	treatment of severe hypoglycemia in adult and pediatric patients with diabetes
Route of Administration	intranasal
Dosage Form	Nasal powder
Strength	3 mg
Dose and Frequency	A single 3 mg dose delivered intranasally
How Supplied	single-use nasal dosing device containing 3 mg of glucagon available in a shrink-wrapped packaging containing 1 device or 2 devices
Storage	temperatures up to 30°C (86°F); keep in the shrink-wrapped packaging until ready to use

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 28, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, glucagon AND 110674. Our search identified 0 previous reviews.

APPENDIX C. HUMAN FACTORS STUDY

The following HF study documents can be assessed in the EDR via the following links:

HF Results report: \\cdsesub1\evsprod\nda210134\0000\m3\32-body-data\32r-reg-info\32r-medical-device-app-a-hfe-v001.pdf

Residual Risk report: \\cdsesub1\evsprod\nda210134\0000\m3\32-body-data\32r-reg-info\32r-medical-device-app-c-rrr-v001.pdf

Medical Device Description report: \\cdsesub1\evsprod\nda210134\0000\m3\32-body-data\32r-reg-info\32r-medical-device-v001.pdf

APPENDIX D. REVIEW OF PRODUCT SAMPLE[b]

We received 5 product samples for evaluation. Our evaluation confirmed that the device has multiple indicators to signify that the entire dose of glucagon powder has been administered: (b) (4) the green line is no longer visible, and the plunger is inaccessible. We find that these features should indicate to users that the device has been actuated to administer the dose and is no longer useable, especially if the user is slightly familiar with the product's labeling prior to attempting to administer a dose.

Device

The device is single use, and contains a dose of nasal glucagon. The user interface is shown in Figure 1.

(b) (4)

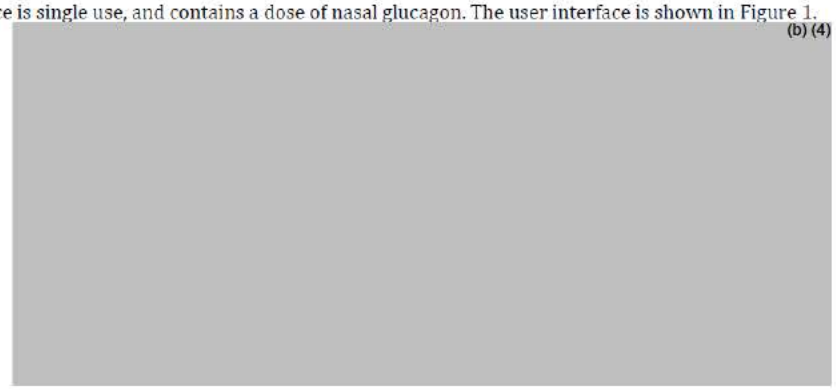


Figure 1. Nasal glucagon device

(b) (4)

[b] Images from the HF Results report submitted to the EDR on June 28, 2018: \\cdsesub1\evsprod\nda210134\0000\m3\32-body-data\32r-reg-info\32r-medical-device-app-a-hfe-v001.pdf

APPENDIX E. INFORMATION REQUESTS

Information request sent on October 17, 2018 to request the study protocol report, including the moderator script. In addition, we requested clarification regarding the failures with fully actuating the nasal device.

Lilly's response was submitted to the EDR on October 25, 2018:
\\cdsesub1\evsprod\nda210134\0009\m1\us\1111-quality-response-to-questions-17-oct-2018.pdf

Information request sent on November 9, 2018 to request clarification regarding a discrepancy in the study protocol and study results reports regarding the use of the paper IFU during the validation study.

Lilly's response was submitted to the EDR on November 13, 2018:
\\cdsesub1\evsprod\nda210134\0014\m1\us\1111-quality-response-to-question-09-nov-2018.pdf

Information request sent on December 17, 2018 to request clarification regarding the parts of the product labeling used by study participants during the study (instructions on the tube, instructions on the nasal device, or the paper IFU).

Lilly's response was submitted to the EDR on December 20, 2018:

\\cdsesub1\evsprod\nda210134\0020\m1\us\1111-quality-response-to-question-17-dec-2018.pdf

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,[c] along with postmarket medication error data, we reviewed the following Baqsimi labels and labeling submitted by Eli Lilly.

