CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208401Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: APPROVAL

NDA 208401
Review #1

Drug Name/Dosage Form	Lisinopril Oral Solution
Strength	1 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Silvergate Pharmaceuticals, Inc.
US agent, if applicable	None.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Amendment SD 18	18-MAR-2016	Process
Amendment SD 15	14-MAR-2016	DP
Amendment SD 14	26-FEB-2016	DP, Process
Amendment SD 12	19-JAN-2016	DP
Amendment SD 11	11-JAN-2016	DP, Micro
Amendment SD 9	10-DEC-2015	DP, Micro
Amendment SD 8	23-NOV-2015	DP, Micro
Amendment SD 4	30-SEP-2015	DP
Original SD 1	30-JUN-2015	All

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Rao Kambhampati	Branch 1/DNDP1/ONDP
Drug Product		
Process	Sung Kim	Branch VII/DPA III/OPF
Microbiology	Erika Pfeiler	Branch 1/DMA/OPF
Facility	Ebern Dobbin	Branch II/DIA/OPF
Regulatory Business Process Manager	Maryam Kord Bacheh Changi	Branch 1/DRBPM1/ OPRO
Application Technical Lead	Wendy Wilson-Lee	Branch 1/DNDP1/ONDP
Environmental Assessment (EA)	Rao Kambhampati	Branch 1/DNDP1/ONDP
Labeling and Labels		

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	REVIEW DATE	COMMENTS
(b) (4)	Type II	(b) (4)	Lisinopril Dihydrate	Adequate	2/24/15 (Annual Report #8 + Amendment #15)	Reviewer: Rao V. Kambhampati, Ph.D. (ONDP)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	19777	Zestril tablets

2. CONSULTS:

No consults.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

1. OPQ recommends **APPROVAL** of NDA 208401 for Lisinopril Oral Solution, 1 mg/mL.

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

There are no OPQ Phase 4 commitments.

II. Summary of Quality Assessments

A. Drug Substance [Lisinopril] Quality Summary

Lisinopril, known chemically as 1-[N^2-[(*S*)-1-Carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate, is a white to off-white, crystalline powder, with a molecular weight of 441.52 (for dihydrate). Lisinopril is soluble in water, sparingly soluble in methanol, and practically insoluble in ethanol. The applicant referenced DMF (b) (4) for supporting drug substance chemistry, manufacturing, and controls information. Lisinopril has no known polymorphic forms. (b) (4) manufactures lisinopril under NDA 208401. (b) (4) The drug substance specification assures the identity, quality, strength, and purity of the drug substance. Batch analysis results demonstrate that the drug substance can be manufactured with consistent quality and purity. The drug substance is stored at (b) (4). The retest period is (b) (4) months.

B. Drug Product [Lisinopril Oral Solution] Quality Summary

Lisinopril Oral Solution, 1 mg/mL, is a ready-to-use aqueous formulation. Each 1 mL of the solution contains 1.09 mg of lisinopril dihydrate, equivalent to 1 mg of Lisinopril, and the following inactive ingredients: purified water, xylitol, sodium citrate, citric acid, sodium benzoate, and either hydrochloric acid or sodium hydroxide is added for pH adjustment. All of the excipients are commonly used, compendial grade excipients. The antimicrobial effectiveness testing supports the concentration of (b) (4) in the formulation. The solution is clear to slightly opalescent with a pH range of 4.3 – 5.1. 150 mL of the solution is packaged in 150-cc round, white, opaque, high-density polyethylene (HDPE) bottles with a white, polypropylene, child-resistant closure with a heat induction layered inner seal. The drug product is (b) (4).

The proposed specification assures the identity, purity, strength, and quality of the drug product. Batch analysis results demonstrate that the drug product can be manufactured with consistent quality and purity. No new impurities or degradants were observed in the drug product batches that were reported in the submission. (b) (4)

[redacted]

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	None
Non Proprietary Name of the Drug Product	Lisinopril Oral Solution
Non Proprietary Name of the Drug Substance	Lisinopril Dihydrate
Proposed Indication(s) including Intended Patient Population	Treatment of hypertension in patients 6 years of age and older
Duration of Treatment	Chronic
Maximum Daily Dose	Initial titration – 10 mg once daily Maintenance dose – 20 mg – 40 mg once daily
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations: There was no biopharmaceutics review for NDA 208401. The application did not include any biowaiver requests or dissolution methods.

