

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213224Orig1s000**

**PRODUCT QUALITY REVIEW(S)**



**DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS**  
**INTERCENTER CONSULT MEMORANDUM**

<b>Date</b>	12/16/2019		
<b>To:</b>	Meghna Jairath		
<b>Requesting Center/Office:</b>	CDER/OND	<b>Clinical Review Division:</b>	DMEP
<b>From</b>	Peter Petrochenko OPEQ/OHT3/DHT3C		
<b>Through (Team)</b>	Rumi Young, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
<b>Through (Division) *Optional</b>	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
<b>Subject</b>	NDA 213224, Octreotide Acetate Injection ICC 1900319 ICCR2019-04781		
<b>Recommendation</b>	<p><b>Filing Recommendation Date: 6/7/2019</b></p> <p><input type="checkbox"/> CDRH did not provide a Filing Recommendation</p> <p><input checked="" type="checkbox"/> Device Constituent Parts of the Combination Product are acceptable for Filing.</p> <p><input type="checkbox"/> Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, <a href="#">See Appendix A</a></p> <p><input type="checkbox"/> Device Constituents Parts of the Combination Product are Not Acceptable for Filing - <a href="#">See Section 5.4</a> for Deficiencies</p> <p><b>Mid-Cycle Recommendation Date: 8/26/2019</b></p> <p><input type="checkbox"/> CDRH did not provide a Mid-Cycle Recommendation</p> <p><input type="checkbox"/> CDRH has no approvability issues at this time.</p> <p><input checked="" type="checkbox"/> CDRH has additional Information Requests, <a href="#">See Appendix A</a></p> <p><input type="checkbox"/> CDRH has Major Deficiencies that may present an approvability issue, <a href="#">See Appendix A.</a></p> <p><b>Final Recommendation Date: 1/14/2020</b></p> <p><input checked="" type="checkbox"/> Device Constituent Parts of the Combination Product are Approvable.</p> <p><input type="checkbox"/> Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, <a href="#">See Section 2.3</a></p> <p><input type="checkbox"/> Device Constituent Parts of the Combination Product are Not Approvable - <a href="#">See Section 2.2</a> for Complete Response Deficiencies</p>		

Digital Signature Concurrence Table		
Reviewer	Team Lead (TL)	Division (*Optional)

## 1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 213224
Sponsor	Sun Pharmaceutical Industries Limited
Drug/Biologic	Octreotide Acetate Injection
Indications for Use	For the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors
Device Constituent	Pen-Injector
<a href="#">Related Files</a>	n/a

Review Team	
Lead Device Reviewer	<i>Peter Petrochenko</i>

## 2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

- Approvable – the device constituent of the combination product is approvable for the proposed indication.
- Approvable with PMC or PMR, [See Section 2.3](#)
  - Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

Section	Adequate			Reviewer <u>Notes</u>
	Yes	No	NA	
<a href="#">Device Description</a>	X			
<a href="#">Labeling</a>	X			
<a href="#">Design Controls</a>	X			
<a href="#">Risk Analysis</a>	X			
<a href="#">Design Verification</a>	X			Injection force of the final finished device after stability/shipping was provided interactively. Previously the Sponsor wanted to leverage break loose and glide force of the plunger/cartridge only (which includes one out of specification result in the 18-months study) in place of injection force of the completely assembled device. Sponsor agreed to add injection force of the final finished device at release, investigation any failures and reject batches per their sampling plan.

				Injection time was not provided; however, the justification is acceptable since this is a manually driven injector with different doses.
<a href="#">Consultant Discipline Reviews</a>			X	
<a href="#">Clinical Validation</a>			X	
<a href="#">Human Factors Validation</a>			X	Reviewed by CDER/OND/DMEPA
<a href="#">Facilities &amp; Quality Systems</a>			X	Reviewed by CDRH/OC

**2.1. Comments to the Review Team**

- CDRH does not have any further comments to convey to the review team.
- CDRH has the following comments to convey to the review team:

Comment #1:

While the sponsor addressed the cartridge glide force failures observed over stability, we recommend CDER OPQ to assess if this impacts their review of the (b) (4) processes of the cartridge since the root cause of the observed high forces was due to (b) (4) the cartridge. CDRH ultimately accepted the response and observed failures since their process detected the failures, their follow-up quality activities were adequate (root cause investigation, sampling plan/batch rejection) and they added injection force testing of the final finished device to their release testing program.

**2.2. Complete Response Deficiencies**

- There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
- The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

**2.3. Recommended Post-Market Commitments/Requirements**

CDRH has Post-Market <a href="#">Commitments or Requirements</a>	<input type="checkbox"/>
CDRH does not have Post-Market Commitments or Requirements	<input checked="" type="checkbox"/>

## **TABLE OF CONTENTS**

1. SUBMISSION OVERVIEW.....	2
2. EXECUTIVE SUMMARY AND RECOMMENDATION.....	2
2.1. Comments to the Review Team.....	3
2.2. Complete Response Deficiencies.....	3
2.3. Recommended Post-Market Commitments/Requirements.....	3
3. PURPOSE/BACKGROUND.....	6
3.1. Scope.....	6
3.2. Prior Interactions.....	6
3.2.1. Related Files.....	6
3.3. Indications for Use.....	6
3.4. Materials Reviewed.....	6
4. DEVICE DESCRIPTION.....	7
4.1. Device Description.....	7
4.2. Steps for Using the Device.....	10
4.3. Device Description Conclusion.....	10
4.4. Facilities Information.....	11
4.5. Quality System Documentation Triage Checklist.....	11
5. LABELING.....	11
5.1. General Labeling Review.....	11
5.2. Device Specific Labeling Review.....	12
5.3. Clinical Labeling Review.....	12
5.4. Labeling Review Conclusion.....	12
6. DESIGN CONTROL SUMMARY.....	13
6.1. Summary of Design Control Activities.....	13
6.2. Design Controls Information Requests and Responses.....	13
6.2.1. IR #1.....	13
6.3. Applicable Standards and Guidance Documents.....	22
6.4. Design Control Review Conclusion.....	22
7. RISK ANALYSIS.....	24
7.1. Risk Management Plan.....	24
7.2. Hazard Analysis and Risk Summary Report.....	24
7.3. Risk Analysis Review Conclusion.....	26
8. DESIGN VERIFICATION REVIEW.....	29
8.1. Performance/Engineering Verification.....	29
8.1.1. Essential Performance Requirement Evaluation.....	29
8.1.2. Verification of Design Inputs Evaluation.....	33
8.1.3. Evaluation of Test Methods.....	34
8.2. Design Verification Review Conclusion.....	37
8.3. Discipline Specific Sub-Consulted Review Summary.....	39
9. CLINICAL VALIDATION REVIEW.....	39
9.1. Review of Clinical Studies Clinical Studies.....	39
10. HUMAN FACTORS VALIDATION REVIEW.....	39
11. FACILITIES & QUALITY SYSTEMS (Deferred to CDRH/OC).....	39
11.1. Facility Inspection Report Review.....	39

11.2.	Quality Systems Documentation Review .....	40
11.3.	Control Strategy Review .....	40
11.4.	Facilities & Quality Systems Review Conclusion (Deferred to OC) .....	41
12.	APPENDIX A (INFORMATION REQUESTS) .....	42
12.1.	Mid-Cycle Information Requests .....	42
12.2.	Interactive Information Requests.....	43
12.2.1.	Interactive Information Requests sent on 12/17/2019.....	43
12.2.2.	Interactive Information Requests sent on 1/7/2020.....	45

### 3. PURPOSE/BACKGROUND

#### 3.1. Scope

Sun Pharmaceutical Industries Limited is requesting approval of Octreotide Acetate Injection. The device constituent of the combination product is a Pen-Injector.

CDER/OND has requested the following [consult](#) for review of the device constituent of the combination product:

please review the new NDA

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
- Risk Assessment
- Labeling pertaining to the device
- Design controls

This review will not cover the following review areas:

- Human Factors (deferred to DMEPA)
- Facilities and Compliance (Separate CDRH OC Consult)
- Fluid path extractables leachables
- Drug compatibility

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

#### 3.2. Prior Interactions

None

##### 3.2.1. Related Files

N/A

#### 3.3. Indications for Use

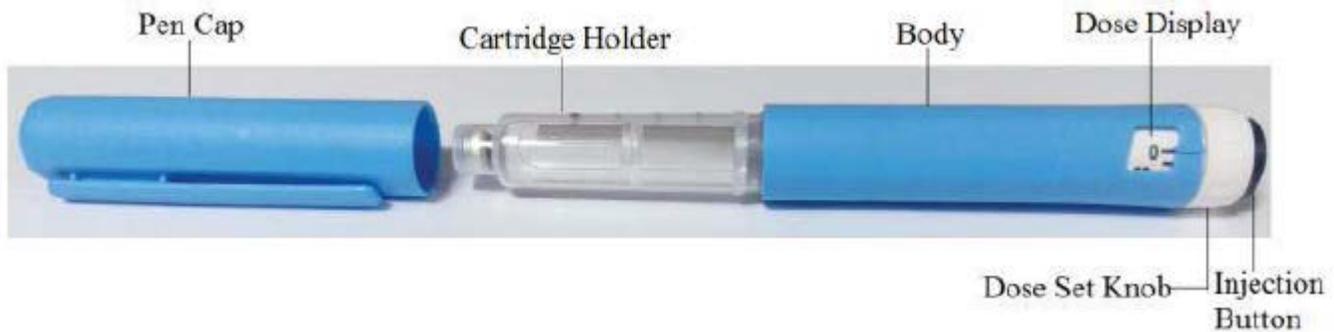
Combination Product	Indications for Use
Octreotide Acetate Injection	For the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors
Pen-Injector	<a href="#">Delivery of the Drug Product</a>

#### 3.4. Materials Reviewed

<a href="#">Materials Reviewed</a>
All files in 3.2.P.5 and 3.2.P.7
Response to IRs

## 4. DEVICE DESCRIPTION

### 4.1. Device Description



Octreotide Acetate Injection, 2.5 mg/mL, is filled in 3 mL colorless USP (b) (4) glass cartridges with 10 mm gray (b) (4) rubber plunger stopper and combination seal (cream inner and gray outer). One filled and sealed cartridge of Octreotide Acetate Injection, 2.5 mg/mL, packed in one transparent cartridge holder and assembled with the help of blue body subassembly (dark blue button and white dose set knob) and light blue cap for pen injector.

**Table 3.2.P.1:4**

	Components	Description for Sun's Product
Primary	Cartridge	3 mL colorless USP (b) (4) glass cartridge
	Plunger Stopper	10 mm grey (b) (4) plunger (b) (4)
	Seal	Combination (b) (4) seal (b) (4) cream/outer (b) (4) grey (b) (4)
Secondary	Pen	Disposable pen, Blue body subassembly with dark blue button and white dose set knob
	Cap	Light blue cap for disposable liquid pen
	Cartridge Holder	Transparent cartridge holder for disposable liquid pen

Changes from Wave 1 to Wave 2, in outer appearance of the fully assembled device are provided below in image 1.0:

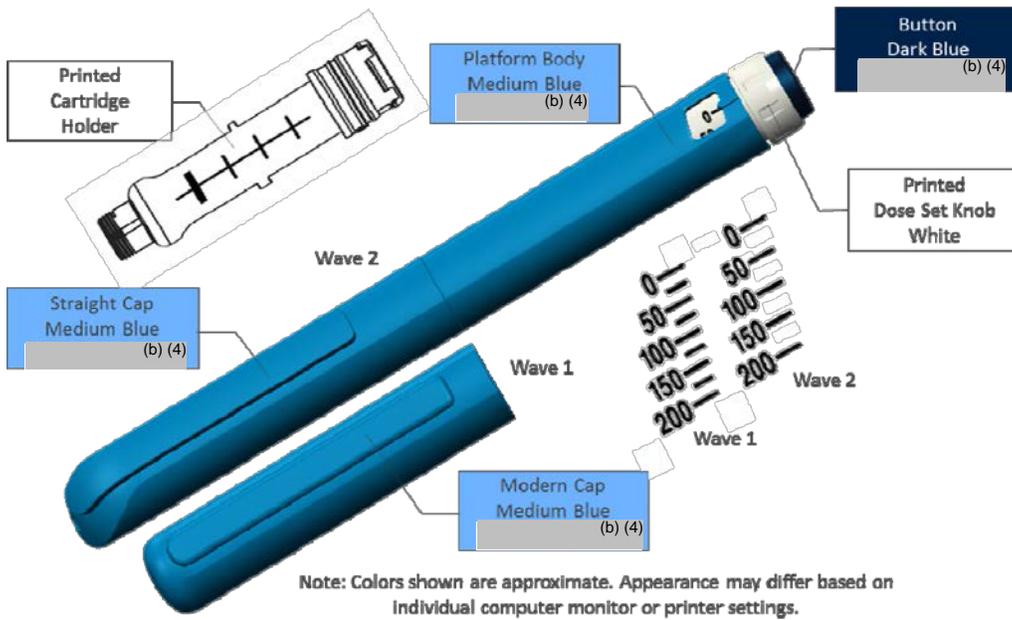


Table 3.0 Summarizes general characteristics of the injector:

