CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209379Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: **April 28, 2019**
From: **Hitesh Shroff, Ph.D.**
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: **CMC Review #1 of NDA 209379**

Subject: Final Recommendation for NDA 209379

At the time when the CMC Review #1 was completed on March 28, 2019 it had noted the following pending issues:

- The label/labeling issues were not resolved.

Because of these deficiencies, the NDA was not recommended for approval from the OPQ perspective.

The applicant submitted the revised immediate container labels and Prescribing Information (PI) on April 26, 2019. The resubmitted CMC sections of the labeling/labels were reviewed and found acceptable. **(See the Attachment)**

Recommendation:
This NDA is now recommended for Approval from the OPQ perspective.

Application Technical Lead's Assessment and Signature

The NDA is recommended for Approval from quality perspective.

Hitesh Shroff, Ph.D.
Application Technical Lead,
Branch V Division of New Drug Products II
April 28, 2019

Memorandum

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

Date: **April 26, 2019**

From: **Caroline Strasinger, Ph.D.**
Reviewer, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: **Labeling Review #1 of NDA 209379**

Subject: **Final Recommendation**

Labeling Review #1 had noted the following pending issues with Highlights, and Sections 3, 11 and 16 with Full Prescribing Section:

Regarding the PI

a) Highlight Section

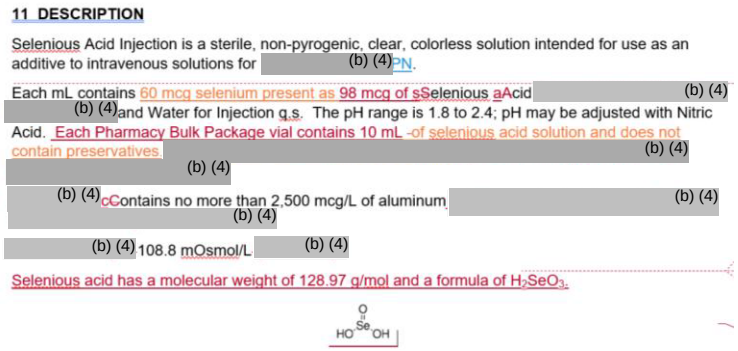
- Per good labeling practices USP should not be used in the Highlights Section
- Change format to Injection: 600 mcg/10 mL (60 mcg/mL) of selenium as a Pharmacy Bulk Vial

b) Full Prescribing Information

Section 3: Dosage Forms and Strengths

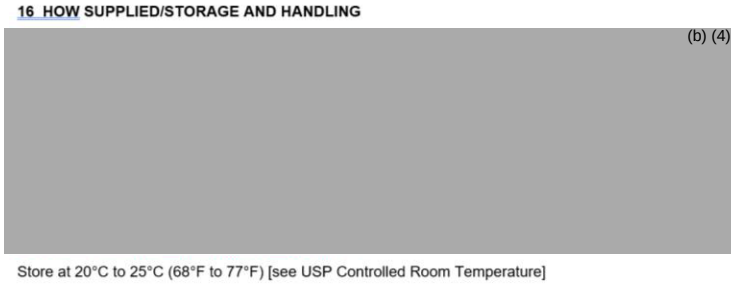
- Change format to Injection: 600 mcg/10 mL (60 mcg/mL) of selenium present as selenious acid
- Include clear colorless solution in a 10 mL Pharmacy Bulk Package vial.

Section 11: Description



- Include the formatting elements above for clarity
- Alter the equivalency presentation to read "Each mL contains 60 mcg selenium present as 98 mcg of selenious acid…"
- Include the structure, formula and molecular weight of selenious acid
- Selenious acid has a molecular weight of 128.97 g/mol and a formula of H_2SeO_3.

Section 16: How Supplied/Storage and Handling



- Include the formatting elements above for clarity
- Alter the equivalency presentation to read (b) (4) in a 10 mL Pharmacy Bulk Package vial.

On April 26, 2019, the above deficiencies were agreed to by the applicant and an updated PI was submitted. Relevant updated sections of the PI are included as an attachment below. The carton and container remain adequate.

OVERALL ASSESSMENT AND RECOMMENDATION:

NDA 209379 is now recommended for approval from the labeling perspective. The Applicant provided updated Prescribing Information on April 26, 2019. The Carton and Container remain adequate per Labeling Review #1.

Attachment: Final PI

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SELENIOUS ACID INJECTION safely and effectively. See full prescribing information for SELENIOUS ACID INJECTION.

