CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208686Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: APPROVAL

NDA 208686
Review # 1

Drug Name/Dosage Form	Enalapril Maleate Oral Solution
Strength	1 mg/1 mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Silvergate Pharmaceuticals, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Amendment (SD 15)	July 26, 2016	Process, Drug Product
Amendment (SD 14)	July 19, 2016	Labeling
Amendment (SD 12)	July 8, 2016	Labeling
Amendment (SD 11)	July 1, 2016	Microbiology
Amendment (SD 9)	June 20, 2016	Labeling
Amendment (SD 8)	June 7, 2016	Process, Drug Product
Amendment (SD 6)	February 29, 2016	Labeling
Amendment (SD 5)	February 26, 2016	Labeling
Amendment (SD 4)	January 27, 2016	Labeling
Amendment (SD 2)	January 22, 2016	Micro, Facilities
Original	November 24, 2015	All

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	ONDP/DNDAPI/Branch I
Drug Product	Sherita McLamore-Hines	ONDP/DNDP I/Branch I
Process	Sung Kim	OPF/DPA III/Branch VII
Labeling	Dan Berger, Stephanie Emory	ONDP/DNDP I/Branch I
Microbiology	Denise Miller	OPF/DMA/Branch II
Facility	Cassandra Abellard	OPF/DIA/B2
Biopharmaceutics	Zhuojun Joan Zhao	ONDP/DB/Branch I
Regulatory Business Process Manager	Dahlia Woody	OPRO/DRBP I/Branch I
Application Technical Lead	Wendy Wilson-Lee	ONDP/DNDP I/Branch I
Environmental Assessment (EA)	Dan Berger, Stephanie Emory	ONDP/DNDP I/Branch I

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	3/24/2016	LoA provided Dt.: 3/30/2015.
	Type II			Adequate	3/25/2016.	LoA provided Dt.: 11/19/2015.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	18998	Vasotec (enalapril maleate) Tablets [RLD]
NDA	204308	EPANED Kit (enalapril maleate) for Oral Solution

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	Complete	Drug product expiry of 22 Months is appropriate	7/5/2016	Malick Mbodji

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 208686 for Epaned (enalapril maleate) Oral Solution. **Please include the following comment in the action letter:**

> *Based on the data submitted and in accordance with ICH Q1E, we grant a 22 month expiry for EPANED (enalapril maleate) Oral Solution when stored refrigerated in the commercial packaging. We grant a 60 day in-use period, after dispensing, when stored at room temperature in the commercial packaging.*

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

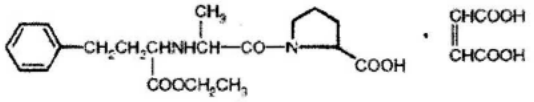
II. Summary of Quality Assessments

EPANED (enalapril maleate) Oral Solution is a ready to use oral solution that will replace the currently marketed EPANED Kit for Oral Solution owned by Silvergate Pharmaceuticals (NDA 204308). The EPANED Kit requires preparation prior to administration. The reference listed drug is Vasotec (enalapril) Tablets, 2.5 mg, 5 mg, 10 mg, and 20 mg (NDA 18998).

The ready to use oral solution (NDA 208686) offers ease of use for patients and health care providers. Pediatric patients and patients who experience difficult swallowing are the most likely consumers of this product. The ready to use product simplifies weight-based dosing in pediatrics. Due to high potential for degradation, the recommended storage condition refrigerated. However, in-use stability data supports storage for up to 60 days at room temperature after dispensing from the pharmacy. This in-use storage condition adds to the ease of use for patients and health care providers.

A. Drug Substance [Enalapril Maleate] Quality Summary

EPANED (enalapril maleate) Oral Solution is the maleate salt of enalapril, the ethyl ester prodrug of a long-acting angiotensin-converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1). Enalapril maleate is a white to off-white, crystalline powder with a molecular weight of 492.52. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol. Its empirical formula is $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$, and its structural formula is:



All drug substance manufacturing and testing facilities listed under NDA 208686 are in good standing as of the GRMP date. The applicant references two DMFs – (b) (4) and (b) (4) – for all chemistry, manufacturing, and controls information supporting the drug substance. Both DMFs are adequate to support NDA 208686 as of the GRMP date.