**Table 3.0**

Device Characteristics	Applicable (Yes/No)	Details	Document reference
Injector/Platform Name	Yes	(b) (4)	ERD 18-035, Section 1. Scope
Specifications	Yes	Customer Specifications and Design Input Specifications	ERD 18-035 ERD 18-106
Injection tissue	Yes	Subcutaneous injection	ERD 18-106, Section 4.1
Depth of Injection	Yes	Subcutaneous injection	ERD 18-106, Section 4.1
Audible / visual feedback	Yes	Dose increment indication is audible and dose set knob is visual, end of dose is also visible.	ERD 18-035, Section 5.2.1 Quality Criteria ERD 18-106, Section 6.3.1 functional requirements, SID 12
Cap Removal Force	Yes	Its normal end user action. It comes under ergonomics/ comfortable to use.	ERD 18-035, Section 5.2.3 Quality Criteria ERD 18-106, Section 6.3.1 functional requirements SID 10, product functions ID 142-02, 142-03
Dose Accuracy	Yes	Volumetric Accuracy per ISO 11608-1	ERD 18-035, Section 5.2.1 Quality Criteria ERD 18-106, Section 6.3.1 functional requirements SID 3
Activation Force	No	Not Applicable	Not Applicable
Visibility of medication / container dose	Yes	Cartridge holder is transparent so that user can see medication inside glass cartridge	ERD 18-035, Section 3.1.4 ERD 18-106, Section 6.3.1 functional

			requirements SID 14
Last dose specifications	Yes	It is as per ISO 11608-1:2014	ERD 18-106, Section 6.3.1 functional requirements SID 3, Input/Cust. Req. ID 251
Safety Features	Yes	Ergonomics and comfortable to use	ERD 18-106, Section 6.3.1 functional requirements SID 10
Needle specifications, length and gauge	Yes	Needle 31 G x 5mm	ERD 18-035, Section 1. Scope ERD 18-106, Section 1.3.1
Connection type	Yes	User replaceable needles	ERD 18-106, Section 1.0 Description
Conformance to applicable standards	Yes	All applicable regulations, standards and guidance are mentioned	ERD 18-106, Section 5.0
Type of use (Single use, disposable, reusable)	Yes	Multi use, disposable	ERD 18-106, Section 1.0 Description
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Yes	Self-administration or administered by Health Care Provider	ERD 18-106, Section 4.1 Intended Use
Injection mechanism (e.g., manual piston, spring, gas, etc.)	Yes	Manual piston	ERD 18-035, Section 3.1.5.1 ERD 18-106, Section 1.0 ERD 18-106, Section 2.1.2
Method of actuation, any Automated Functions	No	No automated function	Not Applicable
Residual Medication	Yes	Total deliverable volume is minimum 2.8mL. However Cartridge would be filled with (b) (4)	ERD 18-106, Section 1.3.2
Delivered Volume (for single dose or selectable volume range for multi-dose pens)	Yes	It is multi-use, variable dose, disposable pen where four doses would be delivered viz. (b) (4) i) 20 µL ii) 40 µL iii) 60 µL iv) 80 µL	ERD 18-106, Section 1.3.2 and 1.3.3
Drug Container Type	Yes	3.0mL standard glass cartridge	ERD 18-035, Section 1. Scope, ERD 18-106, Section 1.3.1
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	Yes	Dose marking is in mcg however delivery would be in corresponding µL as concentration of drug is 2500 µg/mL.	ERD 18-035, Section 3.1.3 System markings, ERD 18-106, Section 1.3.3
		It can be administered at home or in	

Environments of use, Storage conditions and expiry	Yes	clinical environment. (b) (4)	ERD 18-106, Section 4.1.1.1 ERD 18-106, Section 4.1.1.2
Graduation marks / fill lines	Yes	Cartridge holder has dark colored markings to show the position of inside rubber stopper.	ERD 18-106, Section 1.3.3 system markings
Preparation and administration	Yes	The fully assembled drug device combination product would be supplied to the end user. During first use, user will detach the cap, attach the needle, prime the pen, set the dose and insert the needle at injection site and deliver the dose as per instructions given in Instructions For Use (IFU).	ERD 18-035, Section 1. Scope ERD 18-106, Section 2.0
Complete Material composition of injector	Yes	Fully assembled pen injector device is composed of several components, sub-components and sub-assemblies.	ERD 18-035, Section 1.0 scope, 3.1.1 Materials

#### 4.2. Steps for Using the Device

1. Pull off the pen cap.
2. Take a new needle and tear off the paper tab. Push the needle straight onto the pen and turn clockwise until it is tight. Pull off the outer needle cover and keep it for later.
3. Prime the pen (if it is new). - Turn the dose set knob and set it to "200". With the needle pointing up push in the injection button all the way until it stops. Repeat this procedure until you see a stream.
4. Routine use (for every dose) - Attach a new needle. Turn the dose set knob to select the correct dose you need to inject. - Insert the needle into selected injection site. Push and hold the injection button for 10 seconds. Then pull the needle from skin.
5. Put outer needle cover on needle. Unscrew and pull off needle and throw it away.
6. Replace the pen cap.

#### 4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A	Mid-Cycle Deficiencies: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A	Final Deficiencies: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A
<u>Reviewer Comments</u>		
Device description and steps for use is acceptable. Additionally, the Sponsor has provided a direct side by side comparison of their device to the RLD device.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		

**4.4. Facilities Information**

**NOTE: A separate consult is being done for compliance by OC.**

**4.5. Quality System Documentation Triage Checklist**

**NOTE: A separate consult is being done for compliance by OC.**

**5. LABELING**

**5.1. General Labeling Review**

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors			X
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
<u>MRI</u> Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

<p><b>Reviewer Comments</b>          Labeling is adequate.</p>
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**5.2. Device Specific Labeling Review**

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Labelled volume (Dose Markings)	X		

**5.3. Clinical Labeling Review**

The following Clinical Labeling Review was completed by

- Insert Consultant Name ; The full memo is located in [Appendix B.](#)
- The Lead Reviewer

Below is a summary of the review & [recommendation](#):

Clinical Labeling is reviewed by CDER Clinical team and Instructions for Use are reviewed by DMEPA. A cursory review was done by the Lead Reviewer and no issues were identified regarding device labeling specifically.

**5.4. Labeling Review Conclusion**

LABELING REVIEW CONCLUSION		
<b>Filing Deficiencies:</b> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A	<b>Mid-Cycle Deficiencies:</b> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A	<b>Final Deficiencies:</b> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A
<a href="#">Reviewer Comments</a>		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		

**No Additional Information Requests – Finalize Labeling Review Section**

## 6. DESIGN CONTROL SUMMARY

### 6.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		
Design Inputs/Outputs	Yes	No	N/A
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial			X
Bioequivalence Study utilized to-be-marketed device		X (IR resolved)	
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		

### 6.2. Design Controls Information Requests and Responses

#### 6.2.1. IR #1

1. In your Summary of Container Closure System, you provided a comparison between the “existing” and “commercial” versions of the pen injector and stated that “*there is some minor changes to the secondary packaging components between the exhibit and propose commercial pen injector.*” More information is necessary to ensure this change does not affect device function. Please clarify whether the design change affected any internal and/or mechanical components and which version(s) were used for all applicable device testing including the provided batch analyses, stability, and all clinical studies. If the testing you have performed used different versions, please provide a complete justification for each modification and whether it is expected to affect device performance, specifically, whether essential performance requirements (Dose Accuracy, Activation/Break loose/Glide Forces, Needle Length/Gauge) and other performance requirements (Ex. cap removal force) are affected.
  - a. Additionally, your device description is only provided in the Summary of Container Closure System and is missing information on several device characteristics. This information is required to ensure the device functions safely and effectively in the intended environment of use. Please provide a complete device description of the final finished device you intend to market. In your description, be sure to include pictures and/or diagrams of internal device components. A complete device description should also include (following aspects should be selected only if they apply to your device): the Injector/Platform Name, Specifications, Injection tissue and depth of injection, Audible / visual feedback, Cap Removal Force, Dose Accuracy, Activation Force, Visibility of medication container/Dose, Last Dose Specifications and Safety Features, Needle Specifications (Length(s), Gauge(s)), Connection type, Conformance to applicable standards,

Type of Use (e.g. single use, disposable, reusable, other), Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use), Injection mechanism (e.g., manual piston, spring, gas, etc.), Method of actuation, any Automated Functions, Residual Medication, Delivered Volume (for single dose or selectable volume range for multidose pens), Drug Container Type, Dose Units of Measure (e.g., mL, Units, mg, increments, etc.), Environments of use, Storage conditions and expiry, Graduation marks / fill lines, Preparation and administration (describe all that are applicable), Safety Features, Complete Material composition of injector, and other characteristics which may be applicable to your device. Please note if this information is provided elsewhere in the submission you may simply reference it.

**Response:**

Please note that comparison between existing and commercial pen components for Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL Pen Injector along with diagrams has been provided in section 3.2.P.7.1 of original NDA submission under leaf “Summary of Container Closure System” (page # 3 of 11).

Details of changes in internal as well as external pen components between the exhibit and proposed commercial pen injector are summarized in **Attachment-1**. Device supplier uses terminology ‘Wave 1’ for exhibit batch pen components and ‘Wave 2’ for pen components for commercial batches. These changes are implemented to make the delivery device more robust and better in look and feel and are not expected to affect device performance. As there is no design change with respect to functional performance of the device, the specifications for delivered dose volume, break loose and glide force remains same for both the versions. Also other performance requirements like cap removal force specifications are same for both the versions.

Information on version of device used for device testing is provided in Table 1.0 and Comparison of essential performance requirements is provided in Table 2.0

**Table 1.0**

Type of Analysis / Study	Exhibit pen components (Wave1)	Commercial pen components (Wave2)
Stability	Yes	No
Clinical (Bioequivalence)	Yes	No
Design Verification Test including dose accuracy	Yes	Yes
Human Factors Study (Formative) with straight cap	Yes	No
Human Factors Study (Summative or validation) with straight cap	No	Yes

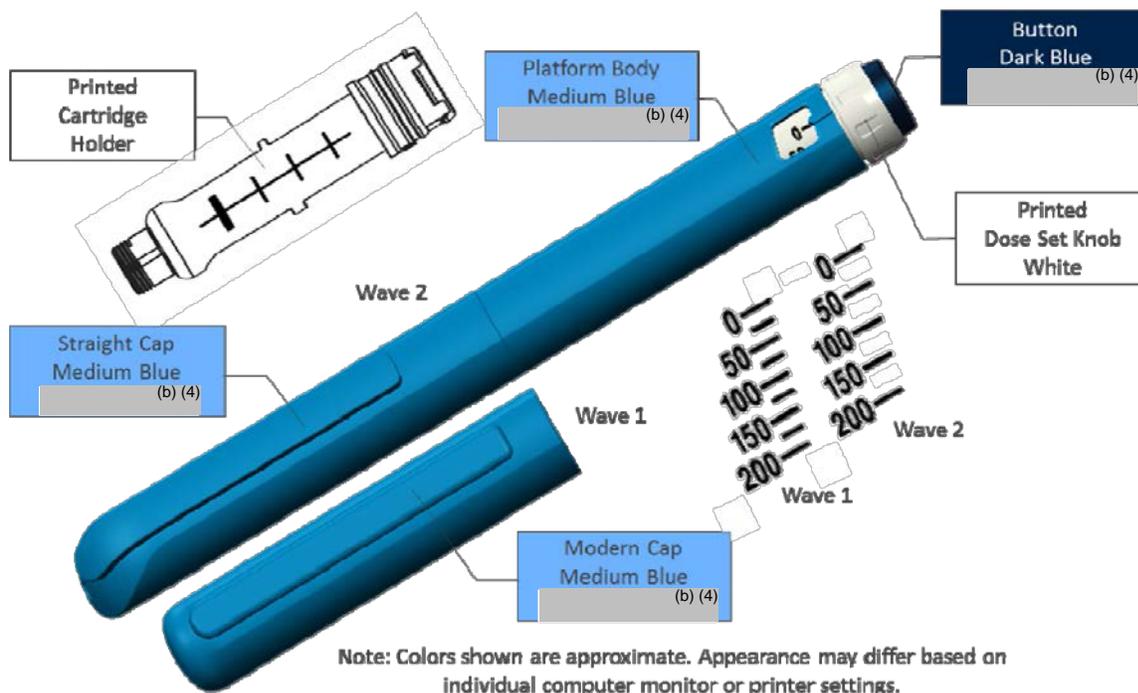
**Table 2.0**

Essential Performance Requirements	Exhibit batch pen components	Commercial pen components

Delivered dose volume	i) 20 $\mu$ ii) 40 $\mu$ iii) 60 $\mu$ iv) 80 $\mu$ L	(b) (4)	i) 20 $\mu$ L ii) 40 $\mu$ L iii) 60 $\mu$ L iv) 80 $\mu$ L	(b) (4)
Break loose force*	(b) (4)			
Glide Force*	(b) (4)			
Reference Design Verification Summary Report	ERD 6017-17-734-052 Revision 01		ERD 6017-17-734-173 Revision 03	
Other Performance Requirements	(b) (4)			
Cap removal force	(b) (4)			
*Break loose and glide force test is conducted on primary containers (3.0mL standard glass cartridge). There is no change in primary containers for exhibit batch and commercial version of drug device combination product.				

Changes from Wave 1 to Wave 2, in outer appearance of the fully assembled device are provided below in image 1.0.

**Image 1.0**



Design details and internal mechanical components for device are provided below in Image 2.0 and Image 3.0.

- a. Please note that complete device description including functional specifications as well as external device compatibility, storage conditions, material details are provided in Customer Specification and Design Input Specifications (DIS) documents for both the versions of pen components. Please note that Customer Specification (page # 21 of 702) and Design Input Specifications (DIS) (page # 41 of 702) have already been provided in section 3.2.P.7 of original NDA submission under leaf “*Component Specification and Test Data*”.

Information on device characteristics, its applicability, brief details and document references are summarized in below table.

**Table 3.0**

<b>Device Characteristics</b>	<b>Applicable (Yes /No)</b>	<b>Details</b>	<b>Document reference</b>
Injector/Platform Name	Yes	(b) (4) Disposable Pen	ERD 18-035, Section 1. Scope
Specifications	Yes	Customer Specifications and Design Input Specifications	ERD 18-035 ERD 18-106
Injection tissue	Yes	Subcutaneous injection	ERD 18-106, Section 4.1
Depth of Injection	Yes	Subcutaneous injection	ERD 18-106, Section 4.1
Audible / visual feedback	Yes	Dose increment indication is audible and dose set knob is visual, end of dose is also visible.	ERD 18-035, Section 5.2.1 Quality Criteria ERD 18-106, Section 6.3.1 functional requirements, SID 12
Cap Removal Force	Yes	Its normal end user action. It comes under ergonomics/ comfortable to use.	ERD 18-035, Section 5.2.3 Quality Criteria ERD 18-106, Section 6.3.1 functional requirements SID 10, product functions ID 142-02, 142-03
Dose Accuracy	Yes	Volumetric Accuracy per ISO 11608-1	ERD 18-035, Section 5.2.1 Quality Criteria ERD 18-106, Section 6.3.1 functional requirements SID 3
Activation Force	Yes	Provided interactively (see IR section); (b) (4)	Provided interactively
Visibility of medication / container dose	Yes	Cartridge holder is transparent so that user can see medication inside glass cartridge	ERD 18-035, Section 3.1.4 ERD 18-106, Section 6.3.1 functional requirements SID 14

Last dose specifications	Yes	It is as per ISO 11608-1:2014	ERD 18-106, Section 6.3.1 functional requirements SID 3, Input/Cust. Req. ID 251
Safety Features	Yes	Ergonomics and comfortable to use	ERD 18-106, Section 6.3.1 functional requirements SID 10
Needle specifications, length and gauge	Yes	Needle 31 G x 5mm	ERD 18-035, Section 1. Scope ERD 18-106, Section 1.3.1

