CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212097Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 212097
Review 1

Drug Name/Dosage Form	Glucagon injection
Strength	0.5 mg per 0.1 mL or 1 mg per 0.2 mL in pre-filled pen or auto-injector
Route of Administration	Subcutaneous
Rx/OTC Dispensed	Rx
Applicant	Xeris Pharmaceuticals Inc.
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original and amendments	Original submission (8/10/2018) and amendments (8/29/18, 9/19/18, 9/20/18, 9/24/18 (EBR), 11/21/18 (MBR), 12/28/18 (label), 2/7/19 (Filter validation), 2/06/18, 2/07/19, 2/14/19 (Mfg. & DP related), 3/06/19 (micro), 3/13/19, 3/22/19 (label), 4/15/2019 (Mfg. site description), 4/16/19 (DP spec.), 4/19/19 (label), 5/3/2019, 5/13/19, 6/14/19, 7/10/19, and 8/7/19	Quality module 3, 1.14, and 1.11

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber	Branch II/New Drug API
Drug Product	Muthukumar Ramaswamy	Branch VI/New Drug Products II
Process/Facility	Ramesh Dandu	Branch IV/Process Assessment II
Microbiology	Renee Marcsisin	Microbiology Assessment
Facility (CDRH)	Payal Patel	CDRH
Biopharmaceutics	Not applicable	
Regulatory Business Process Manager	Anika Lalmansingh	Branch I/Regulatory Business Process Management I
Application Technical Lead	Muthukumar Ramaswamy	Branch VI/New Drug Products II
Environmental Analysis (EA)	Muthukumar Ramaswamy	Branch VI/New Drug Products II

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	Bachem	Glucagon	Adequate	3/15/2019 & 3/19/2019 (Drug substance reviewer)	LOA 6/4/2018
	Type III	(b) (4)		Adequate	3/28/2019 (Micro review)	4/16/2018
	Type III			Adequate	5/8/19 (DP reviewer)	LOA 6/7/2018
	Type III			Adequate	5/8/19 (DP Reviewer)	LOA 6/7/2018
	Type V			Adequate	2/19/2019 (microbiology review)	LOA 6/6/2018
	Type V			Adequate	3/19/2019 (microbiology review)	LOA 4/18/18
	Type V			Adequate	1/16/2019 (microbiology review)	LOA 6/19/18
	Type III			Adequate	Sufficient information in the NDA	LOA 6/06/18

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND NDA	115091 20928	Glucagon injection (Xeris) 505(b)(2) pathway relying on NDA 20928 for safety and effectiveness information

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharmacology/Toxicology	Complete	Acceptable. (Impurities and Leachables)	5/2/19	Dr. Braithwaite
DPA, St. Louis	Complete	Acceptable (method verification for impurities and Assay)	2/13/19	Dr. Cynthia Sommers (PM)

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality for NDA 212097 is approval.

II. Summary of Quality Assessments

A. Product Overview

This NDA is a 505(b)(2) application for glucagon injection. The currently marketed glucagon for injection products requires reconstitution of lyophilized powder in a diluent before use. The proposed Gvoke injection is a ready-to use sterile solution provided as a pre-filled pen or auto-injector for subcutaneous administration.

Gvoke injection is a sterile, clear, colorless to pale yellow solution. Each single-dose pre-filled syringe (Gvoke™ PFS) or auto-injector (Gvoke HypoPen™)) contains 0.5 mg of glucagon in 0.1 mL of the drug product or 1 mg of glucagon in 0.2 mL of the drug product. Finished product is packaged in foil pouch (b) (4)
The 0.5 mg strength product is intended for pediatric patients weighing less than 45 kg and 1 mg strength product is intended for patients 12 years and older weighing greater than 45kg.

Proposed Indication(s) including Intended Patient Population	*Severe hypoglycemia*
Duration of Treatment	*Refer to CTDL memo*
Maximum Daily Dose	*1mg*
Alternative Methods of Administration	*Not applicable*

B. Quality Assessment Overview

Drug Substance
Glucagon is a lyophilized powder. Glucagon is synthesized by solid phase synthesis at Bachem AG, Switzerland. With the exception of drug substance specifications and historical batch release data, the sponsor referenced all drug substance information to Bachem's DMF (b) (4). Glucagon is stored at (b) (4) °C in (b) (4) closure with a retest period of (b) (4) months. Drug substance information provided in the NDA and DMF was reviewed by Dr. M. T. Haber. He concluded that CMC information in the NDA and DMF is adequate to support the NDA. Please refer to Dr. Haber's review dated 03/19/2019 in Panorama for additional details.

Drug Product

The proposed drug product (Gvoke injection) is a clear, colorless to pale yellow, sterile solution filled in a 1 mL single-dose pre-filled syringe (PFS) fitted with manual plunger rod and backstop (Gvoke PFS™, Configuration B) or provided as a PFS integrated in an auto-injector (Gvoke HypoPen®, Configuration A) for convenience. Both pre-filled pen and auto-injector are further packaged in foil pouches (b) (4). The product is intended for storage at 25°C. Short-term excursions are permitted between 15° and 30°C (59° and 86°F). The product is not intended for storage in refrigerator or in freezer.

Each mL of Gvoke injection contains 5 mg of glucagon, 5 (b) (4) mg of trehalose dihydrate USP, and 6.0 mg of 1N sulfuric acid NF in dimethyl sulfoxide. DMSO constitutes (b) (4)% of the total drug product formulation. Both the pre-filled syringe and auto-injector will be available in two strengths: 0.5 mg of glucagon in 0.1mL of the drug product and 1.0 mg of glucagon in 0.2 mL of the drug product. All excipients associated with the drug product are present in approved products. The applicant is proposing to use an over fill volume of (b) (4) to allow the withdrawal of labeled amount (0.1 mL and 0.2 mL) of drug product from the prefilled syringe.

The drug product is filled in 1 mL (b) (4) syringe and sealed with (b) (4) plunger. Per NDA, the plastic components associated with container closure system comply with 21 CFR indirect food additives, USP <661>, USP <87>, and US<88>. The NDA contains letters of reference to access DMFs associated with container closure system components (b) (4) Ready to–use syringe system and rubber plunger). Dr. Ramaswamy reviewed the DMFs associated with product contact surfaces (b) (4) NDA contains adequate dimensional information on the components associated with the primary container closure system. The applicant provided adequate extractable and leachable data in the NDA to support the safety of the closure components proposed for use.

The stability data provided in the application also supported the compatibility of active ingredient with excipients and container closure components. Please refer to M. Ramaswamy's drug product review dated 5/7/19 and 8/6/19 in Panorama for additional information.

The microbiology reviewer, Dr. Marcsisin reviewed the container closure component sterilization information and integrity of the container closure system to maintain its integrity during storage and handling. For additional details, please refer to Dr. Marcsisin' s review dated 3/19/19 in Panorama. Device functionality and design aspects of the proposed auto-injector and pre-filled syringes including reliability studies are reviewed by CDRH reviewer.