E. Novel Approaches: None.

F. Any Special Product Quality Labeling Recommendations

This product is formulated as a ready-to-use solution that does not require further dilution or preparation. Both the prescribing information and carton/container labels distinguish this aspect of the product from other approved liquid formulations.

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Based on our review of the submission, we recommend **APPROVAL** of NDA 208401 for Lisinopril Oral Solution, 1 mg/mL. All facilities associated with the manufacture, testing, and packaging of the drug substance and drug product are in good standing. Based on the stability data provided in the submission and in accordance with ICH Q1E, we grant a 24 month expiry for Lisinopril Oral Solution when stored at controlled room temperature [redacted] (b) (4).

This product is an alternative to the Lisinopril Oral Suspension USP, which requires compounding at the pharmacy. The oral solution is a ready-to-use product that does not require further compounding prior to administration to the patient. The applicant identified palatability as a significant quality attribute and conducted studies during development to optimize the formulation and patient experience. (b) (4)

(b) (4)

The drug substance DMF supporting the application remains adequate. The submission included sufficient information to support the product design and control strategy. (b) (4)

Based on the justification provided in the submission, we grant the categorical exclusion from conducting the environmental assessment in accordance with 21 CFR 25.31(a) and 21 CFR 25.15(d). The carton and container labels as well as the prescribing information and all other labeling are acceptable from an OPQ perspective. The OPQ review team will continue to engage in labeling discussions with DCRP until final regulatory action.

Application Technical Lead Signature: OPQ recommends APPROVAL of NDA 208401.

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: 2016.03.23 10:49:31 -04'00'

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any of its specifications whether or not the batch has been already distributed. 5) Results of stability testing are not used in determining appropriate storage conditions and expiration dates. 6) There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. The final classification of the inspection was VAI.

Site Risks and Critical Parameters

All laboratory testing equipment needs to be qualified, methods validated, audit trails and calibrations up to date.

PAI or Acceptable Decision

No PAI was required based on the sites history of compliance having VAI classifications for the past three inspections. The site's history shows that the firm has been successful in their ability to develop test methods and perform analytical testing. The evaluation of the risks associated with facility product, and process did not reveal any evidence of high risks associated with the CTL profile for laboratory testing. A review of the production load did not show a significant increase which could lead to issues due to a firms lack of readiness for an increase in production. The firm demonstrates a strong history of method development and analytical laboratory testing services. The CTL profile is within scope of the firm's operations. The firm is **ACCEPTABLE** based on the sites responsibilities to perform drug substance release testing.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

After completion of the review of this application, supporting documents, the recent inspection results and documentation, it has been confirmed that there are no outstanding manufacturing risks that prevent the approval of this application. Based on the inspectional history and the review during the pre-approval inspections, the manufacturing facilities as listed above for NDA 208401 are found to be acceptable.

Ebern Dobbin – 3/22/2016
Consumer Safety Officer, OPQ/OPF/DIA/IABII

Secondary Review Comments and Concurrence:

I concur with the Approval recommendation.

Christina Capacci-Daniel, PhD – 3/22/2016
Consumer Safety Officer / Acting QAL, OPQ/OPF/DIA/IABII

ASSESSMENT OF THE BIOPHARMACUETICS

29. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Applicant's Response: N/A

Reviewer's Assessment: N/A

30. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Applicant's Response: N/A

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

A biopharmaceutics review was not conducted. The application did not include any biowaiver requests or dissolution methods/acceptance criterion.

ASSESSMENT OF MICROBIOLOGY

31. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Drug Product: Qbrelis™ Lisinopril Liquid Oral Solution is a 1 mg/ml/150 mL multidose oral solution that contains sodium benzoate (b) (4)

The drug product was tested for Antimicrobial Effectiveness using a method consistent with USP Chapter <51>. This testing was performed using product containing (b) (4)%, and (b) (4)% of the labeled (b) (4) content. Sodium benzoate content is assayed at release and on stability, with acceptance criteria of (b) (4)% of the labeled content. Additionally, AET is currently being performed on three registration stability batches of drug product.