Device Characteristics	Applicable (Yes/No)	Details	Document reference
Connection type	Yes	User replaceable needles	ERD 18-106, Section 1.0 Description
Conformance to applicable standards	Yes	All applicable regulations, standards and guidance are mentioned	ERD 18-106, Section 5.0
Type of use (Single use, disposable, reusable)	Yes	Multi use, disposable	ERD 18-106, Section 1.0 Description
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Yes	Self-administration or administered by Health Care Provider	ERD 18-106, Section 4.1 Intended Use
Injection mechanism (e.g., manual piston, spring, gas, etc.)	Yes	Manual piston	ERD 18-035, Section 3.1.5.1 ERD 18-106, Section 1.0 ERD 18-106, Section 2.1.2
Method of actuation, any Automated Functions	No	No automated function	Not Applicable
Residual Medication	Yes	Total deliverable volume is minimum 2.8mL. (b) (4)	ERD 18-106, Section 1.3.2
Delivered Volume (for single dose or selectable volume range for multi-dose pens)	Yes	It is multi-use, variable dose, disposable pen where four doses would be delivered viz. i) 20 µL (b) (4) v) 40 µL vi) 60 µL vii) 80 µL	ERD 18-106, Section 1.3.2 and 1.3.3

Drug Container Type	Yes	3.0mL standard glass cartridge	ERD 18-035, Section 1. Scope, ERD 18-106, Section 1.3.1
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	Yes	Dose marking is in mcg however delivery would be in corresponding $\mu$ L as concentration of drug is 2500 $\mu$ g/mL.	ERD 18-035, Section 3.1.3 System markings, ERD 18-106, Section 1.3.3

Device Characteristics	Applicable (Yes /No)	Details	Document reference
Environments of use, Storage conditions and expiry	Yes	It can be administered at home or in clinical environment. (b) (4)	ERD 18-106, Section 4.1.1.1 ERD 18-106, Section 4.1.1.2
Graduation marks / fill lines	Yes	Cartridge holder has dark coloured markings to show the position of inside rubber stopper.	ERD 18-106, Section 1.3.3 system markings
Preparation and administration	Yes	The fully assembled drug device combination product would be supplied to the end user. During first use, user will detach the cap, attach the needle, prime the pen, set the dose and insert the needle at injection site and deliver the dose as per instructions given in Instructions For Use (IFU).	ERD 18-035, Section 1. Scope ERD 18-106, Section 2.0
Complete Material composition of injector	Yes	Fully assembled pen injector device is composed of several components, sub-components and sub-assemblies.	ERD 18-035, Section 1.0 scope, 3.1.1 Materials

**Reviewer Comments:**

The deficiency requested the Sponsor to: clarify whether their design change affected any internal and/or mechanical components, clarify which version(s) were used for all applicable device testing, and provide a justification for each modification and whether it affected device performance. The Sponsor has replied that they used a 'Wave 1' version for exhibit batch pen components and 'Wave 2' for pen components for commercial batches. The Sponsor argues that changes in Wave 2 make the delivery device "more robust" and "better in look and feel" and do not affect performance. Table 1.0 in the response above shows that Wave 1 was used for the clinical BE study, stability testing, verification, and formative HF testing; while Wave 2 was also used for verification testing and summative HF. Table 2.0 shows that the verification test requirements are the same for both versions and that both versions had the same acceptance criteria. This bridges the Wave

1 to the Wave 2 device acceptably. The modifications are minor and do not appear to affect performance (main changes are pen cap shape, markings, etc.). The Sponsor additionally provided a more complete device description. This is acceptable.

The response above also mentions that activation force is not applicable. In this case it is not activation force, but injection force that is an essential performance requirement (discussed below)

**Reviewer Comments**

**The following IRs were sent and resolved as part of the review.**

1. In your Summary of Container Closure System, you provided a comparison between the “existing” and “commercial” versions of the pen injector and stated that “*there is some minor changes to the secondary packaging components between the exhibit and propose commercial pen injector.*” Please clarify whether the design change affected any internal and/or mechanical components and which version(s) were used for all applicable device testing including the provided batch analyses, stability, and all clinical studies. If the testing you have performed used different versions, please provide a complete justification for each modification and whether it is expected to affect device performance, specifically, whether essential performance requirements (Dose Accuracy, Activation/Break loose/Glide Forces, Needle Length/Gauge) and other performance requirements (Ex. cap removal force) are affected.
  - a. Additionally, your device description is only provided in the Summary of Container Closure System and is missing information on several device characteristics. This information is required to ensure the device functions safely and effectively in the intended environment of use. Please provide a complete device description of the final finished device you intend to market. In your description, be sure to include pictures and/or diagrams of internal device components. A complete device description should also include (following aspects should be selected only if they apply to your device): the Injector/Platform Name, Specifications, Injection tissue and depth of injection, Audible / visual feedback, Cap Removal Force, Dose Accuracy, Activation Force, Visibility of medication container/Dose, Last Dose Specifications and Safety Features, Needle Specifications (Length(s), Gauge(s)), Connection type, Conformance to applicable standards, Type of Use (e.g. single use, disposable, reusable, other), Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use), Injection mechanism (e.g., manual piston, spring, gas, etc.), Method of actuation, any Automated Functions, Residual Medication, Delivered Volume (for single dose or selectable volume range for multidose pens), Drug Container Type, Dose Units of Measure (e.g., mL, Units, mg, increments, etc.), Environments of use, Storage conditions and expiry, Graduation marks / fill lines, Preparation and administration (describe all that are applicable), Safety Features, Complete Material composition of injector, and other characteristics which may be applicable to your device. Please note if this information is provided elsewhere in the submission you may simply reference it.
2. Risk Analysis Documentation – 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.
3. We acknowledge you have provided verification testing of your device in your submission. You did not provide a specification for Injection Time, although your labeling indicates a specific injection

time. Please provide a justification why you have not included injection time in your verification testing or release/stability/shipping testing. Alternatively provide Design Verification Documentation traced to the design inputs of the device constituent which applies to injection time. Ensure that you utilize test methods and preconditioning that simulate the intended use of your product. You should use and justify a statistically significant sample size for this verification testing. Provide valid justifications for the acceptability of any test results that do not pass its acceptance criteria.

- a. Additionally, you have not clarified whether your verification testing was performed with the final to-be-marketed version of the device. 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 (or different device design) 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.

### 6.3. Applicable Standards and Guidance Documents

#### Generally Applicable Standards and Guidance Documents:

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

#### Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products	NA	Y
ISO 11608- 1:2014. Needle-based injection systems for medical use — Requirements and test methods — Part 1: Needle-based injection systems.	Y	Y

### 6.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
<b>Filing Deficiencies:</b> <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	<b>Mid-Cycle Deficiencies:</b> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	<b>Final Deficiencies:</b> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A

**Reviewer Comments**

CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor:  Yes  No

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
<b>Information Request #</b>	<p><b>1. We acknowledge you have provided verification testing of your device in your submission.</b>  <b>You did not, however, provide a specification for Injection Time, although your labeling indicates a specific injection time. Please provide a justification why you have not included injection time in your verification testing or release/stability/shipping testing. Alternatively provide Design Verification Documentation traced to the design inputs of the device constituent which applies to injection time. Ensure that you utilize test methods and preconditioning that simulate the intended use of your product. You should use and justify a statistically significant sample size for this verification testing. Provide valid justifications for the acceptability of any test results that do not pass its acceptance criteria.</b></p> <p><b>a. Additionally, you have not clarified whether your verification testing was performed with the final to-be-marketed version of the device. 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 (or different device design) 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.</b></p> <p><b>b. You have not provided a biocompatibility assessment of the device, including the material components, the manufacturing processes, the clinical use of the device including the intended anatomical location, and the frequency and duration of exposure. This information is required to ensure the device is safe. Please provide a justification or documentation to support the biocompatibility of your device constituent including test reports and protocols to ensure that the system components are biocompatible commensurate with the level and duration of patient contact. Refer to the FDA Guidance titled Use of International Standard ISO 10993-1, "Biological evaluation of medical devices</b>  <b>- Part 1: Evaluation and testing within a risk management process" – Guidance for Industry and Food and Drug Administration Staff</b></p>	

	<b>issued in June 2016 (<a href="https://www.fda.gov/media/85865/download">https://www.fda.gov/media/85865/download</a>) for more details.</b>
<b>Sponsor Response</b>	Addressed in Design verification section
<b>Reviewer Comments</b>	See section below
<b>Response Adequate:</b>	<input checked="" type="checkbox"/> <b>Yes</b> <input type="checkbox"/> <b>No, See IR # Sent on</b> <input type="text"/> <small>Click or tap to enter a date.</small>

## 7. RISK ANALYSIS

### 7.1. Risk Management Plan

The Sponsor has developed a process FMEA, which was provided interactively. Additionally, the Sponsor analysed use errors in the formative/summative HF studies. (b) (4) supplies the customized pen injector and the Sponsor leveraged the dFMEA from (b) (4) (report was provided in 3.2.P.7. Component Specification and Data).

<b>Risk Analysis Method</b>	<b>Latest Approval Date</b>
Design failure modes and effects analysis (DFMEA)	(b) (4) LOA provided for MAF- (b) (4) review
Application Failure Modes and Effects Analysis (AFMEA) or (UFMEA) – Part of Human Factors study	08 August 2017 Formative HF study
Risk Management Summary Report (RMSR)	Conducted by (b) (4) (supplier) for the pen platform, provided in NDA (2018)
Application Failure Modes and Effects Analysis (AFMEA) or (UFMEA) – Part of Human Factors study	13 March 2019 Summative HF study
Application Failure Modes and Effects Analysis (AFMEA) or (UFMEA) – Separate document	07 September 2019 – Provided interactively (excerpt below)
Process Failure Modes and Effects Analysis (PFMEA)	21 September 2019 - Provided interactively (excerpt below)

### **Reviewer Comments**

The approach is acceptable and covers the requirements outlined in the initial IR to the Sponsor.

### 7.2. Hazard Analysis and Risk Summary Report

Sponsor's uFMEA (AFMEA):

SUN PHARMA		Application Failure Mode and Effect Analysis										Device Development									
A-FMEA												New Rating									
Sr No #	Process / Function	Potential Failure Mode(s)	Potential Cause(s) of failure	Potential Effects(s) of failure	Current Controls		Rating				Recommended action(s)	Responsibility & Target completion date	Action(s) taken & Completion date	O C C	S E V	D E T	R P N	O C C	S E V	D E T	R P N
					Prevention Controls	Detection Controls	O C C	S E V	D E T	R P N											
1	Pen Storage	Before first use, does not store pen at intended temperature of 36°F to 46°F (2°C to 8°C).	User does not follow IFU	Potential for spoiled drug and compromise drug efficacy	Store new unused pens in the refrigerator between 36° to 46° F (2° to 8° C) in the carton.	IFU Training	High	Critical	Almost Certain	16											
		After first use, does not store pen between 59°F to 77°F (15°C to 25°C) for up to 28 days.	User does not follow IFU	Potential for spoiled drug and compromise drug efficacy	Store in-use pens at controlled room temperature between 68°F to 77°F (20°C to 25°C). Excursions between 59°F (15°C) and 86°F (30°C) are allowed for up to 28 days.																
		Stores pen on needle	User does not follow IFU	Potential for air in needle or contaminated needle if reusing same needle.	Do not store a pen with a needle attached.																
		Does not protect from light	User does not follow IFU	Potential for spoiled drug and compromise drug efficacy.	Do not store the pen in direct sunlight																

pFMEA describing the process, risks, and mitigations:

Quantitative Risk Assessment of Cartridge packing line (Room No. (b) (4))	
(b) (4)	

(b) (4) Risk Management Plan (leveraged for dFMEA). The report defines risk severity, residual risk evaluation, risk management activities, evaluation, reporting, etc. Excerpt shown below:

**1.2 Failure Mode and Effects Analysis (FMEA)**

The FMEA methodology is used to identify, estimate, evaluate and control the risk associated to the use of the Disposable Pen System in the scope of the Intended Use. Four types of FMEAs as listed below are performed using the (b) (4) Disposable Pen:

**1.2.1 Use FMEA**  
 Use FMEA has been performed to identify, estimate, evaluate and control the failure modes that could occur during the use of the product by the end-user. The product was analyzed as one system during the Use FMEA activities. Reasonably foreseeable misuses of the product by the end-user were identified and analyzed as part of the Use FMEA.

**1.2.2 Design FMEA**  
 Design FMEA is used to identify, estimate, evaluate and control the product design failure modes that lead to the product failure modes. These product design failure modes are identified through the cascade (from Use FMEA) (see Flowchart 1) and/or through the product knowledge.

**1.2.3 Process FMEA**  
 Process FMEA is used to identify, estimate, evaluate and control the process failure modes that lead to the product failure modes. These process failure modes are identified through the cascade (from Design FMEA) (see Flowchart 1) and/or through the product and process knowledge.

**Reviewer Comments**

The Sponsor's risk management process leverages the design FMEA from the supplier, (b) (4) has a complete risk management plan, which is continuously applied during the (b) (4) Disposable Pen life cycle and additional risks, if identified, are reviewed and documented following the process described in the document submitted in the NDA by the Sponsor. In addition, the Sponsor has a risk management process for use risks and final assembly processes.

**7.3. Risk Analysis Review Conclusion**

RISK ANALYSIS REVIEW CONCLUSION		
<b>Filing Deficiencies:</b> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input checked="" type="checkbox"/> N/A	<b>Mid-Cycle Deficiencies:</b> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	<b>Final Deficiencies:</b> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A
<b>Reviewer Comments</b> The risk analysis provided is sufficient.		
<b>CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor:</b> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		

	<b>Date Sent:</b> <small>Click or tap to enter a date.</small>	<b>Date/Sequence Received:</b> <small>Click or tap to enter a date.</small>
<b>Information Request #</b>	Risk Analysis Documentation – 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	

	<p>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.</p>
<b>Sponsor Response</b>	<p>Please note that as a part of human factor studies, Application Failure Modes and Effects Analysis (AFMEA) or User FMEA have been conducted which include risks associated with the device constituent part. This risk analysis included user tasks, critical task, potential use errors, clinical impact, risk severity, mitigations, study technique, measures and failure definition. Please note that human factors studies have been provided in section 5.3.5.4 of original NDA submission. Please note that recommendations from formative study were implemented before conducting summative validation study. Sun has also conducted and prepared separate AFMEA document to analyse the occurrence, severity and detection rating for each potential failure modes. Copy of this risk analysis have been provided herewith in <b>Attachment 2</b>. This analysis was conducted to identify, eliminate or minimize the impact of potential risks associated with end user of the final finished combination product. AFMEA concludes that Octreotide Acetate Injection, 2.5mg/mL, Pen Injector, 2.8mL is a low risk product and use errors will not cause serious consequences. All residual risks are mitigated and risk control measures already implemented.</p> <p>Sun and device supplier has conducted risk analysis as per established ISO standard - ISO 14971 Medical devices - Application of risk management to medical devices.</p> <p>Design Failure Modes and Effects Analysis (DFMEA) had also been conducted for the Disposable Liquid Pen (DLP) platform by device supplier, (b) (4). Same DLP platform is used to customize the Sun Pharma’s Octreotide pen. Sun Pharma has provided Letter of Authorisation (LOA) for (b) (4) MAF (b) (4) which contains DFMEA for DLP platform in section 1.4.1 of original NDA submission under leaf “DMF Letter of Authorization”. Also Risk Management Summary Report (RMSR) is part of original NDA submission, section 3.2.P.7.2 “Component Specification and Test Data” (page # 163 of 702). The (b) (4) RMSR provides a detailed overview on how residual risks are identified and managed for the (b) (4) system, including UFMEA, DFMEA and PFMEA. Risk benefit analyses are also included for all moderate (level 2) and higher risks.</p> <p>Sun Pharma has also conducted Process Failure Modes and Effects Analysis (PFMEA) for Octreotide pen assembly and final packaging. PFMEA was conducted to identify potential failure modes, unwanted events, its root causes and measures to mitigating those during assembling of device constituent parts</p>

with drug filled cartridges and then labelling and packaging. Copy of this risk assessment has been provided herewith in **Attachment 3**.