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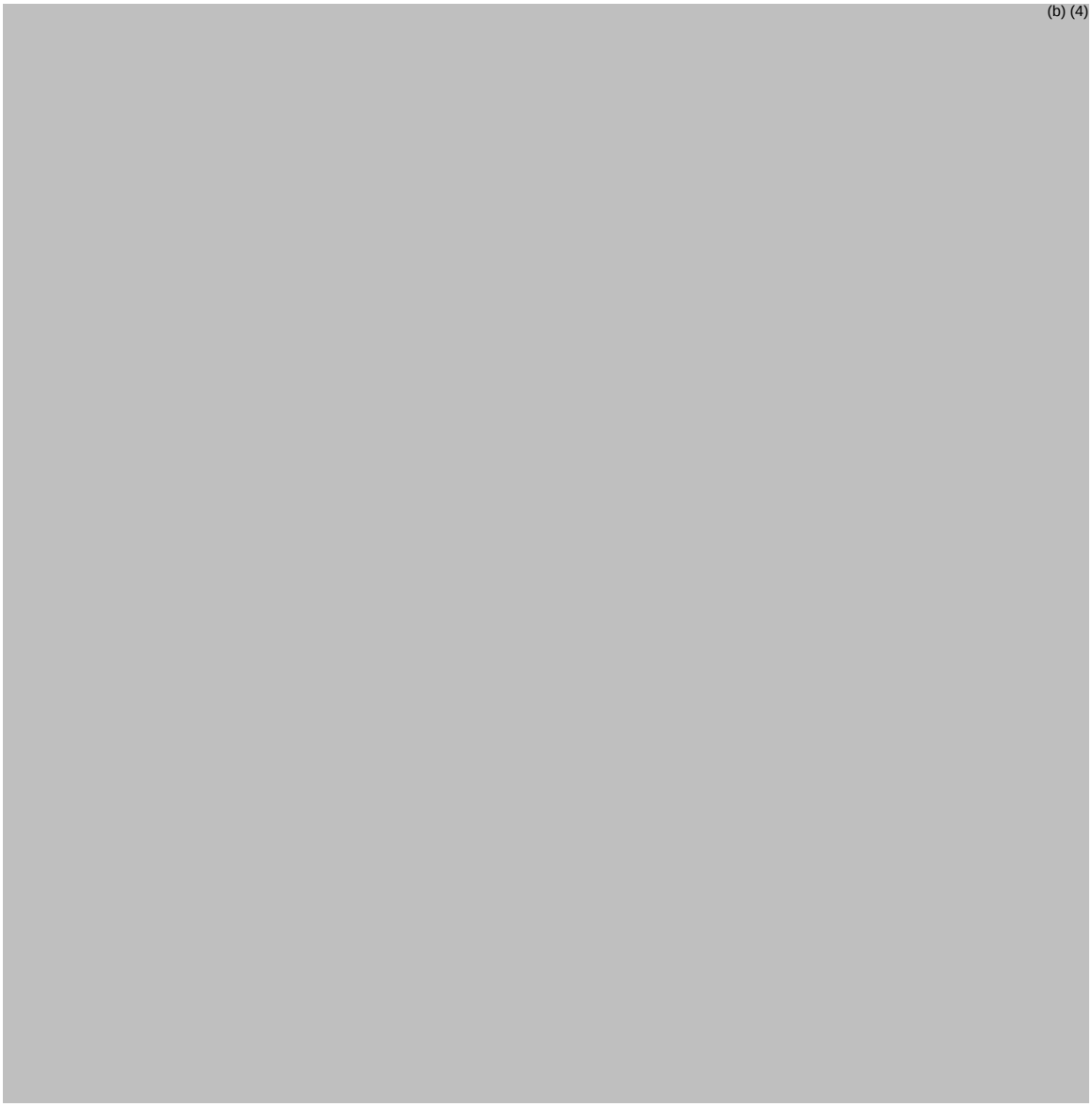
(b) (4)



OVERALL ASSESSMENT AND SIGNATURES:

OPQ CMC review concludes that there are no outstanding deficiencies related to drug substance, drug product, microbiology, process, facilities, environmental analysis, container, and carton label. Facilities recommendation is approval. *OPQ overall recommendation for NDA 212097 is approval.*

Muthukumar Ramaswamy, Ph.D. 8/7/2019

Application Technical Lead Name and Date:

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MICROBIOLOGY

Product Background: Treatment of severe hypoglycemia

NDA: 212097

Drug Product Name/Strength: Glucagon injection, 0.5 mg for pediatric patients and 1 mg for patients 12 years and older

Route of Administration: Subcutaneous injection

Applicant Name: Xeris Pharmaceuticals, Inc.

Manufacturing Site: Pyramid Laboratories, Inc. (b) (4)
Costa Mesa, CA 92626

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): **N/A**

Review Summary: **The drug product is** (b) (4) **filled. The formulation and filling equipment** (b) (4) **The syringes and piston/plunger stoppers are received ready-to-use.**

List Submissions Being Reviewed: 08/10/2018, 09/24/2018, 02/07/2019, 03/06/2019

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks:

- **An Information Request was sent to the applicant on 09/21/2018 and a response was received on 09/24/2018.**
- **An Information Request was sent to the applicant on 01/24/2019 and a response was received on 02/07/2019.**
- **An Information Request was sent to the applicant on 02/20/2019 and a response was received on 03/06/2019. The original deficiencies are italicized below.**

Concise Description Outstanding Issues Remaining: None

Supporting Documents:

- (b) (4)
- **Microbiology reviews** (b) (4)

List Number of Comparability Protocols (ANDA only): N/A

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** A clear, colorless to slight yellow, sterile, non-aqueous formulation containing (b) (4) % w/w of API, supplied in a 1 ml pre-filled syringe (PFS) with a (b) (4) ml target fill volume for the 1 mg strength or a (b) (4) ml target fill volume for the 0.5 mg strength, and given as a subcutaneous injection

- **Drug product composition –**

Component	Concentration (% w/w)	PFS 1 mg		PFS 0.5 mg		Function
		To deliver at least (mg/unit)	To fill[1] (mg/unit)	To deliver at least (mg/unit)	To fill[1] (mg/unit)	
Glucagon	(b) (4)	1.00	(b) (4)			Drug substance
Trehalose dihydrate		11.1				(b) (4)
DMSO		(b) (4)				
1 N sulfuric acid						

[1]Overfill to guarantee label claim

- **Description of container closure system –** The primary container closure system is a pre-filled syringe (PFS) with a staked stainless steel needle (cannula), (b) (4) (b) (4) syringe barrel, (b) (4) plunger stopper (piston), and (b) (4) flexible needle shield. The PFS determines the fluid pathway. The drug product comes in two presentations, a PFS with an auto-injector (configuration A) and a PFS with manual plunger rod and backstop (configuration

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Ramesh Dandu

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Yong Hu

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Date: 8/02/2019 11:38:54PM
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Risk Assessment