SELENIOUS ACID INJECTION, for intravenous use
Initial U.S. Approval: 2019

----------DOSAGE FORMS AND STRENGTHS----------
Selenious Acid Injection, USP: 600 mcg/10 mL (60 mcg/mL) of selenium as a Pharmacy Bulk Package vial. (3)

3 DOSAGE FORMS AND STRENGTHS

Selenious Acid Injection, USP: 600 mcg/10mL (60 mcg/mL) of selenium as a clear, colorless solution in a 10 mL Pharmacy Bulk Package vial.

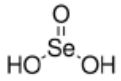
11 DESCRIPTION

Selenious Acid Injection, USP is a sterile, non-pyrogenic, clear, colorless solution intended for use as a trace element and additive to intravenous solutions for PN.

Each mL contains 60 mcg selenium present as 98 mcg of selenious acid and Water for Injection q.s. The pH range is 1.8 to 2.4; pH may be adjusted with Nitric Acid. Each Pharmacy Bulk Package vial contains 10 mL of selenious acid solution and does not contain preservatives.

Selenious Acid Injection, USP contains no more than 2,500 mcg/L of aluminum and has a calculated osmolarity of 108.8 mOsmol/L.

Selenious acid has a molecular weight of 128.97 g/mol and a formula of H_2SeO_3.



16 HOW SUPPLIED/STORAGE AND HANDLING

Selenious Acid Injection, USP is a clear, colorless solution available as 600 mcg/10mL (60 mcg/mL) of selenium in a 10 mL Pharmacy Bulk Package vial.

Carton of 25 vials (NDC 0517-6560-25)

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]
For storage of admixed solution, see *Dosage and Administration (2.3).*

Caroline Strasinger

Digitally signed by Caroline Strasinger
Date: 4/26/2019 10:55:17AM
GUID: 5051dfdd000013b995075b4d54108ed8

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 4/26/2019 11:23:25AM
GUID: 502d0913000029f9798ca689a802fa55

Hitesh Shroff

Digitally signed by Hitesh Shroff
Date: 4/28/2019 10:11:07AM
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QUALITY ASSESSMENT

Recommendation: As of this review, this 505 (b)(2) NDA is *not* ready for Approval in its present form per 21 CFR 314.125(b)(6).

NDA 209379

OPQ Review #1

Drug Name/Dosage Form	Selenious acid injection, USP for intravenous use
Strength	60 µg/mL (600 µg/10 mL)
Route of Administration	Injection
Rx/OTC Dispensed	Rx
Applicant	American Regent, Inc., Shirley, NY
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	10/31/2018	OPQ
Amendment	1/11/2019	Drug product and Microbiology
Amendment	3/08/2019	Drug Substance
Amendment	3/20/2019	Process

Quality Review Team

DISCIPLINE	REVIEWER	Secondary Assessment
Drug Substance	Martin Haber	Donna Christner
Drug Product and Labeling	Caroline Strasinger	Moo-Jhong Rhee
Process	Allison Aldridge	Nallaperumal Chidambaram
Microbiology	Samata Tiwari	Neal Sweeney
Facilities	Allison Aldridge	Vidya Pai
Regulatory Business Process Manager	Oumou Barry	N/A
Application Technical Lead	Hitesh Shroff	N/A
Environmental Analysis (EA)	Caroline Strasinger	Moo-Jhong Rhee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Active	Not reviewed, Information provided in NDA	LOA: October 9, 2017
	Type III			Active	Not reviewed, Information provided in NDA	LOA September 18, 2017
	Type III			Active	Not reviewed, Information provided in NDA	LOA May 30, 2018
	Type III			Active	Not reviewed, Information provided in NDA	LOA December 11, 2015
	Type V			Active	Not reviewed, Information provided in NDA	LOA April 19, 2005

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
		(b) (4)

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The Office of Process and Facilities (OPF) has made a final overall "Approval" recommendation for the facilities involved in this application.

The label/labeling has not been finalized as of this review.

Therefore, from the OPQ perspective, this NDA is ***not*** deemed ready for approval in its present form per CFR 314.125(b)(6) until the label/labeling is finalized.

II. Summary of Quality Assessments

A. Product Overview

Selenious acid injection, USP, 60 µg/mL is a sterile, non-pyrogenic, clear solution intended for use as an additive to intravenous solutions for parenteral nutrition. Selenium injection, 40 µg/mL is marketed for many years as an unapproved drug by the applicant for use as supplement to intravenous solutions for parenteral nutrition.