B. Drug Product [Enalapril Maleate Oral Solution] Quality Summary

EPANED Oral Solution is a non-sterile, ready-to-use oral solution. Each 1 mL of solution contains 1 mg of enalapril maleate, USP equivalent to 0.764 mg of enalapril. Inactive ingredients include citric acid, mixed berry flavor, purified water, sodium benzoate, sodium citrate, and sucralose. It may also contain

hydrochloric acid or sodium hydroxide for pH adjustment. EPANED Oral Solution is clear and colorless with a mixed berry flavor. The manufacturing process consists of [redacted] (b) (4) All drug product manufacturing and testing facilities listed under NDA 208686 are in good standing as of the GRMP date.

EPANED Oral Solution will be commercially available in a 150-mL, white, round, high-density polyethylene bottle with a white, polypropylene, child-resistant cap and tamper-evident seal. Each bottle contains 150 mL (NDC 52652-4001-1). The recommended storage condition is store refrigerated (2°C-8°C (36°F-46°F) in a tightly closed container. Protect from freezing and excessive heat. Patients may store EPANED Oral Solution at room temperature (25°C/77°F) for up to 60 days.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	EPANED
Non Proprietary Name of the Drug Product	Enalapril maleate Oral Solution
Non Proprietary Name of the Drug Substance	Enalapril maleate
Proposed Indication(s) including Intended Patient Population	Treatment of hypertension in adults and children older than one month; Treatment of symptomatic heart failure; Treatment of asymptomatic left ventricular dysfunction
Duration of Treatment	Chronic
Maximum Daily Dose	40 mg in adults; 5 mg in pediatrics
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

This NDA does not include any Biopharmaceutics information to be reviewed.

E. Novel Approaches

None.

F. Any Special Product Quality Labeling Recommendations

Based on the data submitted, we grant a 22 month drug product expiry when stored refrigerated instead of the requested (b) (4) month expiry. The data supports a 60 day in-use expiry for patients at room temperature.

OPQ – in consultation with the Labeling and Nomenclature Committee, DMEPA, and DCRP – recommends that the EPANED drug product established name retain the drug substance salt – enalapril maleate. Changing to the free base enalapril may cause medication errors as the current product for oral solution is based on the salt form. A switch to the free base may cause confusion for health care professionals and patients when determining the appropriate dose when switching to the ready to use product. In addition, the expression of strength for both oral solutions is based on the salt form. A switch to the free base may lead to dosing errors resulting from erroneous calculations of dose or from lack of precise dosing devices allow administration of atypical dose volumes. As such, OPQ recommends retaining the drug substance salt form in the established name for EPANED Oral Solution.

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature: OPQ recommends approval of NDA 208686 for Epaned Oral Solution 1 mg/mL.

Wendy I. Wilson -S

Digitally signed by Wendy I. Wilson -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300396790, cn=Wendy I. Wilson -S
Date: 2016.04.05 08:53:09 -04'00'

On behalf of the OPQ Review Team

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

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

Reviewer's Assessment:

Not applicable. The proposed dosage form is a ready-to-use oral solution, therefore, there is no need for dissolution testing.

Reviewer's Assessment:

Not applicable. The formulation for the exhibit batches (Lot: HCP-C used in Pivotal Study SG04-01) is the same as the proposed formulation for commercial manufacture. Therefore, no bridging is required.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:
This NDA does not include any Biopharmaceutics information to be reviewed.
1/19/2016 Zhuojun Joan Zhao, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics /BBI
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Concurrence and Signature:
I concur with Dr. Zhao's conclusion.
1/19/2016
Elsbeth Chikhale, Ph.D.
Biopharmaceutics Lead (acting)
Division of Biopharmaceutics /BBI
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – Ready-to-use oral aqueous clear solution. The product is multi-use [redacted].
- Drug product composition – The drug product is a solution of enalapril maleate (1.00 mg/mL) with citric acid, sodium benzoate, sucralose, sodium citrate and berry flavoring [redacted] purified water.
- Description of container closure system – 150cc round white opaque high-density polyethylene bottle with a white polypropylene child-resistant closure with a [redacted] seal.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity – NA

- [redacted] was only performed on the stability batches; the information provided does not support the effectiveness [redacted] This information was requested on 23 December 2015 for which a response was received on 1 July 2016.