From Initial Risk Identification			*Review Assessment*		
Attribute/	***Factors that can impact the CQA***	***Initial Risk***	***Risk Mitigation***	***Final Risk***	***Lifecycle considerations***
Drug content/ Assay	Formulation, Process, Container closure, method	H	stability studies/in-process controls, method validation	L	none
Impurities/ degradants	Formulation, Process, Container closure, method	H	stability studies, in-process controls, method	L	(b) (4) Post-approval commitments are provided for including relative response factors for impurity calculations.
Appearance	Formulation, Process, Container closure	H	stability studies	L	none
Sterility	Container closure	H	stability studies	L	none
Endotoxins	Container closure	H	stability studies	L	
Particulate matter	Formulation	H	stability studies	L	none
Leachable/ extractables	Formulation, Process, Container closure	M	Optimize formulation qualification of packaging components	L	reference the pharmaceutical development for container closure components
Activation Force Break-loose force Glide force	Device components, Formulation Process, Device Assembly	M	Validated process, component qualification and reliability studies	L	None. Device reliability studies are evaluated by CDRH.
Deliverable volume	Device components, Formulation Process, Device Assembly	H	Validated process	L	None
Closure integrity	Device components, Formulation Process, Device Assembly	H	Validated process	L	None

Muthukumar Ramaswamy

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Reference ID: 4475187

Muthukumar Ramaswamy

Digitally signed by Muthukumar Ramaswamy
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/s/

MUTHUKUMAR RAMASWAMY
08/09/2019 01:08:45 PM

OFFICE OF DEVICE EVALUATION

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

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Date	August 6, 2019
To	Elizabeth Godwin Elizabeth.Godwin@fda.hhs.gov OMPT/CDER/OND/ODEII/DMEP 240-402-3438
Requesting Center/Office	*CDER/OND*
OND Review Division	*DMEP*
From	*Jacqueline Gertz* *CDRH/ODE/DAGRID/GHDB*
Through (Branch Chief)	*CAPT Alan Stevens* *CDRH/ODE/DAGRID/GHDB*
Subject	*Consult for NDA212097* *2018-03410* *1800683*
Final Recommendation	*Recommendation Date: 8/6/2019* *Device Constituents Parts of the Combination Product are Approvable*

Digital Signature Concurrence Table	
Reviewer	Jacqueline Gertz -S Digitally signed by Jacqueline Gertz -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001948760, cn=Jacqueline Gertz -S Date: 2019.08.06 15:53:54 -04'00'
Team Leader/Branch Chief	Alan M. Stevens -S

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	2018-03410
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=3733 http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=3734
ICC tracking # (Lead)	1800683
Submission Number	NDA 212097
Sponsor	Xeris Pharmaceuticals
Drug/Biologic	Glucagon
Indications for Use	G-Pen (glucagon injection) is indicated for treatment of severe hypoglycemia.
Device Constituent	Auto injector – single use
Related Files	This product was previously reviewed under ICC1550632, ICC1600890, ICC1700164, ICC1800106, ICC 1700607

Table 2. Review Team		
Were other disciplines consulted?	☐ **Yes**	☒ **No**

Interim Due Dates	Due Date
Filing	9/3/2018
74-Day Letter	9/24/2018
Mid-Cycle	1/10/2019
Primary Review	5/24/2019
PDUFA/GDUFA Due Date	6/10/2019

Table of Contents

2. PURPOSE/BACKGROUND

2.1. Scope

Xeris Pharmaceuticals is requesting approval of the G-pen. The device constituent of the combination product is an auto-injector.

CDER/OND has requested the following consult for review of the device constituent of the combination product on 08/16/2018:

Review the device components of the combination product

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

- Device performance
- Biocompatibility of the patient contacting components
- Release Specifications for the device constituent

This review will not cover the following review areas:

- Compatibility of the drug with the device materials
- Sterility of the device constituent if applicable
- Human Factors

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

2.2. Prior Interactions

CMC only end of phase 2 meeting
End of phase 2 meeting
In these 2 meetings, only boilerplate comments were provided.

On 10/24/2017 the following comments related to the reliability protocol were sent to the sponsor:

1) Given the intended use your proposed product (i.e. emergency use) we consider the reliability specification provided acceptable, however we recommend additional information is provided to support the reliability specification you have provided. We consider the main object of the reliability report to be establishing the reliability of the device failing to fire. The reliability of the device meeting its functional performance requirements (i.e. dose accuracy, extended needle length, etc.) is important to include within the report, but should not be considered the main objective.. We recommend expanding the fault tree analysis to identify all aspects of the design and manufacturing of the product which support the reliability specification. Specifically the failure mode "Device does not activate" otherwise known as 'Failure to Fire' should be expanded. To clarify any additional risk attributes listed, please provide a detailed component description which describes the function, purpose, and requirements of each subcomponent as it relates to the device firing. In addition, please identify how each critical component requirement identified is controlled throughout the manufacturing process (e.g., 100% of components are visually inspected per requirements established in manufacturing drawing XYZ, etc.).

2) Previously conducted verification testing and/or validated manufacturing controls may be leveraged to support the reliability specification, if applicable. As an example, the quantified capability of the manufacturing controls and/or validation testing that has been conducted can support the confidence of the inspection and manufacturing controls in controlling the basic events of the fault tree analysis. It is recommended that all previous testing which includes verification of critical components associated with reliability (dose accuracy, needle depth, etc.) are placed in table format; the table should identify the function and specification which was evaluated, the sample size tested, sample pre-conditions applied, and results.

Comments sent to the Sponsor in February 2018:

1. We agree that the reliability specification of (b) (4)% may be acceptable for the performance requirements of trigger force, ejection time, delivery volume, and exposed needle length. However, we request a reliability specification of (b) (4)% for successful activation of the auto-injector (i.e. Failure to Fire).

2. We agree with your fault tree analysis approach and we recommend that you utilize a tolerance interval statistical method to determine the sample size necessary to achieve the requested level of reliability for successful activation of the auto-injector (i.e. Failure to Fire). It is unclear if the statistical rationale for the sample size of (b) (4) units is sufficient to achieve the requested level of reliability for both the essential performance requirements and the successful activation of the auto-injector. The reliability of the low-level Failure Modes within your fault tree analysis may need to be controlled to a failure rate below (b) (4) to establish the top level 'Failure to Fire' failure rate less than (b) (4). The probability data for each low-level Failure Mode should be directly linked to the fault tree analysis.

3. You do not appear to be including any in-use conditions as part of your reliability testing. We expect conditions such as injection through clothing, activation orientation, etc. to be included as part of your future reliability study protocol.

2.2.1. Related Files

2.3. Indications for Use

Table 1: Indications for Use

Combination Product	Indications for Use
Glucagon	Treatment of severe hypoglycemia.
Auto-injector	The G-Pen is a disposable single use auto-injector that provides a means to inject a dose of medication subcutaneously from a pre-installed, pre-filled syringe (supplied sterile).