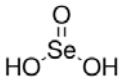
The applicant relied on published literature (b) (4) for safety and efficacy data for this 505 (b)(2) application.

Proposed Indication(s) including Intended Patient Population	Selenious Acid Injection is indicated in adults and pediatric patients as a source of selenium for parental nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.
Duration of Treatment	As needed
Maximum Daily Dose	Adults: 60 (b) (4) µg/day Pediatric Patents ≥ (b) (4) (b) (4)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

The active ingredient, Selenious acid, USP is a colorless, white crystalline, hygroscopic powder with characteristic acid odor. It is soluble in water and freely soluble in alcohol. Its melting point is 70°C. Its empirical formula is H_2SeO_3 and its molecular weight is 128.97 g/mol. The structural formula of selenious acid is as follows:



Selenious acid, USP is manufactured by [redacted] (b) (4) The overall quality of selenious acid, USP is controlled by its specification, which includes description, identification by infrared spectroscopy, assay by iodometric titration, residual solvents, bacterial endotoxins and bioburden. The API particle size and polymorphs of selenious acid are not important because the drug product is an injection. The applicant has provided the certificate of analysis of three process validation batches. The drug substance specification is deemed adequate per drug substance reviewer, Dr. Martin Haber. (See **the Drug Substance** review)

Based on, 24 months of long-term at 25°C and 6 months of accelerated at 40°C stability data of three registration batches of Selenious acid, USP, a re-test period of [redacted] (b) (4) months was established when stored in the proposed container closure system.

The Office of Process and Facilities (OPF) has made an "Adequate" recommendation for all drug substance manufacturing and testing facilities. (See the **Manufacturing Integrated Assessment** review)

The API manufactured by [redacted] (b) (4) is controlled to conform to the requirements (specification) to produce Selenious Acid Injection, USP.

Drug Product:

Selenious acid injection, USP, 60 µg/mL is a sterile, non-pyrogenic, clear, colorless solution for intravenous use as an additive to parenteral nutrition. This product is not for direct intravenous infusion so it must be diluted with parenteral nutrition prior to administration. It is supplied as 10 mL vials. Each mL contains 60 µg selenium as 98 µg selenious acid in water. The pH of the solution is adjusted to 1.8 to 2.4 with nitric acid. There are no preservatives or antioxidants in the drug product formulation.

The drug product is manufactured by Luitpold Pharmaceuticals, Inc.; NY. The manufacturing process includes [redacted] (b) (4) The approximate

drug product batch size is (b) (4). The drug product manufacturing process, in-process controls, drug product release tests and executed batch records were reviewed and deemed satisfactory. (See **Manufacturing Integrated Assessment**)

The environmental monitoring at (b) (4) as well as the microbiology related attributes of the drug product specification including bacterial endotoxins, sterility and container closure integrity etc. were reviewed by Dr. Samata Tiwari and recommended this NDA for approval based on drug product sterility assurance. (See the **Microbiology** review)

The overall control strategy for assuring the drug product's identity, strength, purity and quality is deemed adequate based on raw material controls, drug product specification including description, identity, assay, elemental impurities, volume in vial, bacterial endotoxin, particulate matter and sterility. The non-compendial analytical methods were validated per ICH Q2.

The applicant stated that a low pH of 1.8 to 2.4 is required (b) (4) However, at low pH there may be compatibility issues with the glass vial and rubber stopper. The applicant demonstrated that the potential leachables, e.g., aluminum, (b) (4) levels are below PDEs. In addition, the applicant performed a study with scanning electron microscope and determined that neck, wall or heal regions of the glass vials did not exhibit peeling or delamination of glass flakes. The drug product appeared to be compatible with Kabiven and Clinimix E solutions based on the admixture studies.

Based on the long-term and accelerated stability data of the drug product assuring the identity, strength, purity and quality, a 24-month of expiration dating period when stored at 20ºC- 25ºC in the proposed container closure system is granted. (See the **Drug Product** review)

The Office of Process and Facilities (OPF) has made an "Adequate" recommendation for the drug product manufacturing and testing facilities. (See the **Manufacturing Integrated Assessment**)

The applicant requested categorical exclusion for environmental analysis on the basis that this product will not significantly affect the quality of the human environment in accordance with 21 CFR 25.15 (c). Therefore, claim of a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31(a) was deemed acceptable. (See the **Drug Product** review)

The label/labeling is not finalized at the time of this review.