Information Request: [redacted] in the stability program is acceptable [redacted] over the shelf life of the product, it does not demonstrate the effectiveness at the [redacted]% of label claim. It is recommended that [redacted] be performed on batches of product [redacted] that minimally bracket the acceptable range of [redacted] concentrations.

Summary of Response: [redacted] testing on a product batches with [redacted]% of label claim of the [redacted] was provided in Report SG1406-073. The testing was performed [redacted] acceptance criteria for a [redacted] product were met.

Review of Response: The supplied report supports the effectiveness [redacted]. Continued effectiveness is addressed in the stability program.

- Justification for not having a microbial limit specification for a non-sterile drug product – NA, product has microbial limit specifications.

-ADEQUATE-

REVIEWER COMMENT – There are no quality microbiology concerns.

P.3 Manufacture

P.3.1 Manufacturers

P.3.3 Description of the Manufacturing Process and Process Controls

The drug product is a non-sterile oral solution. The product is [redacted]. The product is stored and shipped under refrigeration. There is no [redacted] for Epaned Oral Solution.

TERMINAL MOIST HEAT STERILIZATION - NA

ETHYLENE OXIDE STERILIZATION - NA

RADIATION STERILIZATION - NA

ASEPTIC FILL MANUFACTURING PROCESS - NA

P.5 Control of Drug Product
P.5.1 Specifications
P.5.2 Analytical Procedures

- Endotoxin – NA
- Sterility – NA
- Microbial Limits - The microbial limits testing proposed for the final drug product are in line with the recommendations of USP <1111> for an aqueous oral product. However, there is no specification for the absence of organisms within the *Burkholderia cepacia* complex. This was requested on 23 December 2015 for which a response received on 22 January 2016.

Information request: Non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate (b) (4) (b) (4). (b) (4) BCC stains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see *PDA J. Pharm Sci Tech* 2011; 65(5):535-43.
In order to control for the presence of BCC in your product you should consider the following:

a. Identify potential sources for introduction of BCC during the manufacturing process and describe the step to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.
b. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g. temperature) before testing.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the precondition step (time, temperature, and solution (s) used), the total number of inoculated organism, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to ensure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.
For more information, we refer you to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.

Summary of Response: The contract manufacturer, [redacted] (b) (4) conducts routine microbiological monitoring of their facilities, including daily testing of the purified water. All isolates recovered in testing the raw material, finished product, and the purified water is reported. The manufacture's method 74.9025 was provided; the method is based on the USP <62> and the EP Section 2.6.13 for testing for the absence of specified organisms. The media used in the method includes Burkholderia cepacia selective agar. Organisms recovered from the selective agars are identified to confirm the presence of *B. cepacia* or BCC. Out of Specification procedures are initiated per SOP DPT-SOP-00727 for samples with confirmed recoveries of *B. cepacia* or BCC.

The absence of *B. cepacia* complex was added to the microbial limit specifications for both release and stability.

Review of Response: The response is adequate; the contract manufacturer tests the purified water, raw materials and finished product for the absence of *B. cepacia* complex. The sponsor has added the absence of *B. cepacia* complex to the release specifications.

-ADEQUATE-

REVIEWER COMMENT – The proposed release specifications are acceptable.

P.7 Container Closure System - NA

P.8 Stability

P.8.1 Stability Summary and Conclusion

MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY: STABILITY CONSIDERATIONS

Proposed storage is [redacted] (b) (4)

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The sponsor will place the first 3 commercial lots of Epaned Oral solution on stability; thereafter, a minimum of one lot will be added to the stability program annually under the following storage conditions:

Long-Term: 5 ± 3°C/ambient RH
Accelerated: 25 ± 2°C/ 60 ± 5% RH

- Container Closure Integrity – NA
- Endotoxin – NA
- [redacted] (b) (4) at the same testing intervals as the Microbial limits testing.

Note: [redacted] (b) (4) is also assessed in the stability program with an acceptance criterion [redacted] (b) (4) of label claim.