Below Table 4.0 provides information on methods used for conducting risk analysis for octreotide drug-device combination product and corresponding latest document approval date.

**Table 4.0**

Risk Analysis Method	Latest Approval Date
Design failure modes and effects analysis	(b) (4) LOA provided for MAF- (b) (4)
Application Failure Modes and Effects Analysis (AFMEA) or (UFMEA) – Part of Human	08 August 2017 (Formative HF study)
Risk Management Summary Report (RMSR)	28 August 2018
Application Failure Modes and Effects Analysis (AFMEA) or (UFMEA) – Part of Human	13 March 2019 (Summative HF study)
Application Failure Modes and Effects Analysis (AFMEA) or	07 September 2019
Process Failure Modes and Effects Analysis	21 September 2019

**Reviewer Comments**

The deficiency requested the Sponsor to provide a risk analysis for the device constituent. The Sponsor stated that as part of human factor studies, Application Failure Modes and Effects Analysis (AFMEA) or User FMEA have been conducted which included risks associated with the device constituent part per ISO 14971. Design Failure Modes and Effects Analysis (dFMEA) had also been conducted for the Disposable Liquid Pen (DLP) platform by device supplier, (b) (4). The platform is used for this pen injector. The Sponsor has also provided Letter of Authorization (LOA) for (b) (4) MAF- (b) (4) which contains the dFMEA. As part of their response, the Sponsor has also provided a Process Failure Modes and Effects Analysis (pFMEA) for the pen assembly and the final packaging. The pFMEA identified potential failure modes, unwanted events, root causes and mitigations during assembly, filling, labelling and packaging. The response is **acceptable**.

**Response Adequate:**

Yes  No, See IR # Sent on [Click or tap to enter a date.](#)

## 8. DESIGN VERIFICATION REVIEW

### 8.1. Performance/Engineering Verification

#### 8.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method <u>Acceptable</u> (Y/N)	<u>Validation</u> (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Delivered Dose Accuracy	Dose(mcg)=50 Dose volume=0.02mL ± (b) (4), K value = Pass if K greater than equal to (b) (4). Dose(mcg)=100 Dose volume=0.04mL ± (b) (4), K value = Pass if K greater than equal to (b) (4). Dose(mcg)=200 Dose volume=0.08mL ± (b) (4), K value = Pass if K greater than equal to (b) (4).	Y Finished Product -Analytical Test Procedure, pg. 44/50	Y (HF Validation for dose selector)	Y	Y
Glide force	Not more than (b) (4)	Y	Y	Y- See IR 12.2.1-12.2.2	Y
Break-loose force	Not more than (b) (4)	Y	Y	Y – See IR 12.2.1-12.2.2	Y
Injection Time	Not Provided	Y (leveraged by break loose and glide force testing above)	N/A	N/A	N/A
Injection Force	(b) (4)	Y	Y	Y	Y

**Reviewer Comment**

Injection time not provided – a justification or complete testing was required and requested with an IR. The Sponsor responded with a justification that injection time is not relevant since it is variable and since they additionally instruct the user to hold the injector for 10 seconds after visual/audio feedback that the injection is complete.

The Sponsor has not directly addressed dial torque of the dose selector or injection force of the button itself. Dial torque measurement, however, is independent from the drug/cartridge, therefore, it can be leveraged from (b) (4) MAF (b) (4), shown below, where the requirement is (b) (4)

The Sponsor makes the argument that injection force (pushing the button) is manual and is a direct push. The risk is present, however, of poorly manufactured components creating friction between the button and container (breakloose and glide forces were tested on the internal container only). However, BL/GF are very low ( (b) (4) and the interference from components or internal friction is not likely to raise the force much higher than (b) (4), which would need further testing.

To note, the MAF from (b) (4) had data on the component alone (likely without aging or shipping) in the current version of MAF- (b) (4), which has an UL of (b) (4) which is acceptable:

(b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Therefore, the device is showing possibility for out of spec glide force and injection force is not reported in the submission. The following IR was issued and resolved (See IR section 12.2.1 and 12.2.2)

8.1.2. Verification of Design Inputs Evaluation

<u>Design Input</u>	<u>Design Output</u>	<u>Verification Method</u>	<u>Results/Deviations</u>	<u>Adequately Verified (Y/N)</u>	<u>Validated through Clinical, Human Factors or Other</u>	<u>Adequately Validated (Y/N)</u>
Delivered Dose Accuracy	Dose(mcg)=50 Dose volume=0.02mL ± (b) (4), K value = Pass if K greater than equal to (b) (4)	32 nos. of pens are taken. For a particular dose volume, 96 values of delivered dose need to be taken. Dose Delivered from Prefilled pen in mL = Weight of sample (g) delivered from Pen injector / Density of the sample	K value: 8.167 K value: 9.800 K value: 8.727	Y	Y	Y
	Dose(mcg)=100 Dose volume=0.04mL ± (b) (4), K value = Pass if K greater than equal to (b) (4)	Calculate mean, standard deviation of dose delivered for 96 values of 32 pen injector for each dose setting (0.02mL, 0.04mL and 0.08mL).	K value: 7.538 K value: 8.083 K value: 7.231			
	Dose(mcg)=200 Dose volume=0.08mL ± (b) (4), K value = Pass if K greater than equal to (b) (4)	Calculate the K <sub>Actual</sub> for each dose volume. Where “K” is tolerance limit factor as per ISO 11608-1:2014.  Pass if $K_{Actual} \geq (b) (4)$ for each dose setting	K value: 10.667 K value: 8.167 K value: 5.529			
Glide force	Not more than (b) (4)	Disassemble the pen and take out cartridge for testing. • Take 32 nos. of filled, crimped, stoppered cartridges	Mean: 4.943 N Mean: 4.941 N Mean: 5.287 N	Y	Y	Y

		<ul style="list-style-type: none"> <li>• Calculate the travel distance “X” in mm using scale from end of stopper touching the</li> <li>• Solution to bottom part of syringe as shown in picture &amp; Set the parameter in machine...</li> </ul>				
Break-loose force	Not more than (b) (4)	<ul style="list-style-type: none"> <li>• Disassemble the pen and take out cartridge for testing.</li> <li>• Take 32 nos. of filled, crimped, stoppered cartridges</li> <li>• Calculate the travel distance “X” in mm using scale from end of stopper touching the</li> <li>• Solution to bottom part of syringe as shown in picture &amp; Set the parameter in machine...</li> </ul>	Mean: 6.607 N Mean: 6.375 N Mean: 6.936 N	Y	Y	Y
Injection Time	Variable, based on dose; also variable depending on force exerted by user.	N/A	N/A	N – N/A	Y	Y

**Reviewer Comment**  
 Injection time is not provided, which was an initial IR. The Sponsor has responded saying that injection time is not a necessary EPR for this device since the injection is manually driven and has different dose selections. This response was discussed above and is acceptable, primarily because the sponsor controls for break loose and glide forces.

8.1.3. *Evaluation of Test Methods*

<b>Title:</b>	Annexure-V-Simulated Shipping Study Protocol
<b>Scope/Objective &amp; Acceptance Criteria:</b>	<i>To check the effect of vibrations &amp; shocks during transportation/manual handling on Pen functionality of Octreotide Acetate Injection, 2.5mg/mL, Pen Injector , 2.8mL packed in 2's thermoformed tray which is further packed in a carton. Such 12 cartons are packed in 3-Ply duplex box and such 8 numbers of 3-Ply duplex boxes are then packed in shipper (5-Ply corrugated box).</i>

	<p>10.1 There should not be any damage to Package &amp; component after performance of Vibration &amp; drop testing.</p> <p>10.2 Physicochemical parameter of test sample should be within specification limit as per approved STP.</p> <p>10.3 Break out force should not be more than (b) (4) &amp; Glide force should not be more than 10N.</p>
<p><u>Methods</u></p>	<p>Vibration study:</p> <p>7.3 Packaging Development Scientist shall place the filled shippers on the vibration table. (Machine Model (b) (4) System). Suitable provision is made at the center of the table in order to keep the shipper in upward orientation during the testing.</p> <p>7.4 Perform the test at fixed frequency at (b) (4) RPM with amplitude of (b) (4) mm and Random mode of vibration for (b) (4) hours &amp; report the visual observation.</p> <p>Drop test study:</p> <p>7.5 Packaging Development scientist shall perform drop test of filled shipper after vibration testing.</p> <p>7.6 Hold the shipper at height (b) (4) as recommended in ASTM (b) (4) for weight ranging from (b) (4) kg and drop the shipper once on each faces as per below figure on flat rigid surface.</p> <p>Shipper Shape - Rectangular</p> <p>Shipper Weight - Approx (b) (4) kgs</p> <p>After vibration test, all the cartons to be checked for Visual Inspection for appearance, damage of the Carton, tray, Pen component, Cartridges, 3 ply shipper and 5 ply shipper.</p> <p>9.2 After drop test, all the cartons to be checked for Visual Inspection for appearance, damage of the Carton, tray, Pen component, Cartridges, 3 ply shipper and 5 ply shipper.</p> <p>9.3 To check physicochemical testing of test samples as per Annexure I.</p> <p>9.4 To check the break out &amp; glide force of filled cartridges as per Annexure II.</p>

<b>Results:</b>	(b) (4)	<p style="text-align: center;"><b>Table 4: Break loose force and Glide force test data</b></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="3" style="text-align: center;">Octreotide Acetate Injection, 2.5mg/mL, Pen Injector, 2.8mL</th> </tr> <tr> <th style="text-align: center;">Sr. No.</th> <th style="text-align: center;">Break loose force (N)</th> <th style="text-align: center;">Glide force (N)</th> </tr> </thead> <tbody> <tr> <td colspan="3" style="text-align: right;">(b) (4)</td> </tr> <tr> <td style="text-align: center;"><b>Mean</b></td> <td style="text-align: center;">9.2221</td> <td style="text-align: center;">8.0968</td> </tr> <tr> <td style="text-align: center;"><b>Std. Dev.</b></td> <td style="text-align: center;">0.7396</td> <td style="text-align: center;">0.7644</td> </tr> <tr> <td style="text-align: center;"><b>COV</b></td> <td style="text-align: center;">8.0199</td> <td style="text-align: center;">9.4408</td> </tr> </tbody> </table>	Octreotide Acetate Injection, 2.5mg/mL, Pen Injector, 2.8mL			Sr. No.	Break loose force (N)	Glide force (N)	(b) (4)			<b>Mean</b>	9.2221	8.0968	<b>Std. Dev.</b>	0.7396	0.7644	<b>COV</b>	8.0199	9.4408
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<b>Std. Dev.</b>	0.7396	0.7644																		
<b>COV</b>	8.0199	9.4408																		
<b>Conclusions/ Reviewer Comments:</b>	<p>The Shipping testing and protocol are not acceptable as they do not cover injection force. Also, the stability testing checked on 9/9/19 (manufactured in 2017).  <b>The follow-up IR above addresses the verification testing absence for injection force.</b></p>																			
<b>Acceptable:</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No																			

**8.2. Design Verification Review Conclusion**

DESIGN VERIFICATION REVIEW CONCLUSION		
<b>Filing Deficiencies:</b> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A	<b>Mid-Cycle Deficiencies:</b> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	<b>Final Deficiencies:</b> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A
<b>Reviewer Comments</b> The verification testing is acceptable and covers all EPRs, except for injection time, which is not covered, since it is variable.		
<b>CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor:</b> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		

	<b>Date Sent:</b> <small>Click or tap to enter a date.</small>	<b>Date/Sequence Received:</b> <small>Click or tap to enter a date.</small>
<b>Information Request #3</b>	<p><b>2. We acknowledge you have provided verification testing of your device in your submission.</b></p> <p><b>You did not, however, provide a specification for Injection Time, although your labeling indicates a specific injection time. Please provide a justification why you have not included injection time in your verification testing or release/stability/shipping testing. Alternatively provide Design Verification Documentation traced to the design inputs of the device constituent which applies to injection time. Ensure that you utilize test methods and preconditioning that simulate the intended use of your product. You should use and justify a statistically significant sample size for this verification testing. Provide valid justifications for the acceptability of any test results that do not pass its acceptance criteria.</b></p> <p><b>a. Additionally, you have not clarified whether your verification testing was performed with the final to-be-marketed version of the device. 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 (or different device design) 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.</b></p> <p><b>b. You have not provided a biocompatibility assessment of the device, including the material components, the manufacturing processes, the clinical use of the device including the intended anatomical location, and the frequency and duration of exposure. This information is required to ensure the device is safe. Please provide a justification or documentation to support the biocompatibility of your device constituent including test reports and protocols to ensure that the</b></p>	