C. Lifecycle Management Consideration (NDA only)

Drug Substance: In addition to USP tests, the drug substance specification should

include melting point and IR spectra.

D. Special Product Quality Labeling Recommendations (NDA only)
None

E. Final Risk Assessment (see Attachment)

F. List of Deficiencies:

The label/labeling has not been finalized yet.

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
March 28, 2019

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QUALITY ASSESSMENT

MICROBIOLOGY

NDA: 209379

Drug Product Name / Strength: Selenious acid Injection, 60 µg/mL (0.6 mg/10 mL), Pharmacy Bulk Package

Route of Administration: Sterile solution for injection, intravenous, single dose

Applicant Name: Luitpold Pharmaceuticals, Inc

Manufacturing Site: Luitpold Pharmaceuticals, Inc., One Luitpold Drive**,** P.O. Box 9001 Shirley, NY 11967

Method of Sterilization: (b) (4)

Review Summary: The submission is recommended for approval on the basis of sterility assurance.

List Submissions being reviewed: July 3, 2018, October 30, 2018 and January 11, 2019

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents:
DMF (b) (4) and associated Microbiology Reviews D(b) (4)M33R01.doc dated 2/3/2017 (adequate) and (b) (4) mic33.doc dated 4/25/2017 (adequate)

Remarks Section: Microbiology Information Requests were issued to the applicant on December 4, 2018, and the applicant forwarded responses on January 11, 2019.

S Drug Substance

The drug substance is not the focus of this review (b) (4)

P.1 Description of the Composition of the Drug Product

(Section 3.2.P.1 Description and Composition.pdf and section 3.2.P.5.1 specifications.pdf)

Description of drug product
Selenious Acid Injection, USP is a single dose, clear, colorless and odorless solution.

Drug product composition –
Quantitative Composition of Selenious Acid Injection, USP is provided in the table below:

Raw material	Function	Content per mL (Bulk Solution)	Content per 10 mL (Fill size 10 (b) (4) mL)
Selenious Acid, USP Active Pharmaceutical Ingredient	Selenious Acid, USP Active Pharmaceutical Ingredient	98 µg	980 µg
Water for Injection, USP (b) (4)	Water for Injection, USP (b) (4)	Q.S. to 1 mL	Q.S. to 10 mL
Nitric Acid, USP pH adjuster	Nitric Acid, USP pH adjuster	Not Applicable	Not Applicable
(b) (4)		Not Applicable	Not Applicable

Note to Reviewer: As per section 3.2.P.2 admixture-study-antimicrobial-efefctiveness.pdf, 98 µg Selenious acid (equivalent to 60 µg selenium) in Water for Injection, USP

* **Description of container closure system** –

The drug product is packaged as 10 mL in a 10 mL vial.

Component	Description	Manufacturer
Vial	10 mL, 20 mm, (b) (4) (b) (4) USP, Tubular, (b) (4)	(b) (4)
Stopper	20 mm, (b) (4)	
Cap	20 mm, Purple Matte, Flip-Off (b) (4)	

Reviewer's Assessment:
The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

Acceptable

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

(Section 3.2.P.2 container-closure-system-Integrity-test-ingress.pdf)

Glass vial and rubber stopper

The container/closure system used for validation were (b) (4) 20 mm stoppers type (b) (4) (same item # as production) and 20 mL tubular glass vials (b) (4) (not the same as proposed for production).

Note to Reviewer: The glass vials used in the CCIT study were different components than proposed for commercial production. Information will be requested.

Test method: Microbial ingress method
Container/closure integrity validation using the microbial challenge method was performed as per SOP-601.01(not provided).

Brief description: Twenty (20) test articles were immersed in two suspensions of *B. diminuta.* Twenty vials served as a negative control. Vacuum is applied to the vessel to reduce the pressure to fifteen inches of mercury for thirty minutes and vials remained immersed for an additional 30 minutes after removal of a vacuum. The test articles were incubated at 30-35°C for 7 days. The applicant states that breached positive vials were used, however, no information was provided regarding the preparation of positive controls and the number of positive units.

Acceptance criteria:

- No evidence of microbial growth is to be observed in any of the test units.
- Positive control units shall be positive for growth.
- Negative control units shall be negative for growth.
- Growth promotion testing performed prior to the vacuum test must show growth of the challenge organism.