- Container label received on June 28, 2018
- Carton labeling received on June 28, 2018
- Instructions for Use received on June 28, 2018
  - \\cdsesub1\evsprod\nda210134\0000\m1\us\proposed-usermanual-clean.docx
- Patient Package Insert received on June 28, 2018
  - \\cdsesub1\evsprod\nda210134\0000\m1\us\proposed-ppi-clean.docx
- Prescribing Information received on September 27, 2018
  - \\cdsesub1\evsprod\nda210134\0004\m1\us\proposed-uspi.docx

F.2 Label and Labeling Images

Container Label (attached to inhaler)

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

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

---

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/

ARIANE O CONRAD
01/30/2019 08:09:50 AM

HINA S MEHTA
01/30/2019 09:36:56 AM

QUYNHNHU T NGUYEN
01/30/2019 10:47:10 AM

MISHALE P MISTRY
01/30/2019 10:50:46 AM

ICCR QUALITY SYSTEM REVIEW MEMO

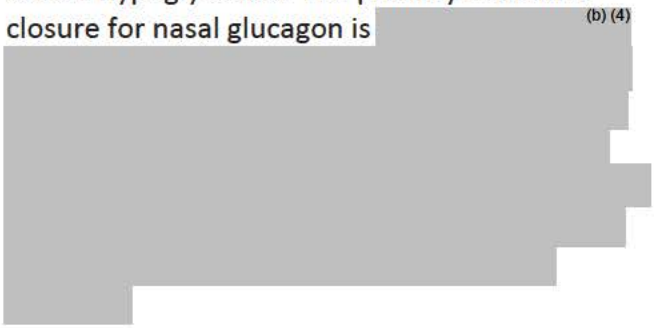
Date:	November 14, 2018
To:	Matthew Ondeck, ICCR Lead Reviewer, Office of Gastrorenal, ObGyn, General Hospital and Urology Devices, Matthew.Ondeck@fda.hhs.gov
Through:	M. Isabel Tejero del Rio, Lead CSO, Office of Gastrorenal, ObGyn, General Hospital and Urology Devices, Isabel.Tejero@fda.hhs.gov
From:	Leslie E. Dorsey, CSO, Office of Gastrorenal, ObGyn, General Hospital and Urology Devices, Leslie.Dorsey@fda.hhs.gov
Applicant/Licensure:	Eli Lilly and Company Lilly Corporate Center, Indianapolis, IN 46285 FEI #1819470
Submission (Type & Number):	NDA 210134
Combination Product Name:	BAQSIMI, Glucagon Nasal Powder
Combination Product Indications for Use:	Severe Hypoglycemia
Device Constituent (Type):	Nasal Inhaler or Spray
ICCR Sharepoint Tracking Number:	ICCR2018-03380
ICCR CTS Tracking Number:	ICC1800591

Pre-Approval Facility Inspection:	Yes, Post-Approval Inspections Also Requested
Documentation Review (Status):	Information Inadequate/IR
CDRH/OC Recommendation:	Withhold

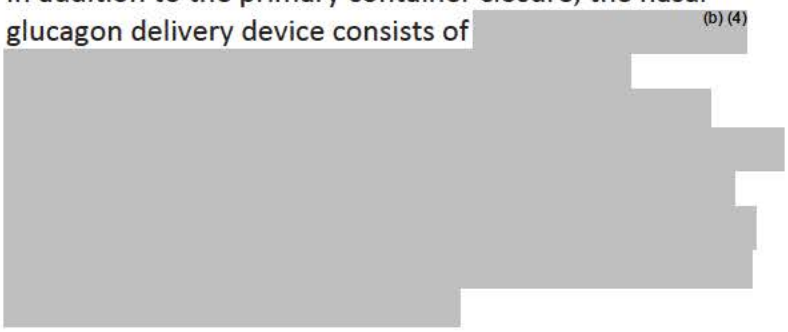
CDRH received a consult from CDER requesting the identification of the device manufacturing sites for NDA 210134 which will require a device inspection.