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Location
Reviewer's guide	001/m1
Pharmaceutican development	001/3.2.P.2
Pharmaceutical development 20	Linked through pharmaceutical development

Description-and-composition	001/3.2.p.1
Specifications	001/ 3.2.P.5.1
Analytical procedures	3.2.P.5.2
Justification of Specifications	3.2.P.5.6
Validation analytical procedures	3.2.p.5.3
Container-closure-system	3.2.p.7
Container-closure-system 1	3.2.p.7
Container-closure-system 2	3.2.p.7
Pharmaceutical development31	3.2.p.2
Pharmaceutical development9	3.2.p.7
Pharmaceutical development10	3.2.p.7
Pharmaceutical development14	3.2.p.7
Pharmaceutical development19	3.2.p.7
Pharmaceutical development18	3.2.p.7
Pharmaceutical development20	3.2.p.7
Pharmaceutical development15	3.2.p.7

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

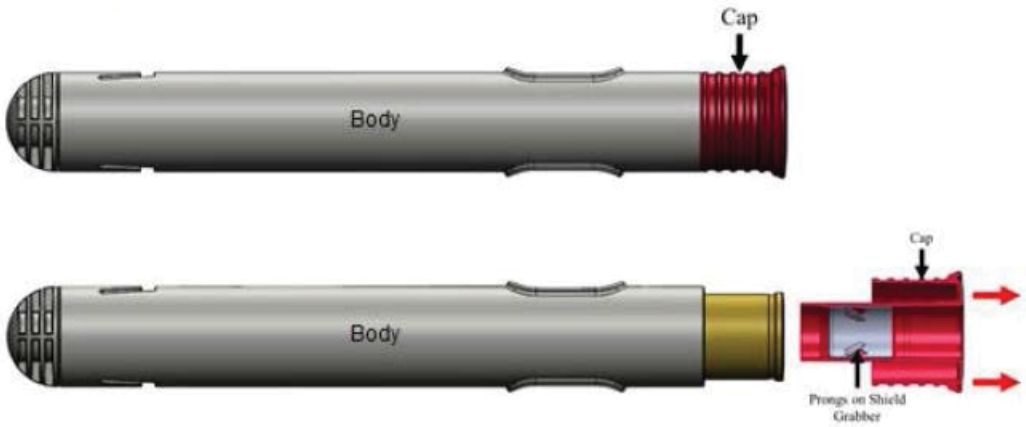
Is the syringe part of a kit?

The G-Pen is a combination product consisting of a prefilled syringe/auto-injector. The drug product is a sterile non-aqueous formulation of synthetic glucagon for subcutaneous injection and under investigation for treatment of severe hypoglycemia in type 1 or insulin-dependent type 2 diabetic patients.
The pre-filled syringe (PFS) is the primary container closure system and is further assembled inside a (b) (4) *auto-injector device.*
The G-Pen is a disposable single use auto-injector that provides a means to inject a dose of medication ***subcutaneously*** *from a pre-installed, pre-filled syringe (supplied sterile). The device is based on* (b) (4) *with a change to the length of the product window on the body of the injector. Key features include:*

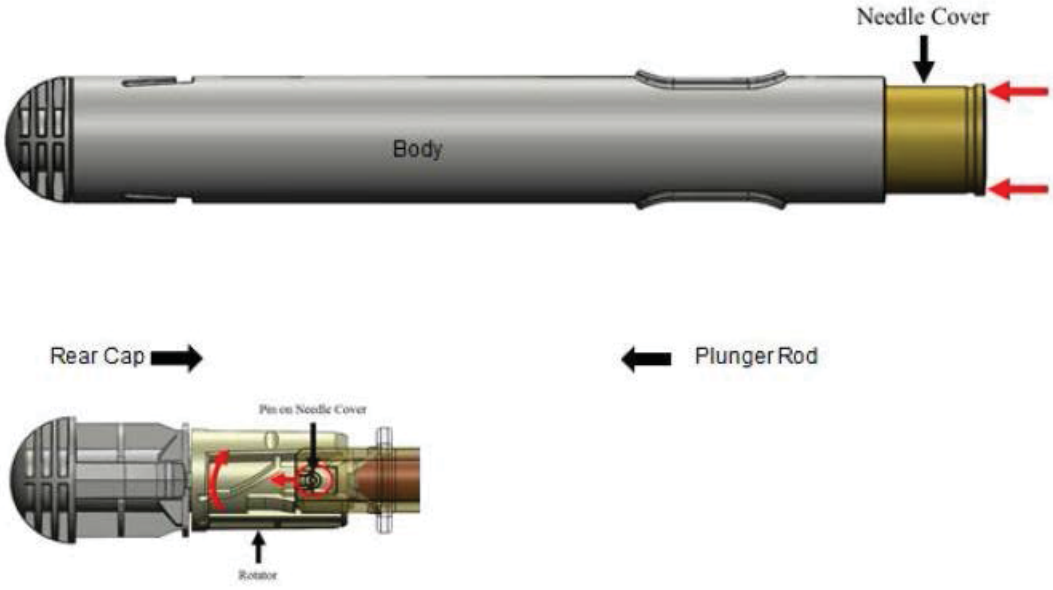
- *The auto-injector holds a 1 mL long plastic syringe with a 27G x ½" staked needle and Flexible Needle Shield*
- *(FNS).*
- *The syringe is pre-filled with either 0.5 mg (100 µL) or 1.0 mg (200 µL) of glucagon drug product formulation*
- *4-Step Operation: remove from packaging, remove protective cap, place against injection site, trigger injection*
- *Audible, Visual & Tactile Feedback*
- *Permanently Hidden Needle*
- *One-Handed Operation*
- *Passive Locking Needle Cover*

Figure 1: Illustrations and Narrative of Critical Components during Activation

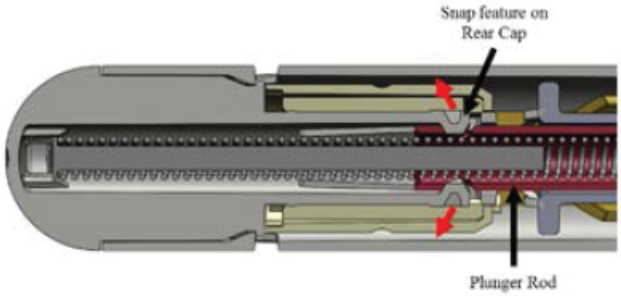
1. The device is readied for use by pulling off the red Cap. In doing so, the prongs on the Shield Grabber, located inside the Cap, grip and remove the Needle Shield of the Pre-Filled Syringe (PFS).



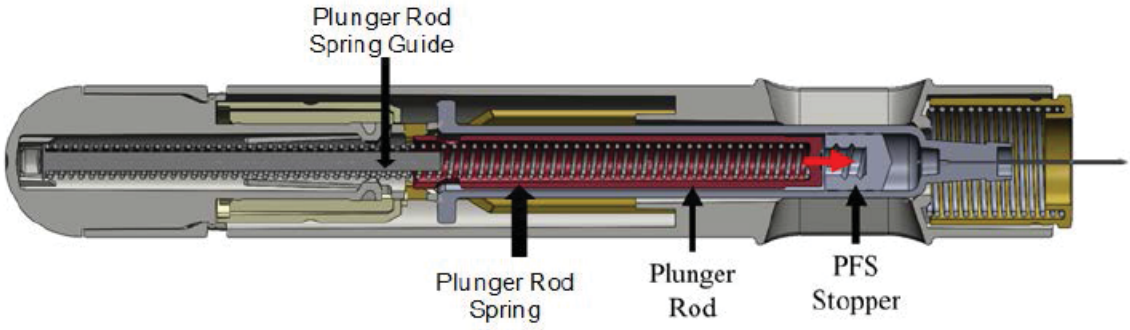
2. The user presses the *Body* with the *Needle Cover* onto the injection site. The Needle Cover moves against the force of the *Needle Cover Spring* (not visible above). The linear force of the pins on the inside of the Needle Cover against the grooves on the inside of the Rotator create an axial motion turning the *Rotator*



3. When the Rotator rotates, a snap feature holding the *Plunger Rod* inside the *Rear Cap* is able to open outward, releasing the Plunger Rod via the force of the *Plunger Rod Spring* (visible in the figure below). The Rear Cap holds one end of the *Plunger Rod Spring* (visible in the figure below) and is itself held in place via the *U-Bracket* (not visible).