Results of test performed on 01/11/2016 are provided and tabulated below:

Sample	# Positive/ # Tested
Test Units	0/20
Positive Control	positive
Growth promotion	satisfactory
Negative Control	0/20

Note to Reviewer: The applicant has not provided the concentration of the challenge microorganism for immersion and growth promotion. Additionally, the applicant has not mentioned if the vials were subjected to the proposed (b) (4) prior to CCIT, the type of media filled in the test vials, the number of breached positive vials and method to prepare breached positive vials. Information will be requested.

IR#1:

Regarding the validation of the container-closure integrity using microbial immersion method:

a) *Please indicate whether the units were subjected to the proposed* (b) (4) *prior to container/closure integrity validation testing.*
b) *The 20 mL glass vials described in the Container Closure Integrity test (CCIT) reports dated 01/11/2016 differ from the two* (b) (4) *vial components proposed for commercial production of the 10 mL vial drug product. Please indicate whether the test vials listed in the reports are identical or equivalent to the container proposed for production of the drug product. If the vials are identical or equivalent to those proposed for production, please provide an explanation*

(e.g., identical neck dimensions). In the absence of equivalency, please provide new CCIT studies for the proposed containers and closures.

c) Please indicate the type of media filled inside the vials.

d) Please indicate the concentration of the challenge organisms used in the microbial immersion test.

e) Please indicate the concentration of microbial inoculum for growth promotion testing.

f) Please describe how the positive control units were prepared for the test and the number of positive control units used in the test.

Applicant's Response:

a) The applicant clarified that the vials used for CCIT were exposed to the proposed (b) (4) prior to the container/closure validation testing. (b) (4)

Note to Reviewer: The Reviewer notes that the proposed (b) (4) However, the applicant has subjected the (b) (4) No information will be requested as (b) (4) was performed.

b) The applicant states that the neck sizes for the 20-mL vial used for CCIT testing and the 10-mL vial proposed for Selenious Acid Injection, USP are identical. The applicant provides a comparison of the neck dimension specifications for the 20-mL and proposed 10-mL vials. The inner neck diameter of both the vials is 12.45-12.95 mm.

c) The applicant states that the vials were filled with Tryptic Soy Broth (TSB).

d) The applicant states that the concentration of the challenge organism used in the microbial immersion test was 9.35×10^8 CFU/mL. The applicant has provided an updated report in section 3.2.P.2 to reflect the changes.

e) The applicant states that the concentration of microbial inoculum for growth promotion testing was 10-100 CFU. Viable plate counts of 49 CFU/plate and 52 CFU/plate were obtained from the two test vials inoculated with the above concentration of challenge organisms.

f) Positive controls were prepared by inserting a piece of capillary tubing into a 16-gauge needle. The needle was then inserted through the rubber stopper of the media filled vial and then subjected to microbial immersion.

Reviewer's Assessment:

The integrity of the proposed container-closure system is validated, and this section was concluded adequate following review of the response to the IR above communicated to the applicant in letter dated December 4, 2018.

Acceptable

Antimicrobial Effectiveness Testing

Not applicable.

Reviewer's Assessment:
The subject drug product is packaged in a single-dose vial; antimicrobial effectiveness testing is not required.

Acceptable

P.3 Manufacture

P.3.1 Manufacturers

Drug product manufacturing:

Luitpold Pharmaceuticals, Inc.
One Luitpold Drive, P.O. Box 9001, Shirley, NY 11967

Microbiological testing of finished product is also performed at the facility listed below:
(b) (4)

P. 3.3 Description of the Manufacturing Process and Process Controls

Buildings and Facilities

(3.2.P.3.3.Manf-process-desc (b) (4) .pdf)

(b) (4)

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Reviewer's Assessment:
The applicant provided an adequate description of the container closure system designed to maintain product sterility.

Acceptable

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(3.2.P.8.1 Stability Summary.pdf)

Drug product exhibit batch #s RD16-003, RD16-0l1, RD15-019 and RD17-084 were subjected to stability evaluation at accelerated (40°C/75% RH), intermediate (30°C/65% RH) and labeled storage (25°C/60% RH) for long term conditions.

Proposed expiry: 24 months

Reviewer's Assessment:

Acceptable

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Sterility	USP <71>	(b) (4)
Bacterial Endotoxins	USP <85>	

*Determined to be acceptable in the previous section following review of the response to the IR communicated to the applicant in letter dated December 4, 2018 to tighten the specification.

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 25°C ± 2°C

Test	Time (Months)						
	0	3	6	9	12	18	24
Sterility	X				X	X	X
Endotoxin	X				X	X	X

Post Approval Stability Commitment

The applicant commits to the first three production lots of the drug product at the long-term stability conditions (25° C ± 2°C). Yearly thereafter, one production batch will be added to the stability program.