- Microbial Limits – Microbial Limits is tested be USP <61> and <62> with the absence of *Burkholderia cepacia* tested by SMA 74.9025.
- Testing intervals is 0, 6, 12, 18, 24, 29, and 36 months for the long term storage conditions. The testing interval for the accelerated storage conditions is 0 and 6 months.
- Specification:
  - TAMC: NMT [redacted] (b) (4) cfu/mL
  - TYMC: NMT [redacted] (b) (4) CFU/mL

- Absence of *Escherichia coli*/mL
- Absence of *Burkholderia cepacia*/mL

Note: The testing for the absence of *Burkholderia* was added in response to the 23 December 2015 information request.

P.8.3 Stability Data

Three batches were placed on stability; batch HCP, HCR, and HCS.

- Stability storage conditions for Registration batches:
  Long term: 5 ± 3°C/ambient RH
  Microbial limits and AET tested at 0, 6, 12, 18, 24, 29, and 36 months
  Accelerated: 25 ± 2°C/ 60 ± 5% RH
  Microbial limits (b) (4) tested at 0 and 6 months
- Specification:
  - TAMC: NMT (b) (4) cfu/mL
  - TYMC: NMT (b) (4) CFU/mL
  - Absence of *Escherichia coli*/mL
  - Absence of *Burkholderia cepacia*/mL

Data up to and including the 12 month time point were submitted. All three lots met the microbial quality acceptance criteria. The testing for the absence of Burkholderia was added after the 12 month time point in response to the 23 December 2015 information request.

-ADEQUATE-

REVIEWER COMMENT – The stability program is acceptable from a quality microbiology perspective.

A APPENDICES - NA

R REGIONAL INFORMATION

R.1 Executed Batch Record – the executed batch records for the three stability lots were submitted in the application.

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

A. PACKAGE INSERT – NA; there are no concerns from a quality microbiology perspective.

Reviewer's Assessment:

The information provided is acceptable and meets the current expectations for a non-sterile oral drug product.

2.3.P.7 Container/Closure System

Reviewer's Assessment: See review of Question 16 above.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

Applicant's Response: There are none

Reviewer's Assessment: The response is acceptable.

Applicant's Response: NA

Reviewer's Assessment: NA

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
The recommendation is to approve from a quality microbiology perspective.
Denise A. Miller
Sr. Microbiology Reviewer
OPQ/OPF/DMA/Branch II

Secondary Review Comments and Concurrence:
I concur with the Microbiology assessment and approval recommendation.

Neal J. Sweeney, Ph.D. 27July2016
Microbiology QAL (Acting)
OPQ/OPF/DMA/Branch II

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

Categorical exclusion is claimed under 21 CFR 25.31(a), no increased use of the active moiety. Exclusion is also claimed under 21 CFR 25.15(d), no extraordinary circumstance exist for this product.

Reviewer's Assessment:

Adequate. The claim of no increased use of the active moiety is acceptable as this ready-to-use formulation replaces the previous reconstituted formulation. No known extraordinary circumstances exist for this product.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: Adequate to support NDA 208686.

Stephanie Emory PhD
Drug Product Reviewer
OPQ/ONDP/Branch I

Dan Berger PhD
Drug Product Reviewer
OPQ/ONDP/Branch I

Secondary Review Comments and Concurrence: I concur.

Wendy Wilson-Lee
Branch Chief (Acting), ONDP

ASSESSMENT OF LABELING

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	EPANED® (enalapril)	Include "maleate" in the established name
Dosage form, route of administration	Oral Solution	Adequate
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	EPANED (b) (4) is a ready-to-use oral solution: 1 mg/mL enalapril maleate.	Adequate

Conclusion: This section is acceptable pending the applicant's acceptance of the noted changes.

(b) "Full Prescribing Information" Section

#3 Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	EPANED (b) (4) is a ready-to-use solution	Adequate
Strengths: in metric system	1 mg/mL of enalapril maleate. Each bottle contains 150 mL.	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	It is a clear, colorless solution packaged in a (b) (4) white, round, high-density polyethylene bottle with a white, polypropylene, child-resistant cap and tamper-evident seal.	Requested applicant to change "colorless solution…" to "colorless solution with a mixed berry flavor…" Also requested applicant to change "(b) (4)" to "150 mL." Otherwise adequate.

Conclusion: This section is acceptable pending the applicant's acceptance of the noted changes.