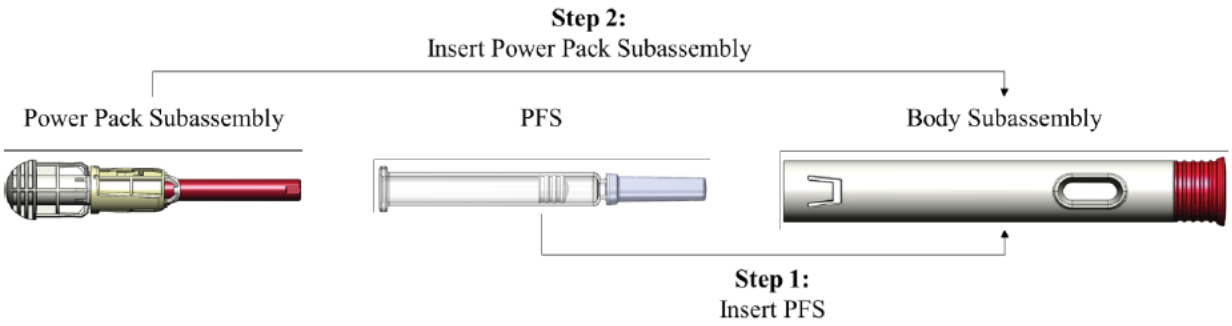


4. Once released, the Plunger Rod travels forward via the *Spring Rod Guide* and makes contact with the PFS Stopper (inside the syringe – itself nested inside the *Body*), which begins the delivery of the drug through the needle. The Plunger Rod travel does not stop until the PFS Stopper reaches the end of its travel.

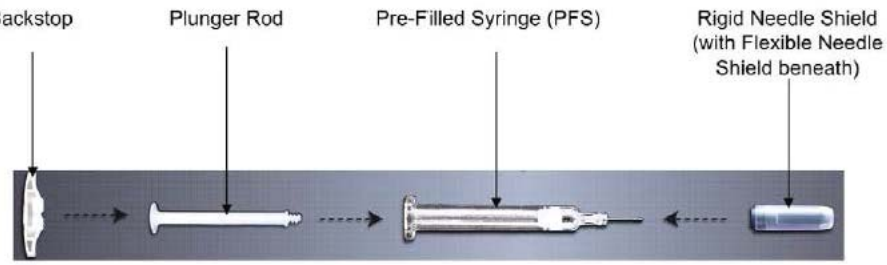


The device is provided in 2 configurations. Configuration 1 is the above auto injector. Configuration B is a stand along PFS.

Figure 1: Assembly process for Configuration A



Configuration B assembly:



The PFS is assembled into an auto-injector and sealed [redacted] (b) (4) *laminate foil pouch (Table 4) to form Configuration A (See 3.2.P.7 Configuration A for more details), or fitted with a plunger rod and back stop and sealed into* [redacted] (b) (4) *laminate foil pouch (Table 5) to form Configuration B (See 3.2.P.7 Configuration B for more details).*

Table 3: PFS Primary Container Components

Item Description	Vendor	Part Number
[redacted] (b) (4)		

Table 4: Auto-Injector Device (Configuration A) Sub-Assembly and Final Packaging Components

Item Description	Vendor	Part Number
[redacted] (b) (4)		

Table 5: Configuration B Device Sub-Assembly and Final Packaging Components

Item Description	Vendor	Part Number
[redacted] (b) (4)		

(b) (4)

4.1.1. Auto-injector and Syringe Device Description

Device Characteristic	N/A	Description / Specification
Syringe Name		G-pen auto injector containing PFS
Doses available		0.5 mg and 1 mg
Priming Dose / Volume		Not provided
Dose accuracy/deliverable volume.		NLT (b) (4) NLT
Injection Time		NMT 5 seconds
Injection tissue and depth of injection		Subcutaneous, abdomen, outer thigh, upper arm (b) (4) Syringe exposed needle length = 12.7 ± 0.4 mm
Audible / visual feedback		Click noise, window to see progress of injection (mostly red means done – red=syringe piston).
Cap Removal Force		(b) (4)
Activation Force		
Break loose force		
Glide force		
Visibility of medication container		Yes
Needle Specifications		27G x ½" staked needle
Type of Use (e.g. single use, disposable, reusable, other)		Single use, emergency use, disposable
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)		Any, most likely non-self-administration
Method of actuation		Pressure against injection site
Automated Functions		Needle extension, drug delivery
Residual Medication	x	
Drug Container Type		Glass pre-filled syringe
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)		mL
Environments of use		Any
Storage conditions and expiry		Shelf life: 24 months at 20-25C
Graduation marks / fill lines	x	
Preparation and administration (describe all that are applicable)		Remove red needle cap, inject
Safety Features		Needle safety cover (post-injection)
Material composition of PFS		Glass

Device Description Stock IR

Device Description Recommendation	
The Sponsor Provided Complete Device Description for the Device Constituent	☒
The Sponsor **DID NOT** Provide Complete Device Description for the Device Constituent	☐
Device Description Information Requests	Section 11.1 Filing IRs - # Section 11.2 74-Day Letter IRs - # Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #
All Information Requests were **Resolved** over the course of the review	☐
There are Complete Response Deficiencies, See Section 12	☐

5. FILING REVIEW

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

Table 4: 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		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	x		
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	x		

Master File Review Instructions

Master File Stock IR

Design Controls Recommendation	
The Sponsor Provided Complete Design Controls for the Device Constituent	☒
The Sponsor **DID NOT** Provide Complete Design Controls for the Device Constituent	☐
Design Control Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #

All Information Requests were **Resolved** over the course of the review	☐
There are Complete Response Deficiencies, See Section 12	☐

6. DESIGN VERIFICATION AND VALIDATION REVIEW

6.1. Summary of Design V&V Attributes

Table 5: Summary of Design V&V Attributes

Design Verification / Validation Attributes		Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing				x
To-be-marketed device was used in the pivotal clinical trial?				x
Selectable dose range on device matches the labeled dose range for the medication?		x		
Verification methods relevant to specific use conditions as described in design documents and labeling		See reliability review below		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)		See reliability review below		
Traceability demonstrated for specifications to performance data		X		
Conformance to applicable standards demonstrated	ISO (b) (4) – Needle based injection systems – Requirements and Test Methods	x		
	ISO (b) (4) – Needles	x		
	ISO – Automated Functions	x		
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry		x		
Discipline -Specific Design Verification / Validation adequately addressed	Biocompatibility	x		
	Sterility	x		