Reviewer's Assessment
The proposed post-approval stability testing program is adequate.

Acceptable

P.8.3 Stability Data

Long-term and accelerated stability studies were performed for three exhibit batches (RD16-003, RD16-0l1, RD15-019 and RD17-084) and the provided results were acceptable.

Reviewer's Assessment:
The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life. In addition, the stability data submitted to date support the microbiological quality of the subject drug product.

Acceptable

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: Not applicable.

A.2.1 Materials of Biological Origin

Reviewer's Assessment: Not applicable.

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: Not applicable.

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: Not applicable.

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: Not applicable.

R Regional Information

Executed Batch Records
Executed batch records were provided for batches RD16-003, RD16-0l1, RD15-019 and RD17-084.
The batch records confirm that (b) (4) were used for the manufacture of the exhibit batches.

Note to Reviewer :As per the page 17/308 of exhibit-batch -record-rd15-019.pdf (and other exhibit batches records) (b) (4)

(b) (4) will be used for the manufacturing of the drug product. Clarification is requested below.

IR 3:
Based on the executed batch record provided for lot# RD15-019 (Section 3.2.R on page 17/308 of exhibit-batch -record-rd15-019.pdf), RD16-003(Section 3.2.R on page 16/297 of exhibit-batch -record-rd16-003.pdf), RD16-011(Section 3.2.R on page 18/289 of exhibit-batch -record-rd16-011.pdf) and RD17-084 (Section 3.2.R on page 28/378 of exhibit-batch -record-rd17-084.pdf), (b) (4)

Applicant's Response:
The applicant clarified that both (b) (4) will be used for the manufacturing of the for the commercial production and were also used for the manufacturing of the exhibit batches. The applicant provides an updated master batch record and the relevant information in section 2.3.P, section 3.2.P.3.3 and section 3.2.P.3.5 respectively.

Note to Reviewer: The additional information regarding (b) (4) will be updated in the sections 3.2.P.3.3 and section 3.2.P.3.5 respectively. Please refer to these sections in the review for the updated information.

Reviewer's Assessment:
This section is adequate following review of the response to the IR below communicated to the applicant in letter dated December 4, 2018.

Acceptable

Comparability Protocols
No CP was included in the application.

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

2.A. Package Insert
The subject drug product is a sterile, preservative-free sterile solution for injection. It is supplied in a 10 mL (b) (4) tubular single dose. The subject drug product is stored at room temperature 20-25ºC (68-77ºF). The closure of the vials shall be penetrated

only one time with a suitable sterile transfer device or dispensing set which allows measured dispensing of the contents. Discard the container no later than 4 hours after initial closure puncture.

Selenious Acid Injection must be diluted in a parenteral nutrition solution before administration. The volume of the parenteral nutritional solution should be NLT (b) (4) mL.

The prescribing information for Selenious Acid Injection diluted to (b) (4) in parenteral nutrition solutions indicates that after dilution the product should be used immediately and, if not used immediately, stored not longer than 24 hours at 2-8°C. After removal from storage at 2-8°C, the product should be used promptly, and the infusion completed within 24 hours. Any remainder diluted product must be discarded.

(b) (4)

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(b) (4)

[redacted]

Reviewer's Assessment:
The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.
Acceptable

Post-Approval Commitments: Not applicable.
Lifecycle Management Considerations: Not applicable.

List of Deficiencies:

None Identified

Primary Microbiology Reviewer Name and Date:
Samata Tiwari, Ph.D. (01/23/2019)
Microbiologist
CDER/OPQ/OPF/DMA/BII

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Neal Sweeney, Ph.D. (01/23/2019)
Senior Microbiologist
CDER/OPQ/OPF/DMA/BII

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 209379

a) Drug Product: Selenious Acid Injection, USP, 60 μg/mL

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
pH	Potential ionization of API	M	(b) (4)	The pH of the drug product is expected to remain within acceptable range during the shelf life of the product as demonstrated by the stability testing. None	None
Prticulate Matter	Formation of glass lamallae at low pH	H to M		Particulate matter remained within acceptable range during the stability testing. Low	None
Bioburden	Manufacturing environment and processes	M		Bioburden is controlled in the drug product at release and stability. Low	None
Sterility	Sterilization	M		Sterility is controlled in drug product at release and stability. Low	None