	<p><b>system components are biocompatible commensurate with the level and duration of patient contact. Refer to the FDA Guidance titled Use of International Standard ISO 10993-1, "Biological evaluation of medical devices</b></p> <p><b>- Part 1: Evaluation and testing within a risk management process" – Guidance for Industry and Food and Drug Administration Staff issued in June 2016 (<a href="https://www.fda.gov/media/85865/download">https://www.fda.gov/media/85865/download</a>) for more details.</b></p>
<p><b>Sponsor Response</b></p>	<p>Please note that the Sun’s Octreotide pen injector device is manually operated, wherein user has to perform critical operating steps without any automated function. This pen injector is multi-use variable dose device unlike single use auto injector device which has automated mechanism for dose delivery.</p> <p>Injection time test is relevant in case of auto injector or automated drug delivery. In pen injector device, time taken for delivery of required dose is dependent on the user as well as volume of the dose to be delivered. Once the dose set knob of the device is dialed to the required dose then user will push injection button all the way down to ensure that pointer on body sub-assembly aligns to “0” mark of the device. This entire step is done by user manually. There is no automated mechanism or component used in the device which will trigger the dose delivery automatically. Hence, injection time is not considered as the test during design verification test.</p> <p>Please also note that in labeling user is instructed to hold the device for 10 seconds (counts) even after injection button is completely pressed down to ensure he/she receives the dose completely.</p> <p>a. Please note that design verification reports of both exhibit (wave I) (page# 119 of 702) and commercial (wave 2) (page # 77 of 702) version of pens had been provided in section 3.2.P.7.2 of original NDA submission under <i>leaf "Component Specification and Test Data"</i>.      Delivered dose accuracy test is part of both design verification tests.</p> <p>Other EPR test (break loose and glide force) is conducted on primary containers (3.0mL standard glass cartridge). There is no change in primary containers for exhibit batch and commercial version of pen components. As stated in <b>Table 1.0</b>, to-be marketed version is used for design verification and HF summative study. Design verification tests were conducted with saline water considering U1e fact that fluid properties (viscosity and density) of Octreotide acetate drug are similar to that of saline water. Report on equivalency of fluid properties has already been provided in section 3.2.P.7.2 of original NDA submission under <i>leaf "Component Specification and Test Data"</i> (page# 115 of 702).</p>

	<p>b. Please note that device supplier (b) (4) has conducted the biocompatibility assessment of exhibit as well as commercial pen components. Please note that ISO (b) (4) compliance statement from device supplier for biocompatibility assessment for exhibit (wave 1) as well as commercial (wave 2) pen components has been provided herewith in <i>Attachment 4</i>. These tests are conducted as per ISO (b) (4), "Biological evaluation of medical devices". Upon agency's requests, (b) (4) can provide detail protocols and reports directly to the agency.</p>
<b>Reviewer Comments</b>	<p>The Sponsor provided a justification for not using injection time as an EPR. The Sponsor claims that injection time is not a relevant parameter, since it is variable with each dose setting and the amount of force applied by the user. This is acceptable since the injection time parameter is also indirectly controlled through dose accuracy testing (and partially through B/L and glide force release testing). The response is acceptable.</p> <p>Biocompatibility was leveraged from (b) (4) has stated that they comply with ISO 10993 and a summary report of all in vitro and chemistry studies was provided. This is acceptable.</p>
<b>Response Adequate:</b>	<input checked="" type="checkbox"/> <b>Yes</b> <input type="checkbox"/> <b>No, See IR # Sent on</b> <a href="#">Click or tap to enter a date.</a>

**8.3. Discipline Specific Sub-Consulted Review Summary**

- No Additional Discipline Specific Sub-Consults were requested
- The following additional Discipline Specific Sub-Consults were requested:

**9. CLINICAL VALIDATION REVIEW**

**9.1. Review of Clinical Studies Clinical Studies**

- There is no device related clinical studies for review
- There are clinical studies for review

**10. HUMAN FACTORS VALIDATION REVIEW**

CDRH Human Factors Review conducted	<input type="checkbox"/>
Human Factors deferred to DMEPA	<input checked="" type="checkbox"/>

**11.FACILITIES & QUALITY SYSTEMS (Deferred to CDRH/OC)**

**11.1. Facility Inspection Report Review**

CDRH Facilities Inspection Review conducted	<input type="checkbox"/>
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CDRH Facilities Inspection Review was not conducted	<input checked="" type="checkbox"/>
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**11.2. Quality Systems Documentation Review**

CDRH Quality Systems Documentation Review conducted	<input type="checkbox"/>
CDRH Quality Systems Documentation Review was not conducted	<input checked="" type="checkbox"/>

**11.3. Control Strategy Review**

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

**Essential Performance Requirements Control Strategy Table**

*\* The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
<u>Dose Accuracy</u>	Release testing - Volume in container Not less than 3.1 ml. Delivered Dose Accuracy – for dose of 50, 100, and 200 mcg	Y
BL Force	Release testing	Y
Glide Force	Release testing	Y
Injection Time	Not Provided – Justification provided – acceptable due to BL and glide forces	N/A
Injection Force	Release testing	Y

**Reviewer Comments**

Th Sponsor’s approach is sufficient except for injection time, for which the Sponsor provided a justification interactively. Sample batch release specification and results for dose accuracy:

15	Delivered Dose Accuracy	Dose(mcg)=50 Dose volume=0.02mL ± (b) (4) K value = Pass if K greater than equal to (b) (4)	In-house	K value: 8.167	K value: 9.800	K value: 8.727
		Dose(mcg)=100 Dose volume=0.04mL ± (b) (4) K value = Pass if K greater than equal to (b) (4)		K value: 7.538	K value: 8.083	K value: 7.231
		Dose(mcg)=200 Dose volume=0.08mL ± (b) (4) K value = Pass if K greater than equal to (b) (4)		K value: 10.667	K value: 8.167	K value: 5.529

**Control Strategy Conclusion**

The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
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**11.4. Facilities & Quality Systems Review Conclusion (Deferred to OC)**

<b>FACILITIES &amp; QUALITY SYSTEMS REVIEW CONCLUSION</b>		
<b>Filing Deficiencies:</b> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A	<b>Mid-Cycle Deficiencies:</b> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A	<b>Final Deficiencies:</b> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A
<u><a href="#">Reviewer Comments</a></u>		
<b>CDRH sent Facilities &amp; QS Deficiencies or Interactive Review Questions to the Sponsor:</b> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		

<<END OF REVIEW>>

## 12. APPENDIX A (INFORMATION REQUESTS)

### 12.1. Mid-Cycle Information Requests

2. In your Summary of Container Closure System, you provided a comparison between the “existing” and “commercial” versions of the pen injector and stated that “*there is some minor changes to the secondary packaging components between the exhibit and propose commercial pen injector.*” More information is necessary to ensure this change does not affect device function. Please clarify whether the design change affected any internal and/or mechanical components and which version(s) were used for all applicable device testing including the provided batch analyses, stability, and all clinical studies. If the testing you have performed used different versions, please provide a complete justification for each modification and whether it is expected to affect device performance, specifically, whether essential performance requirements (Dose Accuracy, Activation/Break loose/Glide Forces, Needle Length/Gauge) and other performance requirements (Ex. cap removal force) are affected.
  - a. Additionally, your device description is only provided in the Summary of Container Closure System and is missing information on several device characteristics. This information is required to ensure the device functions safely and effectively in the intended environment of use. Please provide a complete device description of the final finished device you intend to market. In your description, be sure to include pictures and/or diagrams of internal device components. A complete device description should also include (following aspects should be selected only if they apply to your device): the Injector/Platform Name, Specifications, Injection tissue and depth of injection, Audible / visual feedback, Cap Removal Force, Dose Accuracy, Activation Force, Visibility of medication container/Dose, Last Dose Specifications and Safety Features, Needle Specifications (Length(s), Gauge(s)), Connection type, Conformance to applicable standards, Type of Use (e.g. single use, disposable, reusable, other), Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use), Injection mechanism (e.g., manual piston, spring, gas, etc.), Method of actuation, any Automated Functions, Residual Medication, Delivered Volume (for single dose or selectable volume range for multidose pens), Drug Container Type, Dose Units of Measure (e.g., mL, Units, mg, increments, etc.), Environments of use, Storage conditions and expiry, Graduation marks / fill lines, Preparation and administration (describe all that are applicable), Safety Features, Complete Material composition of injector, and other characteristics which may be applicable to your device. Please note if this information is provided elsewhere in the submission you may simply reference it.
3. You have not provided Risk Analysis Documentation. This information is necessary to ensure all risks associated with the device have been properly identified and mitigated. Please 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.

4. We acknowledge you have provided verification testing of your device in your submission. You did not, however, provide a specification for Injection Time, although your labeling indicates a specific injection time. Please provide a justification why you have not included injection time in your verification testing or release/stability/shipping testing. Alternatively provide Design Verification Documentation traced to the design inputs of the device constituent which applies to injection time. Ensure that you utilize test methods and preconditioning that simulate the intended use of your product. You should use and justify a statistically significant sample size for this verification testing. Provide valid justifications for the acceptability of any test results that do not pass its acceptance criteria.
  - a. Additionally, you have not clarified whether your verification testing was performed with the final to-be-marketed version of the device. 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 (or different device design) 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.
  - b. You have not provided a biocompatibility assessment of the device, including the material components, the manufacturing processes, the clinical use of the device including the intended anatomical location, and the frequency and duration of exposure. This information is required to ensure the device is safe. Please provide a justification or documentation to support the biocompatibility of your device constituent including test reports and protocols to ensure that the system components are biocompatible commensurate with the level and duration of patient contact. Refer to the FDA Guidance titled Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" – Guidance for Industry and Food and Drug Administration Staff issued in June 2016 (<https://www.fda.gov/media/85865/download>) for more details.

## 12.2. Interactive Information Requests

### 12.2.1. Interactive Information Requests sent on 12/17/2019

1. There are outstanding device issues with your applications. We acknowledge you provided long term stability and shipping results which include break loose and glide forces. You also provided an 18-months stability report showing 2 units out of specification for lot JKSEX572. In your design control strategy, you also have elected to not perform testing of the injection force on the final finished device at worst case conditions (aging and shipping). Injection force is an essential performance requirement for the final finished device and verifies the users can inject the drug product up to the maximum labeled shelf life of the device. We recommend that you provide verification testing of the injection force for final finished device after aging and shipping. You may use a bracketed approach (min max dose) and you may define your acceptance criteria as an upper limit. Additionally, we recommend that you add injection force as a release specification for your batch release testing parameters. If you have existing force measurements collected during your dose accuracy testing, you may provide that granted you provide the complete methodology used and it is relevant to how your injector is used in a clinical setting. Also, since break loose and glide force is part of your control strategy in lieu of injection time testing, please explain the out of specification results in the 18-month stability testing.

**RESPONSE (12/24/2019):**

Please note that based on agency's recommendation, Sun has conducted verification testing of the injection force on device after aging and shipping with maximum dose setting (200mcg). Average activation (injection) force test is based on glide force between cartridge and rubber stopper. Minimum dose setting (50mcg) has not been evaluated based on following considerations:

- 1) The travel distance of rubber stopper would be less than 2 mm in case of 50 mcg dose setting. Data are recorded after initial dislodgement of the rubber stopper and also before alignment of "0" mark of dose set knob to the pointer on body sub-assembly. Therefore, for injection force measurement, rubber stopper has to travel minimum 2.5 mm distance at the beginning and shall stop at least 0.5mm before it reaches final position. The travel distance 2.5 mm is not available in 50 mcg dose setting.
- 2) Maximum dose setting has 4.5 mm as travelling distance for the rubber stopper which provides the worst-case scenario for injection force.

Sun has defined acceptance criteria as less than (b) (4) for average activation (injection) force based on design input specification (ERD 18-106 Rev 01) from the device supplier ( (b) (4) ) provided in section 3.2.P.7.2 of original NDA submission. Sun has also developed method which is concurrent with the established method at device supplier to conduct average activation (injection) force test and it is in accordance with ISO (b) (4) (4), 2012. In revised drug product release specification, test procedure, pre-approval stability protocol and post-approval stability protocol provided herewith in *section 3.2.P.5.1, 3.2.P.5.2, 3.2.P.8.1 and 3.2.P.8.2*, respectively, average activation (injection) force test has been included. Results of average activation (injection) force test on aging and shipping samples are provided in Table 1.

Table 1

Pen No.	Average Activation (Injection) Force (N)					
	Shipping			Aging (About 24 months stability sample)		
	JKSEX570A	JKSEX571A	JKSEX572A	JKSEX570A	JKSEX571A	JKSEX572A
1	4.41	5.29	5.09	5.37	5.37	12.28
2	4.96	4.73	4.57	5.08	5.05	14.45
3	4.37	4.53	6.06	5.37	5.77	4.77
4	4.99	4.68	3.99	5.50	6.09	4.86
5	4.74	4.04	5.75	5.5	5.54	4.85
6	5.62	4.17	16.95	5.25	5.44	5.69
7	4.31	5.58	5.30	5.02	5.16	5.30
8	4.37	4.67	7.48	5.51	5.49	3.90
9	3.98	4.40	4.33	4.76	5.44	5.22
10	4.88	4.93	4.26	4.59	5.46	5.32
11	3.88	4.74	4.63	4.71	5.56	4.93
12	5.10	5.27	9.82	5.27	5.56	5.35
13	3.84	4.37	5.67	5.72	5.94	8.11
14	5.78	5.18	5.27	5.68	6.16	4.99
15	3.86	5.04	3.97	4.88	4.90	4.29
16	4.04	4.33	4.18	5.69	5.31	5.10
17	5.19	6.04	14.99	5.36	5.60	4.59
18	4.43	4.46	4.53	5.72	5.71	6.12
19	4.06	5.25	4.85	5.48	5.00	5.28
20	5.43	4.36	8.94	5.63	5.25	14.05

Please note that results of average injection force for batch# JKSEX570A and JKSEX571A for aging and shipping studies are complying with the proposed acceptance criteria of less than (b) (4), however for batch # JKSEX572A, results of average activation force for two samples were found exceeding the proposed specification for both aging and shipping studies. As reported earlier for the same batch, glide force results were also exceeding the specification at 18 months stability testing. Please note that average activation (injection) force test is based on glide force between cartridge and rubber stopper, hence similar observation has been found in case of average activation

(injection) force test also. Investigation and studies were performed for this failure at 18 months station and based on its findings it was concluded that this variability can be mainly attributed to (b) (4) cartridges. Studies have been performed to standardize (b) (4) checks have also been defined to ensure (b) (4). Investigation report and report for standardization (b) (4) have been provided herewith. Pursuant to 21 CFR 314.60(f)(1) we have verified and confirm that this amendment does not include any changes described below:

- I. To add a new indication or other condition of use;
- II. To add a new strength;
- III. To make other than minor changes in product formulation; or
- IV. To change the physical form or crystalline structure of the active ingredient.

**Reviewer Comments:**

The Sponsor has agreed to add injection time as a release spec ( (b) (4) ) and has provided result of the testing on aged samples. Two lots show out of specification sample results. The same batch had glide force results which were also exceeding the specification at 18 months stability testing. A justification for why the lots were out of specification was provided and attributed to (b) (4) cartridges. Studies have been performed by the Sponsor to standardize (b) (4) checks have also been defined to ensure (b) (4). A follow-up IR is recommended to ensure the Sponsor rejects batches which are out of specification.