6.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device			x

Clinical Validation Stock IR

Design Validation Recommendation		
The Sponsor Provided Complete Design Validation for the Device Constituent		☒
The Sponsor **DID NOT** Provide Complete Design Validation for the Device Constituent		☐
Design Validation Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

6.3. Design Verification Review

6.3.1. Syringe Design Verification Testing Summary

Essential Functional Requirements						
	N/A	**Acceptance Criteria**	**Method Acceptable**	**Results/ Deviations**	**Adequate**	
					Yes	**No**
Dose Accuracy		NLT (b) (4)	Yes		x	
Break Loose Force		(b) (4)	ISO		x	
Glide Force			ISO (b) (4)		x	
Visual/Audible Feedback	x					
Device Requirements						
	N/A	**Acceptance Criteria**	**Method Acceptable**	**Results/ Deviations**	**Adequate**	
					Yes	**No**
Injection Depth		(b) (4)	Yes		x	
Injection time		NMT 5 seconds	Yes		x	
Needle Connection Type	x	Needle is staked			x	
Needle Resistance to Bend/Fracture		Avg max force (b) (4)	Yes		x	
Seal Integrity Testing[1]		No leaks	Yes		x	
Separation Force	x				x	
Unscrewing Torque	x				x	
Ease of Assembly	x				x	
Resistance to Overriding	x				x	
Stress Cracking	x				x	
Validation of Graduation Markings	x				x	
Dead Space						
Coring Needle Test	x				x	
Anti-Needle Stick Performance testing[2]	x					

Connectivity to other devices necessary for use[3]	x					
Injection force necessary to depress the plunger and eject the drug contents		(b) (4)			x	
Tip cap removal force			Yes		x	
Piston seal blowback[4]	x					
Sterility	x	Reviewed by CDER				

[1]to assess liquid leakage, air ingress, and dye ingress once the syringe is filled with the drug or biological product as intended and when connected to a connecting device. The sensitivity of the selected test method should be specified and validated. System integrity should be demonstrated throughout the product shelf-life.
[2]of an anti-needlestick mechanism with a glass syringe to demonstrate safety and effectiveness as recommended in FDA's guidance document, "Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features " (August 2005).
[3]e.g., needles, adapters, transfer systems, extension tubing, luer connectors, and sharps prevention features
[4]ability of syringe with tip cap to hold a certain pressure on the piston

6.3.2. Syringe Environmental Conditioning Testing

All Essential Functional Requirements Evaluated under normal and stressed conditioning				
		Adequate	Inadequate	N/A
Normal/Anticipated Conditions	In-Use atmosphere	x		
	Last-Dose Accuracy	Only for multidose		x
	Life-Cycle Testing	x		
Challenge/Stressed Conditions	Free-Fall	x		
	Dry heat/cold storage	x/x		
	Damp Heat	Only for refillable		x
	Cyclical	Only for refillable		x
	Vibration	x		
	Transportation	x		

Reviewer's comments:

Preconditioning of PFS samples was conducted per ISO (b) (4).

In use atmosphere, Vibration, drop test, dry heat and cold storage were tested for: needle shield removal force, BL/GF, deliverable volume.

The transportation studies were conducted in accordance with ASTM D4169-16 for the auto injector (which includes the PFS inside).

Accelerated aging studies have been conducted through 6 months (represent 24 month shelf life).

6.3.3. Auto-injector Validation

Essential Performance Requirement	**Specification**	**Verification**	**Validation**	**Aging / Stability (Y/N)**	**Shipping/ Transportation (Y/N)**	**Lot Release Testing (Y/N)**
Injection Time	<5 seconds	Yes	Yes	Yes	Yes	yes
Dose Accuracy	1mg dose: (b) (4) 0.5mg dose: (b) (4)	Yes	Yes	Yes	Yes	yes
Visual/Audible Feedback	Not tested					no

Activation Force	(b) (4)	Yes	Yes	Yes	Yes	yes
Needle Length	(b) (4)	Yes	Yes	Yes	Yes	yes
Needle Gauge	27G	n/a	n/a	n/a	n/a	n/a
Needle Connection Type	Pre-staked	n/a	n/a	n/a	n/a	n/a
Needle Resistance to Bend / Fracture	Not tested – drop test after activation, passed					
Cap Removal Force	(b) (4)	Yes	Yes	Yes	Yes	yes

6.3.4. Previous Reliability Review Comments

Previous comments regarding the reliability protocol from John McMichael ICC 1800106:

1. We agree that the reliability specification of (b) (4)% may be acceptable for the performance requirements of trigger force, ejection time, delivery volume, and exposed needle length. However, we request a reliability specification of (b) (4)% for successful activation of the auto-injector (i.e. Failure to Fire).

2. We agree with your fault tree analysis approach and we recommend that you utilize a tolerance interval statistical method to determine the sample size necessary to achieve the requested level of reliability for successful activation of the auto-injector (i.e. Failure to Fire). It is unclear if the statistical rationale for the sample size of (b) (4) units is sufficient to achieve the requested level of reliability for both the essential performance requirements and the successful activation of the auto-injector. The reliability of the low-level Failure Modes within your fault tree analysis may need to be controlled to a failure rate below (b) (4) to establish the top level 'Failure to Fire' failure rate less than (b) (4). The probability data for each low-level Failure Mode should be directly linked to the fault tree analysis.

3. You do not appear to be including any in-use conditions as part of your reliability testing. We expect conditions such as injection through clothing, activation orientation, etc. to be included as part of your future reliability study protocol.

6.3.5. Reliability documentation for PFS

From document pharmaceutical development 20:

Fault tree analysis:

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6.3.7. Reliability Checklist

	Information location/ Specification	Adequate	Inadequate	N/A
Pfs and Injector Design Considerations				
Protective packaging		yes		
Activation force	(b) (4)	yes		
Needle insertion • Penetrating clothing	pharmaceutical development 13 pharmaceutical development 18 009/pro-00130 configuration a-injection-through-clothing 009/pro-00131-configuration b injection through clothing	Yes		
Injection depth	(b) (4)	yes		
Drug delivery initiates as intended • Delivery begins when needle is at intended injection depth		Syringe: n/a Injector: needle is always fully extended		
Drug delivery stops as intended • Needle does not retract before intended dose is delivered • Completion signal does not prematurely signal		Syringe: N/a Injector: needle is covered after injection and window is covered in red by syringe piston Needle cover is activated by syringe rod hitting the bottom and activating the needle shield		
Dose accuracy	1mg: (b) (4) 0.5mg: (b) (4)	yes		