#11: Description (21CFR 201.57(c)(12))

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	EPANED (enalapril maleate)	Adequate
Dosage form and route of administration	Oral Solution	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Missing	In the last paragraph, (b) (4) (b) (4) should be replaced with "EPANED Oral Solution is a ready-to-use oral solution. Each 1 mL contains 1 mg of enalapril maleate, USP equivalent to 0.764 mg of enalapril."
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Inactive ingredients include citric acid, mixed berry flavor, purified water, sodium benzoate, sodium citrate, and sucralose. It may also contain hydrochloric acid or sodium hydroxide for pH adjustment.	Adequate
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Long-acting angiotensin-converting enzyme inhibitor	Adequate
Chemical name, structural formula, molecular weight	Chemical name: (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z) 2-butenedioate salt (1:1) Empirical formula: $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$ Molecular weight: 492.52	(b) (4) should be replaced with "enalapril, the ethyl ester prodrug." The following statement should be deleted (b) (4). (b) (4) The structure should be updated to show the chirality of the free base and the geometry of the salt.
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Enalapril maleate is a white to off-white, crystalline powder. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol.	Adequate.

Conclusion: This section is acceptable pending the applicant's acceptance of the noted changes.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	1 mg/mL of enalapril maleate	Adequate
Available units (e.g., bottles of 100 tablets)	150 mL bottle	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	EPANED (b) (4) is a ready-to-use solution that contains 1 mg/mL of enalapril maleate. It is a clear, colorless oral solution with a mixed berry flavor, packaged in a 150-mL, white, round, high-density polyethylene bottle with a white, polypropylene, child-resistant cap and tamper-evident seal. Each bottle contains 150 mL.	Adequate
Special handling (e.g., protect from light, do not freeze)	Store refrigerated (2°C-8°C (36°F-46°F) in a tightly closed container. Patients may store EPANED (b) (4) at room temperature (b) (4) for up to 60 days.	Change room temperature to 20-25°C (68-77°F) to be consistent with the bottle and carton labels.
Storage conditions	Protect from freezing and excessive heat.	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured For: Silvergate Pharmaceuticals, Inc. 6251 Greenwood Plaza Blvd., Suite 101 Greenwood Village, CO 80111	Adequate

Conclusion: This section is acceptable pending the applicant's acceptance of the noted changes.

2. Container and Carton Labeling

1) Immediate Container Label

(b) (4)

Conclusion: The bottle label complies with all applicable CFR requirements and is acceptable.

2) Carton Labeling

(b) (4)

Conclusion: The carton label complies with all applicable CFR requirements and is acceptable.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: Labeling is acceptable pending the applicant's acceptance of recommended changes in the PI and the product description data element in the SPL (add mixed berry flavor in product characteristics section).

Stephanie Emory PhD
Drug Product Reviewer
OPQ/ONDP/Branch I

Dan Berger PhD
Drug Product Reviewer
OPQ/ONDP/Branch I

Secondary Review Comments and Concurrence: I concur.

Wendy Wilson-Lee
Branch Chief (Acting), ONDP

I. List of Deficiencies To Be Communicated

None

II. Attachments

A. Lifecycle Knowledge Management

Final Product Risk Assessment

From Initial Risk Identification		Review Assessment		
Attribute/ CQA	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay	Low	Recommended storage condition is refrigerated to slow the degradation process; Drug product expiry granted (22 months) (b) (4) (b) (4)) and is based on statistical analysis of the available stability data	Acceptable	Drug substance degradation is both pH and temperature dependent; Any requested extension of drug product expiry or in-use period should be based on available data and rigorous statistical analysis
Phase Separation	Low	The solution is aqueous	Acceptable	
Solid State	Low	Polymorph controlled (b) (4) (b) (4)	Acceptable	
Dosing Accuracy	Low	(b) (4) testing for deliverable volume	Acceptable	Formulation changes should be evaluated for potential impact to solution viscosity and delivered volume
Palatability	Medium	Formulated with berry flavor (b) (4)	Acceptable	Formulation changes should be evaluated for potential impact to palatability
Microbial Contamination	Low	(b) (4) (b) (4) microbial quality tested (b) (4)	Acceptable	
Leachables/ extractables	Medium	Extractables study report for bottles, labels, and ink at both low and high pH showed no detectable compounds of interest in any of the aqueous extraction solvents	Acceptable	Changes in container closure and printing inks should be evaluated for potential impact to leachables/extractables profile (b) (4)