*We acknowledge you have established injection/activation force as a release specification. You have provided data which shows a potential out of specification batch, which was properly identified and a root-cause analysis performed. It is unclear, however, if your sampling and rejection process during your routine manufacturing and release testing (as part of your quality system) will identify and reject such lots in the future. Please confirm whether you would reject such a batch during your release testing and provide a brief overview of your testing and release processes prior to distribution of the final finished product.*

*12.2.2. Interactive Information Requests sent on 1/7/2020*

1. We acknowledge you have established injection/activation force as a release specification. You have also provided data for injection force testing after shipping and aging which shows a potential out of specification batch; the batch was properly identified and a root-cause analysis performed. It is unclear, however, if your sampling and rejection processes during your routine manufacturing and release testing (which are part of your quality system and/or in-process controls) will identify and reject such lots in the future. Please confirm whether you would reject such a batch during your release testing and provide a brief overview of your testing and release processes for injection force prior to distribution of the final finished product.

**RESPONSE:**

Please note that each lot manufactured will be tested as per finished product release specification prior to distribution. As per site procedure SOP No. (b) (4)-014, Title: "Handling of out of specification results", any failure in testing parameters for the lot will be investigated. This investigation involves investigation for testing part as well as for manufacturing process. Based on the outcome of the investigations, batch disposition is decided. All batches with confirmed OOS

(Out of Specification) shall be rejected with suitable corrective and preventive action based on the root cause are proposed and implemented.

Please note that average activation (injection) force test shall be analyzed as per finished product release specification and analytical procedure at the time of Acceptance Quality Limit (statistical check) of the final assembled combination product. Sun's sampling and rejection processes during routine manufacturing and release shall identify and reject such lot if it does not meet acceptance criteria as defined in the procedure. This acceptance and rejection criteria is based on ISO standard 2859-1:1999 Sampling procedure for inspection by attributes.

Master batch packaging record having average activation (injection) force test at the time of Acceptance Quality Limit (statistical check) of the final assembled combination product has been provided herewith in *section 3.2.P.3.3*. Please note that result of average activation (injection) force test conducted at the time of final assembled combination product will be reported in finished product certificate of analysis.

Please note that below typographical error has been observed in finished product specification and analytical procedures as mentioned below. Sun apologize for this inadvertently typo error. Corrected specification and analytical procedure have been provided in *section 3.2.P.5.1 and 3.2.P.5.2* respectively

Revised Criteria: (b) (4) for each pen injector. For 32 nos. pen injectors, accept the lot - if less than or equal to three pen injector fails. If four or more than four pen injector fails, additional 48 nos. of pen injectors to be tested. For total 80 nos. pen injectors, accept if six or less than six pen injectors fail. Reject the lot if seven or more than seven pen injectors fails.

The sponsor used sampling plan per ISO 2859- 1:1999.

**Reviewer Comments:**

The sponsor confirms that for any failure they will investigate and determine the root cause. Per their procedures they will reject the batch if it fails to meet the acceptance criteria. There was a typo in their original acceptance criteria and they provided the revised sampling plan.

Since the root cause was determined to be (b) (4) of the barrel (manufacturing), not the design of the device, and they implemented the correct quality activities to detect and managed these non-conformances the product is approvable. It is also noted that ISO 2859-1:1999 is a recognized consensus standard for sampling.

A comment to CDER will be issued regarding their (b) (4) process validation.

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**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.**  
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/s/  
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MEGHNA M JAIRATH  
01/15/2020 10:35:27 AM

**Recommendation: Approval**

**NDA 213224  
Review 1**

Drug Name/Dosage Form	Octreotide acetate injection
Strength	2.5 mg/mL, (b) (4) 2.8 mL pen injector
Route of Administration	Subcutaneous
Rx/OTC Dispensed	Rx
Applicant	Sun Pharmaceutical Industries Ltd.
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original and amendments	Original submission (3/28/2019) and amendments (4/05/19, 5/22/19, 6/11/19, 6/11/19, 8/12/19, 9/09/19, 9/23/19, and 9/30/19).	Quality module 3, 1.14 and 1.11

**Quality Review Team**

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Paresma Patel	Branch II/New Drug API
Drug Product	John Amartey	Branch VI/New Drug Products II
Process	Aditi Thakur	Branch IV/Process Assessment II
Microbiology	Yan Zheng	Microbiology Assessment
Facility	Aditi Thakur	Branch III/ Inspectional Assessment
Biopharmaceutics	Vincent Li	Branch II/Biopharmaceutics
Regulatory Business Process Manager	Leeza Rahimi	Branch I/Regulatory Business Process Management I
Application Technical Lead	Muthukumar Ramaswamy	Branch VI/New Drug Products II
Environmental Analysis (EA)	John Amartey	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	Sun Pharma	Octreotide acetate USP	Adequate. 9/4/2018 (Drug substance reviewer)	LOA 3/16/2019
	Type III	(b) (4)		Adequate information in the NDA	LOA 12/11/2015
	Type III				LOA 6/09/ 2018
	Type III			Adequate 5/14/19 (microbiology review D22514M04R01 )	LOA 2/9/2018
	Type III			Adequate 8/20/19 (microbiology review)	LOA 6/16/2018
	Device master file			Refer to CDRH device review	LOA 01/7/2019

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	141456	

### 2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATI ON	DATE	REVIEWER

## Executive Summary

### I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (OPQ) for NDA 213224 is approval, which includes acceptable recommendation for the facilities listed in the application.

### II. Summary of Quality Assessments

#### A. Product Overview

Octreotide acetate is a synthetic cyclic octapeptide. Octreotide acetate was previously approved under NDA 019667 (Sandostatin injection) for the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with vasoactive intestinal peptide (VIP) secreting tumors. The proposed 505(b)2 application is seeking approval for octreotide injection 2.5mg/mL filled in pen. Reference listed drug (RLD) for this application is Sandostatin injection (1mg/mL in 5mL vial).

The proposed product is a sterile, clear, colorless solution in a multi-dose pen injector. The pen injector can be set to deliver 50, 100, 150 or 200 µg doses. Both The composition of RLD and the proposed drug product are qualitatively same (i.e., contain the same active and inactive ingredients). The two products differ in mannitol content, octreotide content per mL (2.5mg/mL vs. 1mg/mL), packaging (pen vs. vial presentation), and total strength per unit container ( (b) (4) pen vs. 5mg/vial).

The applicant performed BE studies using 200 µg dose and sought waiver for not conducting BE studies for 50, 100, and 150 µg doses. Biopharm reviewer reviewed the request and granted the biowaiver.

Recommended storage condition for the drug product is 2-8 °C in carton. After first use, the product needs to be stored at controlled room temperature between 20°C to 25°C (68°F to 77°F). Excursions between 15°C (59°F) and 30°C (86°F) are allowed for up to 28 days.

<b>Proposed Indication(s) including Intended Patient Population</b>	For the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with vasoactive intestinal peptide (VIP) secreting tumors.
<b>Duration of Treatment</b>	<i>Refer to CTDL memo</i>
<b>Maximum Daily Dose</b>	<i>500µg x 3 times a day</i>
<b>Alternative Methods of Administration</b>	<i>Not applicable</i>

#### B. Quality Assessment Overview

### Drug Substance

Octreotide acetate is a synthetic cyclic octapeptide. Chemically, it is known as D-Phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-L-cysteinamide cyclic (2→7)-disulfide acetate (salt). The applicant provided a brief description of the general properties of the drug substance, organic impurities, and specifications for the drug substance and cross-referenced DMF (b) (4) for all CMC information related to drug substance. CMC information related to the drug substance was reviewed by Dr. Paresma Patel. Dr. Patel's review concluded that CMC information provided in the NDA and DMF is adequate to support the approval of the NDA from drug substance quality perspective. Please refer to D. Patel's drug substance review dated 9/17/2019 in Panorama for additional details.

### Drug Product

The drug product is filled in a 3mL USP (b) (4) glass cartridge sealed with a rubber plunger on one end and a combi seal on the other end. The product filled cartridge is packaged in a multi-dose pen injector. Each mL of the drug product contains 2.5mg of octreotide (as acetate), 3.4mg of lactic acid USP, 22.5 mg of mannitol USP, 5.0 mg of phenol USP in water for injection. A (b) (4) % sodium bicarbonate solution is used to adjust the pH of the solution to a target pH of 4.2. All excipients associated with the product are compendial. The composition of the proposed commercial product is the same as the one used in BE studies.

During storage, the product is in contact with the 3mL glass cartridge, (b) (4) rubber plunger stopper, and the combi-seal. The compatibility of the active ingredient with the excipients and the container closure components was supported by available stability data, extractable information, and applicant's risk assessment.

The drug product is tested for visual clarity, color, appearance, identity, particulate matter, pH, osmolality, assay, impurities, volume container, closure integrity, endotoxin content, sterility, dose accuracy, glide force, and break-loose force. The drug product specifications conform to USP <1> injection, USP <788> particulate matter, US<71> sterility, and USP <85> bacterial endotoxin.

The application contains 6 months of accelerated stability data (25°C/60% RH), 18 months of long-term stability data (5°C) for 3 exhibit batches as well as in-use stability data for a 13-month batch old product stored at 20-25°C for 28 days. Product is sensitive to light. Review of the product quality information for stability batches indicated that the product is stable.

Dr. John Amartey reviewed the drug product information in the NDA. His review covered drug product composition, excipients, container closure system, product compatibility with excipients and container closure system, drug product specification, batch analysis, impurity information, reference standard, and stability information including in-use stability data. OPQ CMC review does not cover the

device aspects of the finished product. CDRH review will cover the acceptability of the proposed device for intended use. Please refer to Dr. Amartey's drug product review dated 12/10/19 in Panorama for additional information.

Based on stability information for product quality attributes, Dr. Amartey granted an expiration period of 24 months for the drug product when stored at 2-8 °C in carton. After first use, the product needs to be stored at controlled room temperature between 20°C to 25°C (68°F to 77°F). Excursions between 15°C (59°F) and 30°C (86°F) are allowed for up to 28 days. Dr. Amartey recommendation for the NDA is approval from drug product perspective.

The applicant also provided break loose force and glide force data for 3 stability batches. I note that one of the three stability batches did not meet the glide force acceptance criteria for the 18-month time point. The stability results for all attributes were acceptable for the 12-month time point for all three batches. Therefore, I am granting a 12-month expiry period for the finished product when stored at 2-8°C.

Dr. Aditi Thakur reviewed the manufacturing process description and process controls. The manufacturing process involves (b) (4)

[Redacted text block]

[Redacted text block]

Microbiology reviewer, Dr. Yan Zhang reviewed the microbiological controls used in drug product manufacturing process. She reviewed the CMC information for (b) (4) processing, sterility, endotoxin controls, antimicrobial effectiveness testing, container closure integrity, filter validation, depyrogenation validation, component sterilization, media fill studies, hold times, stability, and post-approval stability commitment. Dr. Zhang also reviewed Type V DMF (b) (4). Her review concluded that microbiological controls are adequate to support the NDA. Refer to CMC (Microbiology) review dated 8/20/19 in Panorama under NDA 213224.

*Control Strategy:* The critical quality attributes of the product are controlled through batch records instructions, process design, component specifications, in-process controls (bioburden control, visual inspection, product pH verification, and filter integrity), (b) (4) processing techniques, and adequate finished product specification. CMC Reviewer's risk assessment for critical attributes is shown at the end of the review. In conclusion, the final risk is low for the proposed product. No further mitigation necessary (Attachment 1).

*Facility compliance information:* Facility compliance information for the drug product and the drug substance manufacturing facilities was reviewed by Dr. Aditi Thakur. Her review concluded that facilities are acceptable to support the approval of NDA 213224. Please refer to her review in Panorama dated 12/10/2019.

*Environmental assessment:* The applicant sought exemption from environmental impact analysis per 21 CFR25.30 and 21CFR 25.31(a) as the action on this NDA does not increase the use of octreotide acetate. Dr. John Amartey reviewed the request and granted categorical exclusion from submitting environment assessment. Please refer to drug product review dated 12/10/19 for additional information.

*Biowaiver:* The proposed drug product is formulated at higher concentration than the the reference listed drug (2.5mg/mL in pen injector vs.1mg /mL in vial). As result a 200 µg dose of the proposed product would be delivered in 80 µL dose volume in comparison to 200µL of the RLD. The applicant performed a bioavailability study comparing the 200 µg dose of the proposed product to the 200 µg dose the RLD and concluded that it is bioequivalent. BE study was reviewed by clinical pharmacology reviewer. Refer to clinical pharmacology review for additional details. The applicant is requesting biowaiver for the lower strengths (50, 100, and 150 µg doses). Dr. Vincent Li reviewed the request and granted the biowaiver based on the acceptable bioequivalence study results for the highest strength and self-evident bioequivalence of an injection solution per CFR 320.22(b). Please refer to Dr. Vincent Li's review dated 11/12/2019 in Panorama.

*Container and Carton Label Review:* Dosage form, established name, NDC #, Lot #, expiry, and storage conditions are described in the carton and container label. Refer to drug product review for a copy of the label. Labeling for the product will be finalized with DMEPA and OND labeling team during labeling review.

## OVERALL ASSESSMENT AND SIGNATURES:

OPQ CMC review concludes that there are no outstanding deficiencies related to drug substance, drug product, facilities, microbiology, biopharmaceutics and environmental assessment, container and carton label. *OPQ overall recommendation for NDA 213224 is approval.*

***Muthukumar Ramaswamy, Ph.D. 12/18/2019***

***Application Technical Lead Name and Date:***

## ATTACHMENT I: Final Risk Assessments

### A. Final Risk Assessment - NDA

<i>From Initial Risk Identification</i>			<i>Review Assessment</i>		
<i>Attribute/ CQA</i>	<i>Factors that can impact the CQA</i>	<i>Initial Risk Ranking</i>	<i>Risk Mitigation Approach</i>	<i>Final Risk Ranking</i>	<i>Lifecycle Considerations/ Comments</i>
Drug content/ Assay	Solubility, Formulation, Process, Container closure	H	Stability studies/in-process controls.	L	none
Impurities/ degradants	Formulation, Process, Container closure & packaging	H	Stability studies, in-process controls	L	Drug substance is sensitive to light. Mitigated through product label and process. Store in carton.
Appearance	Formulation, Process, Container closure	H	Stability studies	L	none
Sterility	Container closure	H	Stability studies	L	none
	(b) (4)		(b) (4)		
Endotoxins	Container closure	H	Stability studies	L	
	Process		(b) (4)		
Particulate matter	Formulation	H	Stability studies	L	none
pH	Formulation	L	Stability studies	L	None
			(b) (4)		
Leachable/ extractables	Formulation, Process, Container closure	M	Optimize formulation qualification of packaging components and storage conditions.	L	None



Muthukumar  
Ramaswamy

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# CHAPTER VII: MICROBIOLOGY

## [IQA NDA Assessment Guide Reference](#)

<b>Product Information</b>	
<b>NDA Number</b>	213224
<b>Assessment Cycle Number</b>	01
<b>Drug Product Name/ Strength</b>	Octreotide Acetate Injection, 2.5mg/mL, 2.8mL pen injector
<b>Route of Administration</b>	Subcutaneous injection
<b>Applicant Name</b>	Sun Pharmaceutical Industries, LTD
<b>Therapeutic Classification/ OND Division</b>	OND/ODEII/DMEP
<b>Manufacturing Site</b>	Sun House. (b) (4)
	(b) (4)
<b>Method of Sterilization</b>	(b) (4)

**Assessment Recommendation: Adequate**

**Assessment Summary:**

Document(s) Assessed	Date Received
Original submission	03/28/2019
Response to IR	08/12/2019

**List Submissions being assessed (table):**

**Highlight Key Issues from Last Cycle and Their Resolution: N/A**

**Remarks:**

Pen injector needles (b) (4) are not included in the commercial cartridge/pen injection system. (b) (4) needles are 501(k) cleared (b) (4).