The test method for microbial limits and AET were verified to be appropriate for use with the drug product following procedures consistent with harmonized testing to satisfy USP Chapter <61>, <62> and <51> respectively. The release specification for the drug product includes a total aerobic microbial count of NMT (b) (4) CFU/mL, a total yeast and mold count of NMT (b) (4) CFU/mL, and the absence of *Escherichia coli* in 1 mL. These criteria are in agreement with those listed in USP <1111>. Further, the specification states that *Burkholderia cepacia* should be absent per mL. Validation of the recovery of this microorganism was performed for USP <61> and USP <62> methods. The USP <62> method will be performed (b) (4).

The drug product will be tested for microbial limits at time points 0, 6, 12, 18, 24, and 36 months as part of the stability protocol.

74-Day Letter Information Request:
Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism *Burkholderia cepacia*. We recommend that potential sources are examined and sampled as process controls, and 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. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

10 December 2015 Response
The applicant stated that USP <62> had been validated for the detection of *B. cepacia*, but did not provide a validation summary or a revised product specification. A follow-up IR will be sent to request this material.

08 December 2015 Information Request (drafted from courtesy submission of previous IR response)
We acknowledge the 30 November courtesy submission of 74-day letter responses in which you state that USP <62> has been validated to include *Burkholderia cepacia*. Please submit a revised product specification with an acceptance criterion for absence of this microorganism, as well as a summary of the validation studies that you performed.

11 January 2016

The applicant provided the requested information, which was incorporated into the body of the review.

—

22 October 2015 Information Request

The application states that antimicrobial effectiveness testing (AET) will only be performed on registration stability batches. The acceptance criterion for sodium benzoate content in the drug product is (b) (4)% of the label claim; however, the content in all stability batches is (b) (4)%. In order to ensure that the proposed (b) (4) acceptance criterion is adequate, AET should be performed on product containing sodium benzoate content at or below the acceptance criterion.

23 November 2015 Response

The applicant provided the requested information, which was incorporated into the review.

Reviewer's Assessment:

The Microbial Limits & AET specifications for "Qbrelis™ Lisinopril Oral Solution" are acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

2.3.P.7 Container/Closure System

32. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:

Reviewer's Assessment:

N/A, product is nonsterile.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

33. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

Reviewer's Assessment:

N/A, product does not contain substances derived from biological sources.

34. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Reviewer's Assessment:

N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
Recommended for approval.
Erika Pfeiler, Ph.D.
10 February 2016

Secondary Review Comments and Concurrence:
I concur.
Jesse Wells, Ph.D.
10 February 2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

35. Is the applicant's claim for categorical exclusion acceptable?
    Yes.

36. Is the applicant's Environmental Assessment adequate for approval of the application?
    Yes.

Applicant's Response:

Silvergate Pharmaceuticals, Inc. (Silvergate), hereby claims a categorical exclusion from the requirement to submit an Environmental Assessment under 21 CFR 25.31(a) for Lisinopril Oral Solution because action on this NDA does not increase the use of the active moiety.

Furthermore, to the best of Silvergate's knowledge, no extraordinary circumstances exist that might cause this action to have a significant affect on the quality of the human environment (21 CFR 25.15[d]).

Reviewer's Assessment: Acceptable.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: The active ingredient is currently present in the other FDA approved drug products. The EA section of the NDA is recommended for approval on the basis of categorical exclusion claims as according to the 21 CFR 25.31(a) and 21 CFR 25.15 (d).

Rao V. Kambhampati, Ph.D.
Senior Chemist/ONDP/DNDP I/NDPB I

Secondary Review Comments and Concurrence: I concur.

Wendy I. Wilson-Lee, Ph.D.
Branch Chief (Acting), Branch 1/DNDP1/ONDP/OPQ
March 21, 2016

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

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	Qbrelis™ (lisinopril)	Acceptable
Dosage form, route of administration	Oral Solution, for oral use	Acceptable
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	Ready-to-use aqueous oral solution containing 1.0 mg of lisinopril/1 mL of solution.	Acceptable

Conclusion: Acceptable.