Auto-injector Reliability specs				
Successful Activation/failure to fire NLT (b) (4)		yes		
Dose Accuracy (b) (4)	1mg: (b) (4) 0.5mg: (b) (4)	Yes (b) (4)		
Extended Needle Length (b) (4)	(b) (4)	Yes – they call it injection depth		
Activation Force (b) (4)	(b) (4)	yes		
Injection Time (b) (4)	<5seconds	Yes - <5seconds		
Activation orientation	pharmaceutical development 19 009/pro-00128-configuration a injection orientation	Yes Vertical and horizontal Injection time Injection volume		
PFS Reliability specs				
Dose Accuracy (b) (4)		Yes 1mg dose = 0.2mL 0.5mg dose = 0.1mL		
Break loose/glide force (b) (4)	(b) (4)	pass		
Injection Time (b) (4)		n/a		
Activation orientation	pharmaceutical development 14	Yes Horizontal and vertical		

	009/pro-00128-configuration b injection orientation	Injection time Injection volume		
Fault Tree Analysis – unless specified, response is for PFS and AI				
Final finished version of the product used (including drug as needed)		Yes		
Only design and manufacturing elements considered – not use errors		yes		
Probability data included in tree		yes		
Consider potential common cause failures		Yes		
Supporting risk analysis included		Yes		
Events linked to appropriate design/manufacturing controls		Yes		
Statistical tolerance method used		No, but Bayesian hierarchical model was used. Acceptable.		
K factors used to calculate sample size		Yes		
Pre-conditioning protocol for AI– PFS not tested separately				
Shipping		Yes Injection time Injection volume Activation force Extended needle length Failure to fire		

Aging		Yes [redacted] (b) (4) to represent 24 month shelf life. [redacted] (b) (4)		
Storage orientation and conditions		Yes Cap up Cap down		
Activation orientation		Yes Vertical and horizontal Injection time Dose delivered		
Vibration		Yes Injection time Injection volume Activation force Extended needle length Failure to fire		
Shock		Yes Drop from 1 Meter Injection time Injection volume Activation force Extended needle length Failure to fire		
Environmental factors • Temps (extreme/ cyclical) • Altitude/pressure • Air particulates (dust/sand)		Yes – temperatures Altitude/pressure and air particulates not considered (we reviewed the protocol and didn't request it.		

All EPR's tested for each pre-conditioning		Yes Injection time Injection volume Activation force Extended needle length Failure to fire		
Failures underwent root cause analysis		yes		

Reviewer's comments:
Injection through clothing and the effects of device injection orientation are studies that were requested by CDRH in a teleconference on April 17, 2018. They are expected to be completed on September 30, 2018 and so were not submitted for review here. The injection through clothing protocol states that the products will not be labeled for injection through clothing and that this would be considered an off-label use. In the April 17, 2018 teleconference CDRH stated that this information is a likely off label use scenario. They are conducting the study for informational purposes only. The (auto) injection orientation study states that the acceptance criteria are full dose administration in less than 5 seconds. As the cap removal force does not affect the injection orientation, this is acceptable. The tested orientations are upside-down vertically, and horizontal. (b) (4) devices will be tested. This study should not be done for informational purposes only. This is essential to reliable use of the device.

The essential performance requirements for the reliability analysis has the same specifications as the release specifications.

Configuration b (PFS):
Dose accuracy and injection time were assessed with pre-conditioning.
Break loose and glide force testing are provided in pharmaceutical development 20.pdf under the original nda submission. It was included for informational purposes only. The presented data suggest that it did meet the (b) (4)% reliability requirement with a 95% confidence interval. This information should be included in the reliability analysis.

Extended needle length was considered after the fact. The needle passed at (b) (4)% but not at (b) (4)%. (CDRH asked them to provide more information on the acceptability of this in the April 17, 2018 tcon) This information also was not included in the reliability analysis, it should be included.

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Risk Analysis Recommendation		
The Sponsor provided complete Risk Analysis for the Device Constituent		☒
The Sponsor **DID NOT** provide There are Complete Response Deficiencies, See Section 13 Risk Analysis for the Device Constituent		☐
Risk Analysis Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

8. LABELING

8.1. Device Labels

Carton:

(b) (4)

Reviewer Comment

The Rx statement is present on the carton along with storage conditions, manufacturer contact information, and the dose (1mg). A brief description of the instructions for use is included as well.

The instructions for use will be evaluated by CDER/DMEPA using HF.

Labeling Recommendation		
The Sponsor provided complete Labeling for the Device Constituent		☒
The Sponsor **DID NOT** provide complete Labeling for the Device Constituent		☐
Labeling Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

9. DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

9.1. Syringe Release Specifications

Attribute	Specification	Test Method
Dose Accuracy	1mg: (b) (4) 0.5mg: (b) (4)	Final assembly
Needle Shield removal force	(b) (4)	Subassembly and final assembly
Break Loose/Glide Force	(b) (4)	Subassembly and final assembly

9.2. Auto-injector release specifications

Attribute	Specification	Test Method
Dose Accuracy	1mg: (b) (4) 0.5mg: (b) (4)	Subassembly and final assembly
Needle Extension (for automated injectors)	(b) (4)	Subassembly and final assembly
Injection Time (for automated injectors)	<5 seconds	Subassembly and final assembly
Activation force	(b) (4)	Subassembly and final assembly
Cap Removal Force	(b) (4)	Subassembly and final assembly

Release Specification Stock IR

Release Specifications Recommendation		
The Sponsor provided complete Release Specifications for the Device Constituent		☒
The Sponsor **DID NOT** provide complete Release Specifications for the Device Constituent		☐
Release Specifications Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐

There are Complete Response Deficiencies, See Section 12	☐

10. COMPLIANCE

10.1. Review of QS requirements per the 820's

CDRH received a request from CDER to review the applicant's response to deficiencies related to how the firm complied with 21 CFR Part 4 and 21 CFR 820 for the finished combination product for the approvability of NDA 212097. The outstanding questions related to additional information requested to demonstrate compliance with 21 CFR 820.20 (Management Controls), 21 CFR 820.30 (Design Controls), 21 CFR 820.50 (Purchasing Controls) and 21 CFR 820.100 (CAPA). This review evaluated the response provided by the firm.

Management Control, 21 CFR 820.20
The firm provided a brief description of their management structure stating that senior management is responsible for ensuring that roles, responsibilities and authorities related to the Quality Management System are defined, communicated, and implemented throughout the organization.

Design Control, General, 21 CFR 820.30
Xeris Pharmaceuticals utilizes an overall plan that includes a product development process for drug product and a design and development plan for the device design controls. This process uses a phase-gate approach to define and develop supporting Xeris and (b) (4) final device assembly manufacturer) documentation that includes the applicable elements of Design Control per 21 CFR 820.30. Configuration A (the autoinjector) has been jointly developed with (b) (4) and defined within a design and development plan. Design control activities that may have been designated to an external design center are under a Quality Agreement.

Purchasing Controls, 21 CFR 820.50
The applicant provides a breakdown of its supplier's functions within 3.2.P.7 (Container Closure System – Configuration A), as (b) (4) locations) are performing parts of the design and development planning, design inputs, outputs, Verification and Validations, Complaint files, and servicing. The applicant assesses their supplier's manufacturing, regulatory profiles, quality systems to determine the supplier's capabilities to supply Xeris with products that will meet requirements; they have defined roles and responsibilities through Quality Agreements that include change notification and receiving acceptance activities; and perform periodic evaluations of key suppliers to ensure continued conformance to applicable regs and Xeris requirements.