**Concise Description of Outstanding Issues**

**(List bullet points with key information and update as needed): None**

**Supporting Documents:**

The requalification study dated 03/16/2017 for (b) (4) and the requalification schedule were reviewed and found adequate in (b) (4) on 06/20/2018

## S DRUG SUBSTANCE

The manufacturing process for the drug substance is not reviewed because the drug substance is non-sterile.

### P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Product description: The drug product is a 2.8mL colorless, sterile, multiple-dose, aqueous solution filled in a 3mL plunger-stoppered glass cartridge and packaged in a pen injector. The product is a somatostatin analogue with a strength of 2.5 mg/mL. It is subcutaneously administered without dilution/reconstitution. A sterile needle is attached for each administration and the product should be used within 28 days from the first use.

Composition:

Components	Function	Quality Standard	Octreotide Acetate Injection, 2.5 mg/mL, Pen Injector, 2.8 mL			
			Amount			
			(mg/mL)	mg/pen	(%w/v) (b) (4)	
Octreotide Acetate	Active drug substance	USP	2.5	(b) (4)	(b) (4)	
Lactic Acid (b) (4)	(b) (4)	USP	3.4			
Mannitol (b) (4)		USP	22.5			
Phenol (b) (4)		USP	5.0			
Sodium Bicarbonate (b) (4)		USP	q.s. to pH			
Water for Injection		USP	(b) (4)			q.s. to 100
Nitrogen		NF				

(Table reproduced from the submission, 3.2.P.1, pg. 1).

Container closure system (3.2.P.1; 3.2.P.7, source of supply and supplier address)

Primary CCS components	Description	Manufacturer
Cartridge	3mL USP (b) (4) glass cartridge	(b) (4)
Plunger stopper	10mm grey (b) (4) plunger stopper	
Seal	Combination (b) (4) seal for 3mL cartridge	

Secondary CCS: One filled and sealed cartridge is packed in a cartridge holder and assembled with the help of grey body subassembly and dark blue cap for pen injector. The cartridge holder, body subassembly, and cap are manufactured by (b) (4). There are minor changes in external design features of the secondary CCS between exhibit batches and commercial products.

**Assessment: Adequate**

**Assessment: Adequate**

**The executed batch records are acceptable.**

Comparability Protocols-N/A

**2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1**

**2.A. Prescribing Information (1.14.1.3, draft labeling)**

The product is packaged in a disposable pen containing multiple doses of medicine and can be used up to 28 days. The product is a sterile solution intended for subcutaneously injection without dilution. The product contains 2.5mg/mL octreotide, and the recommended starting dose is 50 mcg (b) (4) three times daily. The recommended storage condition is 2-8°C. After the first use, the pens are stored at controlled room temperature (20-25°C), and excursions permitted between 15-30°C for up to 28 days.

**Assessment: Adequate**

**The package insert contains adequate information for microbiology.**

*Primary Microbiology Assessor Name and Date: Yan Zheng, Ph.D. 08/20/2019*

*Secondary Assessor Name and Date (and Secondary Summary, as needed):  
Jesse Wells, Ph.D., Q.A.L. 08/20/2019*



Yan  
Zheng

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Jesse  
Wells

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**BIOPHARMACEUTICS****Product Background:**

The applicant has developed a new drug-device combination product, Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL, Pen Injector. The drug product is a new formulation of octreotide acetate, in a solution with 2.5 times the concentration of the highest available concentration of listed drug SANDOSTATIN® (octreotide acetate) Injection (1 mg/mL). Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL is to be provided in a multi-dose, variable dose disposable pen injector for subcutaneous delivery. Each pen injector delivers a dose of 50, 100, 150, and 200 µg with a dose delivery volume of 20 µL, 40 µL, 60 µL and 80 µL respectively.

**NDA/ANDA:** 213224

**Drug Product Name / Strength:** Octreotide Acetate Injection, 2.5 mg/mL, Pen Injector

**Route of Administration:** Subcutaneous

**Applicant Name:** SUN PHARMACEUTICAL INDUSTRIES LTD.

***Review Summary: ADEQUATE***

The applicant has performed relative bioavailability study of its Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL, Pen Injector (200 µg dose) compared to the reference listed drug SANDOSTATIN® (octreotide acetate) Injection, 1 mg/mL, 5 mL multiple-dose vials (200 µg dose) (NDA # 019667; approved on June 12, 1991) of Novartis Pharmaceuticals Corporation. The study showed that the applicant's product is bioequivalent to the reference list drug despite differences in drug concentration and injection volume (Refer to Clinical Pharmacology review for additional details). The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 213224 and finds the application acceptable from a clinical pharmacology perspective. The applicant is requesting a biowaiver for the lower strengths. The biowaiver for the lower strengths was granted based on the acceptable bioequivalence study of the highest strength and self-evident bioequivalence of an injection solution per CFR 320.22(b).

From a Biopharmaceutics perspective, the 505b2 proposed product is adequate.

**List Submissions being reviewed (table):**

<a href="#">Application 213224 - Sequence 0001 - 0001 (1) 03/28/2019 ORIG-1 /Multiple Categories/Subcategories</a>
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**Highlight Key Outstanding Issues from Last Cycle:** Not Applicable

**Concise Description Outstanding Issues Remaining:** None

*Bridging of Formulations*

**Reviewer’s Assessment:** Adequate

A comparison of the proposed product and the reference listed product (RLD), SANDOSTATIN® (octreotide acetate) Injection.

**Table 3.2.P.1:3**

Product Name	RLD	Sun’s Drug Product
	Sandostatin® (octreotide acetate) Injection 1000 mcg/mL, 5 mL multidose vial (Novartis Pharma Stein AG)	Octreotide Acetate Injection, 2.5 mg/mL, Pen Injector, 2.8 mL
	mg/mL	mg/mL
<b>Active Ingredient</b>		
Octreotide Acetate	1.0	2.5
<b>Inactive Ingredients</b>		
Lactic Acid (b) (4)	3.4	3.4
Mannitol (b) (4)	45.0	22.5
Phenol (b) (4)	5.0	5.0
Sodium Bicarbonate	q.s.	q.s.
Water for Injection	q.s.	q.s.
<b>Dosage Form</b>	Injectable	Injectable
<b>Strength</b>	1000 mcg/mL	2.5 mg/mL
<b>Route of Administration</b>	Subcutaneous or Intravenous	Subcutaneous
<b>Container</b>	5 mL multidose vial	2.8 mL Pen Injector

The proposed product and the RLD differ in concentration of the active (2.5 mg/mL vs 1 mg/mL) and amount of mannitol. The proposed product administers the solution product via the pen injector and does not need to withdraw the product from the vial as in the case of the RLD. The higher concentration of the proposed product results in a 2.5X smaller volume to be administered to the patient. The smaller amount of mannitol will bring the osmolality from around 368 to 270 mOmol/kg. The impact of volume difference is unlikely to cause difference in the bioavailability between the two products as the injection volume is small for both products 200 µL (RLD) and 80 µL (proposed product) for the highest dose, 200 µg. Also, the osmolality difference will also unlikely to cause difference in the bioavailability between the two products as the osmolality could be quickly normalized by the interstitial fluid. The formulation was found to be stable at pH range 3.50 to 5.00. since pH range of Innovator product (Sandostatin) is

3.9-4.5 as per package insert of US RLD, 3.9 to 4.5 pH range was selected with target pH 4.20 ±0.05 (4.15-4.25) by using (b) (4) % W/V Sodium bicarbonate solution for final formulation of Octreotide acetate injection, 2.5 mg/mL, Pen Injector, 2.8 mL. The bioequivalence of the two products for the highest dose, 200 µg, was demonstrated by a bioequivalence study between the two products. Hence, the formulation of the proposed product is bridged to that of the RLD.

### ***Biowaiver Request***

#### **Reviewer's Assessment: Adequate**

The applicant submitted a biowavier. The applicant conducted a bioequivalence study for the highest dose, 200 µg and asked for a biowavier for the other three doses, 50 µg, 100 µg, and 150 µg. The biowavier is granted based on the bioequivalence of the highest dose of the proposed product to the highest dose of the RLD. The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 213224 and finds the application acceptable from a clinical pharmacology perspective (refer to clinical pharmacology review for additional details). Moreover, the concentrations of the other strengths/doses are the same as the highest strength and the only differences between the RLD and the proposed product are smaller administered volumes of the latter. Hence, we would expect the other strengths of the proposed product should be bioequivalent to the corresponding doses of the RLD product. Furthermore, the proposed product is a solution product and hence bioavailability is self-evident. Based on the above reasons, biowavier is granted on the basis of 21 CFR Section 320.22(b).

## **R Regional Information**

### ***Comparability Protocols***

**Reviewer's Assessment: N/A**

### ***Post-Approval Commitments***

**Reviewer's Assessment: N/A**

### ***Lifecycle Management Considerations***

***None***

### ***List of Deficiencies:***

***None***

***Primary Biopharmaceutics Reviewer Name and Date:***



## QUALITY ASSESSMENT



*Vincent Li, Ph.D., 8/18/2019*

***Secondary Reviewer Name and Date (and Secondary Summary, as needed):***

*Haritha Mandula, Ph.D., 11/6/2019*



Vincent  
Li

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Haritha  
Mandula

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Muthukumar  
Ramaswamy

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## ICCR Quality System Review Memo

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**Date:** June 13, 2019, Update September 3, 2019

**To:** Teshara Bouie, OPRO/OPQ, CDER,  
[Teshara.Bouie@fda.hhs.gov](mailto:Teshara.Bouie@fda.hhs.gov)

**CC:** Leeza Rahimi, Pharma D. Senior RPM, OPRO/OPQ, CDER,  
WO 75,Rm 4644 [Leeza.Rahimi@fda.hhs.gov](mailto:Leeza.Rahimi@fda.hhs.gov)

Office of Combination Product, [Combination@fda.hhs.gov](mailto:Combination@fda.hhs.gov)  
Damia Jackson, RPM, OPEQ, CDRH  
[damia.jackson@fda.hhs.gov](mailto:damia.jackson@fda.hhs.gov)

**Through:** Todd Courtney, Assistant Director, OPEQ/OHT1, CDRH  
[Todd.Courtney@fda.hhs.gov](mailto:Todd.Courtney@fda.hhs.gov)

**From:** Christopher J Brown, P.E., Anesthesia Device  
Team/DHT1C/OHT1, CDRH, WO 66, Rm 3428,  
[Christopher.Brown@fda.hhs.gov](mailto:Christopher.Brown@fda.hhs.gov)

**Applicant/Licensure:** Sun Pharmaceutical Industries Limited, Sun House Plot No.  
201 B/1, Western Express Highway, Goregaon (E),  
Mumbai, Maharashtra, India, 400063  
FEI: None

**Submission (Type & Number):** NDA 213224

**Combination Product Name:** Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL Pen  
Injector

**Combination Product Indications for Use:** For the treatment of acromegaly, severe diarrhea/flushing  
episodes associated with metastatic carcinoid tumors, and  
profuse watery diarrhea associated with Vasoactive  
Intestinal Peptide (VIP) secreting tumors

**Device Constituent (Type):** Auto injector or Pen

**ICCR SharePoint Tracking Number:** ICC2019-04870

**ICCR CTS Tracking Number:** ICC1900362

**Pre-Approval Facility Inspection:** No: PAI scheduled for NDA 213225, should be reviewed prior to approval

**Documentation Review (Status):** Complete

**CDRH/OC Recommendation:** 06/13/2019: Approvable – with conditions: See Recommendation, Update 09/03/2019: Approvable

CDRH received a consult from CDER requesting the identification of the device manufacturing sites for NDA 213224 which will require a device inspection. Global Submit link:

<\\CDSESUB1\evsprod\NDA213224\213224.enx>

### **PRODUCT DESCRIPTION**

The Octreotide Acetate Pen Injector is a prefilled, variable dose, multiple dose, disposable device. The injector contains a 3.0 mL glass cartridge with a deliverable volume of 2.8 mL. The pen can deliver doses ranging from 0 µg to 200 µg with dose set markings at 50, 100, 150 and 200. The pen is used with 31-gauge 5mm (recommended size) disposable pen needles. The user attaches the needle, primes the pen (if it is a new pen), dials the dose, and then delivers the injection into a subcutaneous injection site (abdomen or thigh).

Octreotide Acetate Injection, 2.5 mg/mL, Pen Injector, 2.8 mL contains lactic acid (b) (4), mannitol (b) (4), pheno (b) (4), water for injection (b) (4), sodium bicarbonate used for pH adjustment. Figure 1 shows the pen and components

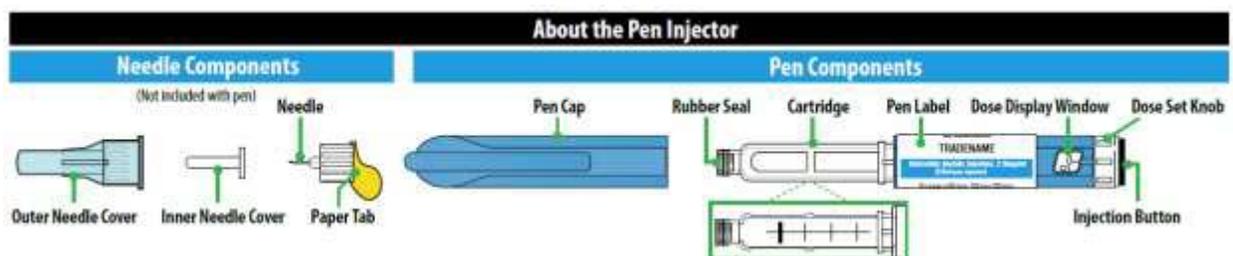




Figure 1. Pen and Components

### Acromegaly

Octreotide acetate is indicated to reduce blood levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) [somatomedin C] in (b) (4) patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses (b) (4).