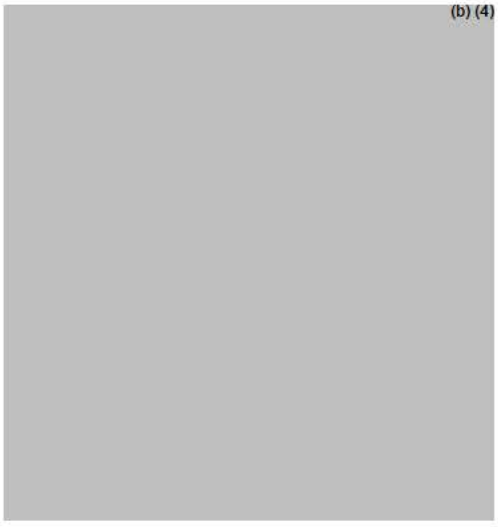
PRODUCT DESCRIPTION

BAQSIMI, Glucagon Nasal Powder, is intended for severe hypoglycemia. The primary container closure for nasal glucagon is (b) (4)



In addition to the primary container closure, the nasal glucagon delivery device consists of (b) (4)





REGULATORY HISTORY

The following facilities were identified as being involved in the manufacturing and/or development of the combination product, BAQSIMI, Glucagon Nasal Powder, in NDA 210134.

Combination Product Applicant

Firm Name: Eli Lilly and Company

Address: Lilly Corporate Center, Indianapolis, IN 46285

FEI #1819470

Responsibility – Eli Lilly and Company is the applicant for this combination product and therefore, has overall responsibility for all manufacturing sites. In addition, it is responsible for the drug product packaging and labeling.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

Inspection Recommendation:

A pre-approval inspection is required because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
- A recent medical device inspection of the firm has not been performed.

Finished Combination Product Manufacturer

(b) (4)

Responsibility – Manufacture of the dosage form and device assembly; primary and secondary packaging and labeling; quality control testing – visual/functional device inspection.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted (b) (4). The inspection covered drug CGMP and was classified NAI.

Inspection Recommendation:

A post-approval inspection is required because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,

- A recent medical device inspection of the firm has not been performed.

DOCUMENTATION REVIEW

Device Consituent Part Type: Nasal Inhaler or Spray

Device Consituent Part Class II

Combination Produc NDA 210134 Proposed Indication for Use: Severe Hypoglycemia

1. Was the last inspection of the finished combination product manufacturing site, (b) (4) OAI for drug or device observations?	YES ☐	NO ☒	NA ☐
2. Is the device constituent a PMA or class III device?	YES ☐	NO ☒	UNK ☐
3. Is the final combination product meant for emergency use?	YES ☒	NO ☐	UNK ☐
4. Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	YES ☒	NO ☐	UNK ☐
5. Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	YES ☐	NO ☒	UNK ☐
6. Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	YES ☒	NO ☐	UNK ☐
7. Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	YES ☐	NO ☒	UNK ☐

cGMP Risk: ☒ High Risk of cGMP issues.

The Quality System requirements applicable to a particular manufacturer may vary based upon the type of constituent parts being manufactured and the aspects of their manufacture that are being performed at that site. All manufacturers are responsible for ensuring compliance with all requirements applicable to the manufacturing activities at their facilities. Where multiple

facilities bear responsibility for various aspects of the manufacturing process, only the holder of the application or clearance for the product is responsible for compliance with all aspects of the Quality System requirements applicable to the entire manufacturing process and across all facilities.

Applicant:	Eli Lilly and Company Lilly Corporate Center, Indianapolis, IN 46285 FEI: FEI #1819470
Finished Combination Product Manufacturer:	(b) (4)

Applicable Sites Eli Lilly and Company ☒ (b) (4)	Management Responsibility, 21 CFR 820.20 The firm provided a summary of how the firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4).	YES ☐	NO ☒
	The firm provided a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.	YES ☐	NO ☒
	21 CFR 820.20 Deficiency 1. Eli Lilly and Company has inadequately addressed the requirement for 21 CFR 820.20, management responsibility. Please provide a summary of how Eli Lilly and Company's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). Also, provide a description of the functions and responsibility of each facility involved in the manufacturing of the combination product.		
Applicable Sites	Design Controls, General, 21 CFR 820.30 The firm explained how it utilized the design control process to develop the combination product under review and provided a description of its design control procedures.	YES ☐	NO ☒