Corrective and Preventive Action (CAPA), 21 CFR 820.100
The applicant's CAPA process identifies potential sources of quality data and analysis to identify existing and potential causes of nonconforming practices and products. Each data input undergoes a risk impact assessment to determine the level of failure investigation required. Any failure investigation is intended to identify the probable root cause to determine the appropriate corrective or preventative action to prevent recurrence. CAPAs are verified and/or validated to ensure such actions are effective and do not adversely affect the finished combination product. Xeris' CAPA system takes into account both the drug and device constituents of the combination product and any issues identified are investigated jointly with the appropriate manufacturing site.

Recommendation:

The response to deficiencies for NDA 212097 Glucagon Injection are adequate from the perspective of the applicable Quality System Requirements. No additional questions or deficiencies are requested at this time.

10.2. Preapproval Inspection

From Payal Patel:

I have gone through this NDA and at this point I would not recommend a Pre-Approval Inspection of the final assembly firm (b) (4) This firm is responsible for Configuration A of the Container Closure System.

A Post-Approval Inspection is recommended in this case. I will follow up with a consult memo and any deficiencies related to the QS requirements per the 820's through Jacqueline.

Please note, the facilities inspection review does not look into firms that manufacture the PFS components of devices; therefore, a review of the firms that manufacture the Auto Injector portion of the device is what was reviewed.

Kind Regards,

Payal

Reviewer's comments:

A pre-approval inspection is not being recommended because the firm was last inspected in January 2019 with an NAI decision.

11.INTERACTIVE REVIEW

11.1. Filing Information Requests

Are there filing review information requests? ☐ No ☒ Yes

Agency Information Request- ADEQUATE

Multiple sections of the reliability test report refer to the document Xeris protocol 00090-01 located in appendix D. This document could not be located within the submission. Additionally, the fault tree analysis for the auto-injector configuration could not be found. If these documents have been submitted, please provide the document name, page number, and eCTD location of this information. If these documents were accidentally not included, please submit the documents.

Reviewer Comments
The requested information was provided.

11.2. 74-Day letter Information Requests

Are there 74-Day Letter information requests? ☒ No ☐ Yes

11.3. Mid-Cycle Information Requests

Are there Mid-Cycle review information requests? ☐ No ☒ Yes

Agency Information Request - ADEQUATE

Information requests

1. Injection time and injection volume were considered in the reliability study. All essential performance requirements should be included in the reliability assessment, including all preconditioning scenarios. The essential performance requirements for a pre-filled syringe with a needle are: break loose and glide force, dose accuracy, and needle length. The essential performance requirements for an auto injector are: failure to fire (successful activation), activation force, extended needle length, injection time and dose accuracy. Please consider all the essential performance requirements in the reliability assessment.

IR response for Configuration B (pre-filled syringe)

All auto-injectors were subject to (b) (4) *(simulation of 24-month shelf life) and then underwent one of the three following testing scenarios:*

(b) (4)

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(b) (4)

12.RECOMMENDATION

12.1. Recommendation to CDER/OND

CDRH is recommending that the device constituent of the combination product is approvable for the proposed indication.

13. Appendix A

13.1. Reliability Consult

Date	7/30/2019		
To:	Jacqueline Gertz, Ph.D		
Requesting Center/Office	CDER/OND	**Clinical Review Division**	DMEP
From	Alan Stevens OPEQ/OHT3/DHT3C		
Subject	NDA 212097, glucagon injection Reliability data		
Recommendation	**Reliability Analysis is Adequate:** ☑ **Yes** ☐ **No** **cGMP Analysis is Adequate:** ☐ **Yes** ☑ **No**		

13.2. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 212097
Sponsor	Xeris
Drug/Biologic	Glucagon injection
Indications for Use	an antihypoglycemic indicated for the treatment of severe hypoglycemia
Device Constituent	Auto-Injector
Route of Administration	Subcutaneous injection

13.3. PURPOSE/BACKGROUND

The purpose of this review memo is to document my assessment of the device reliability data provided in support of NDA 212097 for the glucagon autoinjector.

Two presentations are covered in this review: 0.5mg and 1mg autoinjectors.

13.4. DEVICE DESCRIPTION and PERFORMANCE SPECIFICATIONS

Complete device description is located in the CDRH lead review memo. Shown here is a copy of the adult injector label:

(b) (4)

The following release specifications are listed in Module 3.2.P.5

Parameter	Acceptance Criteria	Method/Description
Injection Depth (Needle Extension)	(b) (4)	Needle length exposure during injection is measured
Activation Force	(b) (4)	The force required to fully depress the Needle Cover is measured
Deliverable Volume (1 mg / 0.5 mg)	NLT (b) (4)	Based on ISO (b) (4); developed to gravimetrically capture the expelled contents with volume determination based on the measured weight and drug product density
Injection Time	≤ 5 Seconds	The time required to completely expel the drug contents from the starting point to the completion point of injection
Cap Removal Force	(b) (4)	The force required for removing the cap is measured

13.5. RELIABILITY ANALYSIS

The primary assessment of the injector reliability is based on the reliability model provided by Xeris. The initial fault tree analysis (FTA) provided by Xeris had fundamental structural issues that were communicated through IR to the applicant. On May 22, 2019, we concluded that the FTA needed to be restructured to address the deficiencies.

A restructured FTA was received on May 30, 2019. The top level FTA is shown here and the complete analysis is contained in Module 3.2.R

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(b) (4)

RELIABILITY ANALYSIS CONCLUSIONS

Reliability Analysis is Adequate: ☑ **Yes** ☐ **No**
cGMP Analysis is Adequate: ☐ **Yes** ☑ **No**

Reviewer Comments

5. The reliability analysis provided by Xeris is adequate.
6. Reliability testing data are supplied in the NDA and covered in the CDRH lead reviewer memo.
7. The response to the July 8, 2019 information request is not adequate. However, this is not specifically a reliability analysis issue and is considered a Quality Systems issue. Meaning that while the existing reliability analysis appears adequate, I am concerned that future production quality defects or other issues that could impact our conclusions may not be properly assessed. These additional deficiencies are being communicated to the lead reviewer.
    1. Review of the SOP documents provided on July 12, 2019 do not appear to explicitly require updating the reliability analysis, as stated in the July 12, 2019 cover letter. The quality procedures should require maintaining the fault tree analysis to assure ongoing product reliability continue to meet the established specification.
    2. CAPA procedure SOP (SOP-QA- (b) (4)) includes ambiguity about how certain types of risks and investigations are handled, for example:

(b) (4)

CDRH sent Device Description Interactive Review Questions to the Sponsor: ☑ **Yes** ☐ **No**

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/s/

ELIZABETH R GODWIN
08/19/2019 08:47:19 AM
Signing on behalf of Jacqueline Gertz CDRH/ODE/DAGRID/GHDB

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/

ELIZABETH R GODWIN
09/10/2019 10:00:33 AM