### Carcinoid Tumors

Octreotide acetate is indicated for the (b) (4) treatment of patients with (b) (4) severe diarrhea and flushing episodes associated with (b) (4).

### Vasoactive Intestinal Peptide Tumors (VIPomas)

Octreotide acetate is indicated for the treatment of (b) (4) watery diarrhea associated with VIP-secreting tumors.

## REGULATORY HISTORY

The following facilities were identified as being involved in the manufacturing and/or development of the combination product, Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL Pen Injector, in NDA 213224.

### Combination Product Applicant

Firm Name: Sun Pharmaceutical Industries Limited

Address: Sun Pharmaceutical Industries Limited, (b) (4)

FEI: None

Responsibility – Applicant, Parent firm of Manufacturer

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

An inspection is not required because the firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent

part. It appears that Quality System documentation for the firm and combination product would likely be accessible through the manufacturing firm.

**Finished Combination Product Manufacturer**

Firm Name: Sun Pharmaceutical Industries Limited

Address: Halol-Baroda Highway, Halol 389 350, Gujarat, India

FEI:3002809586

Responsibility – Drug product manufacture, packaging, release testing and stability testing.  
Drug substance release testing.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection was conducted 11/27/2018 to 12/6/2018. The inspection covered drug CGMP and was classified NAI. An inspection was conducted 8/27/2018 to 8/31/2018. The inspection covered drug CGMP and was classified VAI. An inspection was conducted 2/12/2018 to 2/23/2018. The inspection covered drug CGMP and was classified VAI.

An inspection is not required because a recent medical device inspection of the firm was acceptable. (b) (4)

**Update: 09/03/2019:** An analysis of the firm’s inspection history over the past 2 years showed that an inspection was conducted 6/3/2019 to 6/11/2019. The inspection covered both drug CGMPs and medical device QS and was classified VAI.

**Device Constituent Part Manufacturer or Specification Developer (If Applicable)**

N/A

## DOCUMENTATION REVIEW

Device Constituent Part Type: Auto injector or Pen

Device Constituent Part Class Class II: E.g. Prefilled Syringe, Auto Injector, Inhaler, Vaginal Ring, IUD

Device Constituent Part Clearance Type(Delete line if not applicable): Unknown

Combination Product NDA 213224 Proposed Indication for Use: For the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors

1. Was the last inspection of the finished combination product manufacturing site, Sun Pharmaceutical Industries Limited, OAI for drug or device observations?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	NA <input type="checkbox"/>
2. Is the device constituent a PMA or class III device?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>
3. Is the final combination product meant for emergency use?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>
4. Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>	UNK <input type="checkbox"/>
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 <input checked="" type="checkbox"/>	NO <input type="checkbox"/>	UNK <input type="checkbox"/>
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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>
7. Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>	UNK <input type="checkbox"/>

cGMP Risk:  Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.

High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure,

or positive compliance history, please document your rationale below for not conducting a full ICCR review.

The device is not a life sustaining device when used with vulnerable populations and is used to manage side effects of disease. Since the one OAI classification (2016) the firm has had three acceptable inspections.

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: Sun Pharmaceutical Limited  
 Sun Pharmaceutical Industries Limited, (b) (4)  
 (b) (4)  
 FEI: FEI: None

Finished Combination Sun Pharmaceutical Industries Limited  
 Product Manufacturer: Halol-Baroda Highway, Halol 389 350, Gujarat, India  
 FEI: 3002809586

Applicable Sites	Management Responsibility, 21 CFR 820.20	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
Sun Pharmaceutical Limited <input checked="" type="checkbox"/>	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).		
Sun Pharmaceutical Industries Limited <input type="checkbox"/>	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 <input checked="" type="checkbox"/>	NO <input type="checkbox"/>

	<p><i>21 CFR 820.20 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)</i></p> <p>The firm explained the functions of the manufacturing firms, they provided the Global Quality Manual (GQM <sup>(b) (4)</sup>) that summarizes how the firm has established responsibility to assure that the combination product is manufactured in compliance with applicable 21 CFR Part 4 requirements. The summary covered audits, quality elements, change management, deviations, manufacturing controls, validation and other quality assurance and compliance management areas.</p> <p>The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.</p>		
<p>Applicable Sites</p> <p>Sun Pharmaceutical Limited <input checked="" type="checkbox"/></p>	<p>Design Controls, General, 21 CFR 820.30</p> <p>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.</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>
	<p>The firm provided a copy or a summary of the plan used to design the combination product.</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>

<p>Sun Pharmaceutical Industries Limited ☒</p>	<p><i>21 CFR 820.30 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)</i></p> <p>Per the firm, the requirements for design review, design transfer, design change and design history File (DHF) are stated in Standard Operating Procedure “Drug Device Combination Product Development” (SOP No: (b) (4)). Responsibility matrix for device manufacturer and Sun (combination product manufacturer) has also been provided in this SOP. In Global Standard Operating Procedure “Design Controls for Device Combination Product Development and Manufacturing” ((b) (4)) design control procedures are also described in detail, it also defines responsibility of various stakeholders and activities of each stage.</p> <p>Per the firm, Sun along with the device manufacturer have performed formal documented reviews of documents and design results, at appropriate stages of the device’s design development. Meeting minutes are also documented in DHF. List of various documents reviewed and approved by Sun are provided. Signed copies of this document are provided in section 3.2.P.7.2 of original NDA submission.</p> <p>Design Outputs, Inputs and other design control elements were provided by the firm. The firm provides the container closer and part specifications to complement the drug specifications. The firm identified firm (b) (4) that developed Disposable Liquid Pen (DLP) injector components for Sun Pharmaceutical Industries Limited to deliver an Octreotide Acetate Injection. These components are based on (b) (4) Disposable Liquid Pen Platform components for which (b) (4) is holding MAF (b) (4). This Octreotide Acetate Injection, 2.5mg/mL, 2.8mL pen injector is customized to meet the requirements as specified by Sun Pharmaceutical Industries Limited. (b) (4) provided a table that correlates the contents of Device Master File MAF (b) (4) with supplemental documentation pertaining to the customized Octreotide Acetate Injection, 2.5mg/mL, 2.8mL pen injector. The document addresses the firm specification including biocompatibility, printing, shelf life, stability, the risk factors, human factors identified by firm and other criteria. The firm through (b) (4), identifies the design input, output and verification requirements and provided the design reviews and acceptance (by firm) evidence. The firm, through (b) (4), summarizes the verification test results, with deviations (which I reviewed) and summarizes the equivalency between the verification drugs dose accuracy and the target drug. The firm addressed the risk management process, report and activities and provided a summary. The firm provided the validation report, summarized the inputs and issues, results and conclusions. Human Factors was addressed. The firm summarized the design change process associated with the validation, research, and inputs. The firm described how design change process was used to create an iterative pen design and IFU. Additionally, the quality systems report</p>
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	<p>indicates the firm has documentation to cover all 21 CFR 820.30 elements. The DHF index was provided by the firm.</p> <p>The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.</p>		
Applicable Sites	Purchasing Controls, 21 CFR 820.50	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
Sun Pharmaceutical Limited <input checked="" type="checkbox"/>	The sponsor firm should summarize its procedure(s) for purchasing controls.		
Sun Pharmaceutical Industries Limited <input checked="" type="checkbox"/>	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 <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	The summary should define how the firm maintains records of acceptable suppliers and how it addresses the purchasing data approval process.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	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 <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	The firm should explain how it will ensure that changes made by contractors/suppliers will not affect the final combination product.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	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 <input checked="" type="checkbox"/>	NO <input type="checkbox"/>

*21 CFR 820.50 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)*

The firm provided the supplier's agreement for the purchasing of pen injectors components (glass cartridges, plunger stopper and combination seal, cartridge holder, body subassembly and cap for pen injector). The agreement addressed change control, and established responsibility for cGMP, and other quality control obligations for the supplier firms. The firm provided the SOP for the Vendor Management for Primary Printed Packaging Materials.

The applicant's criteria for selection and initial qualification of supplier of the injector pen and pen injector components (glass cartridge, plunger stopper, cartridge holder) at development stage are described in Pharmaceutical Development report provided in section 3.2.P.2 of original NDA submission. Vendor evaluation process consists of review and approval of vendor's technical documents, conducting vendor site audits and based on audit findings categorizing vendor as 'approved', 'not approved', and 'under observation'. Requalification of approved vendor, discontinuation/de-registration of vendor, continuous evaluation of supply for quality and annual risk assessment are also conducted to monitor supplier.

Per the firm, a list of approved vendors is maintained and updated on regular basis, this list ensures that incoming material is from approved vendor only.

In addition to vendor qualification program, quality/contract agreement between Sun and vendor also facilitate control over the suppliers. Per the firm, incomings lots of packaging material are analyzed as per acceptance specification and based on the results obtained, lots are either released or rejected. Per the firm, material received at manufacturing sites are tested and released as per SOP "Testing and Releasing of Packaging Materials" (SOP # (b) (4)) provided in section 3.2.P.7.2 of original NDA submission.

In accordance with quality agreement, supplier must notify Sun changes affecting existing products, process or specification for Sun's approval of such changes prior to its implementation. Evaluation of such changes shall be performed as per change control procedure defined in SOP "Change Control Programme" (SOP No: (b) (4)). Per the firm, impact assessment and risk analysis of proposed change is conducted to evaluate whether proposed change will affect functional performance or intended use of the drug product. All such changes shall be reported to agency considering appropriate reporting category.

Sun notes that they use development agreement as a tool to meet all specified requirements captured in the quality agreement. Potential suppliers or contractors are only selected and finalized if both the parties agree with specified requirements along with development timeline. Development agreements

	<p>between Sun and (b) (4) are provided in section 3.2.P.7.</p> <p>The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.</p>		
Applicable Sites	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 <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
Sun Pharmaceutical Limited <input checked="" type="checkbox"/>	The CAPA system should require:	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
Sun Pharmaceutical Industries Limited <input checked="" type="checkbox"/>	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;	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	d. Verification or validation of the actions taken.	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	<p>21 CFR 820.100 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)</p> <p>The firm provided the SOPs Deviation Process ( (b) (4) ) and Corrective and Preventive Actions (CAPA) (b) (4) , and SOP Investigation Process. The procedures together summarize the CAPA procedures and address the Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products. The SOPs address the investigation of nonconformities and their causes, and identification and implementation of actions needed to correct and prevent recurrence of nonconformities. They address verification or validation of the actions taken. The procedures address responsibilities, risk assessments, record keeping, termination or closure, effectiveness and other relevant areas.</p> <p>The information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.</p>		
Applicable Sites	Installation, 21 CFR 820.170 (check none if Installation is not required for the combination product)  NA/NONE	YES <input type="checkbox"/>	NO <input type="checkbox"/>

Sun Pharmaceutical Limited <input type="checkbox"/>	<i>21 CFR 820.170 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)</i>
Sun Pharmaceutical Industries Limited <input type="checkbox"/>	NA
None: <input checked="" type="checkbox"/>	

<p>Applicable Sites</p> <p>Sun Pharmaceutical Limited <input type="checkbox"/></p> <p>Sun Pharmaceutical Industries Limited <input type="checkbox"/></p> <p>None: <input checked="" type="checkbox"/></p>	<p>Servicing, 21 CFR 820.200 (check none if Servicing is not required for the combination product)</p> <p>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.</p>	<p>YES <input type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>
<p><i>21 CFR 820.200 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)</i></p> <p>NA</p>			
<p>Applicable Sites</p> <p>Sun Pharmaceutical Limited <input type="checkbox"/></p> <p>Sun Pharmaceutical Industries Limited <input checked="" type="checkbox"/></p> <p>None: <input type="checkbox"/></p>	<p>Production and Process Controls</p> <p>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.</p> <p>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)).</p> <p>The firm provided information for the environmental control and contamination control for the finished combination product in the SOPs ‘The Microbiological Monitoring for Parenteral Manufacturing Area’ and ‘Material Movement’ for contamination controls. The SOPs reference multiple other environmental control procedures and instructions that appear to form a complete system of monitoring and address environmental conditions. The procedures provided, and references appear to address the training and monitoring requirements, procedures for collection and measurement, gowning, alert and action limits, investigations frequency and other program requirements.</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>
<p><i>Production and Process Control In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)</i></p>			

<p>Applicable Sites</p> <p>Sun Pharmaceutical Limited <input type="checkbox"/></p> <p>Sun Pharmaceutical Industries Limited <input checked="" type="checkbox"/></p> <p>None: <input type="checkbox"/></p>	<p><i>The firm provided a narrative of the manufacturing process and flow diagrams for manufacturing and packaging.</i></p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>
<p>Applicable Sites</p> <p>Sun Pharmaceutical Limited <input type="checkbox"/></p> <p>Sun Pharmaceutical Industries Limited <input checked="" type="checkbox"/></p> <p>None: <input type="checkbox"/></p>	<p><i>Production and Process Control In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)</i></p> <p>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.</p> <p>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)).</p>	<p>YES <input checked="" type="checkbox"/></p>	<p>NO <input type="checkbox"/></p>

*Production and Process Control In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)*

SOPs Testing and Release of In Process, Final Product and Validation/Verification Samples (SOP (b) (4)) and Batch Release Procedure ((b) (4)) were provided and reviewed. The manufacturing process is described as the manufacturing (b) (4)

The firm references several other SOPs addressing for example; analysis, out of trend, data reporting, etc. The procedures define the release criteria for all finish products, record and review verification procedures. The procedures address discrepancies, responsibility, analysis result review, and statistical criteria for testing using AQL sampling procedures.

The firm describes and provides results of in-process testing during manufacturing for the container closure with objective comparison criteria.

The firm provided SOP (b) (4) that described in-process checking during on line packing. The firm describes the procedures for defect identification, and characterization. The firm provided the finished product analytical test procedure that provided limits and procedures for volume variation, amount, sterility, bacterial endotoxins, osmolality, and mechanical testing (such as glide force, and break loose force). The firm provided acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product.

Documentation Review Recommendation:

*No Deficiencies Identified.* The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable quality system requirements showed no deficiencies. No additional information is required for the documentation review.

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

06/13/2019: The approvability of application for NDA 213224 Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL Pen Injector should be delayed for the following reasons:

- (1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies. A pre-approval inspection is not recommended for the following facility:

- a. Sun Pharmaceutical Industries Limited



Update: 09/03/2019 - The application for NDA 213224 Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL Pen Injector is approvable from the perspective of the applicable Quality System Requirements. The recommended inspection(s) were conducted and deemed acceptable

OC Decision: Approvable (Recommend approval to CDER) . See update above.

Reviewer: \_\_\_\_\_

Christopher Brown

Assistant Director: \_\_\_\_\_

Todd Courtney

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**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.**  
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/s/  
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TESHARA G BOUIE  
09/09/2019 03:54:35 PM