Eli Lilly and Company☒ (b) (4)	The firm provided a copy or a summary of the plan used to design the combination product.	YES ☐	NO ☒
	21 CFR 820.30 Deficiency 2. (b) (4) has inadequately addressed the requirement for 21 CFR 820.30, design controls. Please explain how (b) (4) utilized the design control process to develop the combination product under review and provide a description of (b) (4) design control procedures. The procedures description must include how requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are fulfilled. Provide a copy or a summary of the plan used to design the combination product. Explain how (b) (4) utilized the design control process to develop the combination product under review.		
Applicable Sites Eli Lilly and Company☒ (b) (4)	Purchasing Controls, 21 CFR 820.50 The sponsor firm should summarize its procedure(s) for purchasing controls.	YES ☐	NO ☒
	The summary should describe the firm's supplier evaluation process and describe how it will determine type of and extent of control it will exercise over suppliers.	YES ☐	NO ☒
	The summary should define how the firm maintains records of acceptable suppliers and how it addresses the purchasing data approval process.	YES ☐	NO ☒
	The summary should explain how the firm will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.	YES ☐	NO ☒
	The firm should explain how it will ensure that changes made by contractors/suppliers will not affect the final combination product.	YES ☐	NO ☒
	The firm should provide a description of how it applied the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).	YES ☐	NO ☒

	21 CFR 820.50 Deficiency 3. Eli Lilly and Company has inadequately addressed the requirement for 21 CFR 820.50, purchasing controls. Please provide a summary of the procedure(s) for purchasing controls at Eli Lilly and Company. The summary should: a. Describe Eli Lilly and Company's supplier evaluation process and describe how it will determine type and extent of control you will exercise over suppliers. b. Define how Eli Lilly and Company maintain records of acceptable suppliers and how Eli Lilly and Company addresses the purchasing data approval process. c. Explain how Eli Lilly and Company will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.		
	Please explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how Eli Lilly and Company applies the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).		
Applicable Sites Eli Lilly and Company ☒ (b) (4)	Corrective and Preventive Action (CAPA), 21 CFR 820.100 The sponsor firm should provide a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System.	YES ☐	NO ☒
	The CAPA system should require: a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;	YES ☐	NO ☒
	b. Investigation of nonconformities and their causes;	YES ☐	NO ☒
	c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and	YES ☐	NO ☒
	d. Verification or validation of the actions taken.	YES ☐	NO ☒

	21 CFR 820.100 Deficiency 4. Eli Lilly and Company and (b) (4) have inadequately addressed the requirement for 21 CFR 820.100, corrective and preventive actions. Please summarize the procedure(s) for Eli Lilly and Company and (b) (4) Corrective and Preventive Action (CAPA) System. The CAPA system should require: a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products; b. Investigation of nonconformities and their causes; c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and d. Verification or validation of the actions taken.		
Applicable Sites Eli Lilly and Company☐ (b) (4) None: ☒	Installation, 21 CFR 820.170 (check none if Installation is not required for the combination product) If applicable for the combination product, the firm should provide a summary of how it has established installation, inspection instructions, and test procedures for the installation of the combination product.	YES ☐	NO ☐
Applicable Sites Eli Lilly and Company☐ (b) (4) None: ☒	Servicing, 21 CFR 820.200 (check none if Servicing is not required for the combination product) Where servicing is a specified requirement for the combination product, the firm should provide a summary of how it has established and maintained instructions and procedures for performing and verifying that servicing of the combination product meets the specified requirements.	YES ☐	NO ☐

Applicable Sites Eli Lilly and Company☒ (b) (4) None: ☐	Production and Process Controls, 21 CFR 820.70 The sponsor should provide a summary of the procedure(s) for environmental and contamination controls of the facility where the final manufacturing of the finished combination product, if such conditions could adversely affect the combination product. If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).	YES ☐	NO ☒
	Production and Process Control Deficiency 5. Please provide a summary of the procedure(s) for environmental and contamination controls of (b) (4) or the facility where the final manufacturing of the finished combination product, if such conditions could adversely affect the combination product.		
Applicable Sites Eli Lilly and Company☒ (b) (4) None: ☐	The sponsor should provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review. This information should display the important aspects of the production process. If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).	YES ☐	NO ☒
	Production and Process Control Deficiency 6. Please provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review. This information should display the important aspects of the production process.		
Applicable Sites Eli Lilly and Company☒ (b) (4) None: ☐	The sponsor should explain how it will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. The firm should specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. The firm should also provide the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product.	YES ☐	NO ☒

	If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).		
	Production and Process Control Deficiency 7. Please explain how [redacted] (b) (4) will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. Eli Lilly and Company should specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. Eli Lilly and Company should also provide the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product.		

Documentation Review Recommendation: *Deficiencies Identified.* After reviewing the provided documents related to 21 CFR Part 4 requirements during the documentation review of the application in reference to applicable 21 CFR 820 regulations of the finished combination product, the following deficiencies have been identified. Please provide complete responses as well as where in the application we can find the information, if already provided.

LANGUAGE TO PROVIDE TO THE SPONSOR:

The following deficiencies were identified while doing the documentation review of Application NDA 210134, original submission, glucagon nasal powder, in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

1. Your firm has inadequately addressed the requirement for 21 CFR 820.20, management responsibility. Please provide a summary of how your management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). Also, provide a description of the functions and responsibility of each facility involved in the manufacturing of the combination product.

2. Your firm has inadequately addressed the requirement for 21 CFR 820.30, design controls. Please explain how your firm utilized the design control process to develop the combination product under review and provide a description of your firm's design control procedures. The procedures description must include how requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are fulfilled. Provide a copy or a

summary of the plan used to design the combination product. Explain how you utilized the design control process to develop the combination product under review.

3. Your firm has inadequately addressed the requirement for 21 CFR 820.50, purchasing controls. Please provide a summary of the procedure(s) for purchasing controls at your firm. The summary should:
    a. Describe your supplier evaluation process and describe how it will determine type and extent of control you will exercise over suppliers.
    b. Define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.
    c. Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

4. Your firm has inadequately addressed the requirement for 21 CFR 820.100, corrective and preventive actions. Please summarize the procedure(s) for your firm's Corrective and Preventive Action (CAPA) System. The CAPA system should require:
    a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
    b. Investigation of nonconformities and their causes;
    c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and
    d. Verification or validation of the actions taken.

5. Please provide a summary of the procedure(s) for environmental and contamination controls of your firm or the facility where the final manufacturing of the finished combination product, if such conditions could adversely affect the combination product.

6. Please provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review. This information should display the important aspects of the production process.

7. Please explain how your firm will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. You should specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. You should also provide the acceptance/rejection criteria for the

receiving components/materials, the in-process tests and the release of the finished combination product.

Please note that for combination products manufactured under the CGMP drug operating system, the Applicant/Licensure must also fulfill the requirements under 21 CFR Part 4.4b to show compliance to 21 CFR Part 4 for the finished combination product. To assist in the preparation of the above summaries related to the 21 CFR 820.20, 21 CFR 820.30, 21 CFR 820.50 and 21 CFR 820.100, we recommend the following FDA Guidance: 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003) located at the link: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm.

RECOMMENDATION

The approvability of application for NDA 210134 BAQSIMI, Glucagon Nasal Powder should be delayed for the following reasons:

(1) Deficiencies were identified during the documentation review. Additional information from the firm is needed to complete the documentation review.

(2) A pre-approval inspection is recommended for the following facility:

Eli Lilly and Company

(3) A post-approval inspection is recommended for the following facility:

(b) (4)

OC Decision: Withhold (Issue Device Quality System Deficiencies to CDER or Recommend Inspections)

Reviewer:

Leslie E. Caster -S

Digitally signed by Leslie E. Caster -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13000338511, cn=Leslie E. Caster -S
Date: 2018.11.16 10:43:00 -05'00'

Leslie E. Dorsey

Lead CSO:

Maria Isabel Tejero Del Rio -S

Digitally signed by Maria Isabel Tejero Del Rio -S
Date: 2018.11.14 09:08:08 -05'00'

M. Isabel Tejero del Rio

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

/s/

ANIKA A LALMANSINGH
11/19/2018
Uploaded on behalf of: Leslie E. Dorsey, CSO, Office of Gastrorenal, ObGyn, General Hospital and Urology Devices

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 9/21/2018

TO: Division of Metabolism and Endcrinology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct biopharmaceutical inspection**

RE: NDA 210134

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) declines to conduct a biopharmaceutical inspection for the site specified below.

Rationale

OSIS recently inspected (b) (4) and (b) (4) The outcome from these inspections was classified as No Action Indicated (NAI).

In addition, on August 27, 2018, the Office of Clinical Pharmacology reviewer requested that OSIS cancel the inspection request for (b) (4) because the inspection was no longer needed. Thus, OSIS is cancelling the inspection at (b) (4).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	(b) (4)	
Clinical		
(b) (4)		

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/

ANGEL S JOHNSON
09/21/2018