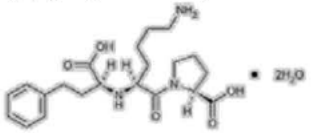
(b) "Full Prescribing Information" Section

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

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Oral solution	Acceptable
Strengths: in metric system	1 mg/mL	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Clear to slightly opalescent solution. 150 mL of the solution is packaged in 150-cc round, white, opaque, high-density polyethylene (HDPE) bottle with a white, polypropylene, child-resistant closure with a heat induction layered inner seal.	Acceptable

Conclusion: Acceptable.

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

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Qbrelis™ (lisinopril)	Acceptable
Dosage form and route of administration	Solution, Oral	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	Each 1 mL of the solution contains 1.09 mg of lisinopril dihydrate, which is equivalent to 1 mg of lisinopril as the active ingredient.	Acceptable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Purified water, xylitol, sodium citrate, citric acid, sodium benzoate, and possibly either hydrochloric acid or sodium hydroxide (b) (4) (b) (4)	Acceptable
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Angiotensin converting enzyme (ACE) inhibitor.	Acceptable.
Chemical name, structural formula, molecular weight	(S)-1-[N^2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dehydrate  $C_{21}H_{31}N_3O_5 \cdot 2H_2O$ Mol. Wt. = 441.5 (b) (4)	Acceptable.
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, pH)	Soluble in water, sparingly soluble in methanol, and practically insoluble in ethanol	Acceptable

Conclusion: Acceptable.

#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	Acceptable
Available units	Bottles of 150 mL	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Clear, to slightly opalescent solution packaged in a white bottle and cap.	Acceptable
Special handling (e.g., protect from light, do not freeze)	N/A	N/A
Storage conditions	Store at controlled room temperature 20°C-25°C (68°F-77°F). Protect from freezing and excessive heat.	Acceptable

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., Ste 101 Greenwood Village, CO 80111	Acceptable

Conclusion: Acceptable.

2. Container and Carton Labeling

1) Immediate Container Label

Bottle Label:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Qbrelis™ (lisinopril). Font size and prominence are acceptable.	Acceptable.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	1 mg/mL. Each mL contains 1 mg of lisinopril.	Acceptable.
Route of administration 21.CFR 201.100(b)(3))	Oral solution	
Net contents* (21 CFR 201.51(a))	150 mL	Acceptable.
Name of all inactive ingredients (Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	N/A	N/A
Lot number per 21 CFR 201.18	Yes	Acceptable.
Expiration date per 21 CFR 201.17	Yes	Acceptable.
"Rx only" statement per 21 CFR 201.100(b)(1)	Rx only	Acceptable.
Storage (not required)	Store at (b) (4) room temperature 20°-25°C (68° -77° F).	Acceptable.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 52652-3001-1	Acceptable.
Bar Code per 21 CFR 201.25(c)(2)***	Yes	Acceptable.
Name of manufacturer/distributor (21 CFR 201.1)	Manufactured for: Silvergate Pharmaceuticals, Inc. 6251 Greenwood Plaza Blvd., Suite 101 Greenwood Village, CO 80111	Acceptable.
Others	READY TO USE KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN Usual Dosing: See Prescribing Information (b) (4)	Acceptable.

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
***Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Acceptable. The final revised bottle label will reflect all the above information.

2) Carton Label

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Qbrelis™ (lisinopril). Font size and prominence are acceptable.	Acceptable.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	1 mg/mL. Each mL contains 1 mg of lisinopril.	Acceptable.
Net contents (21 CFR 201.51(a))	150 mL	Acceptable.
Lot number per 21 CFR 201.18	Yes	Acceptable.
Expiration date per 21 CFR 201.17	Yes	Acceptable.
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	N/A	**N/A**
Sterility Information (if applicable)	N/A	**N/A**
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Yes	Acceptable.
Storage Conditions	Store at (b) (4) room temperature 20°-25°C (68° -77° F) Avoid excessive heat and freezing.	Acceptable.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 52652-3001-1	Acceptable.
Bar Code per 21 CFR 201.25(c)(2)**	Yes	Acceptable.
Name of manufacturer/distributor	Manufactured for: Silvergate Pharmaceuticals, Inc. 6251 Greenwood Plaza Blvd., Suite 101 Greenwood Village, CO 80111	Acceptable.
"See package insert for dosage information" (21 CFR 201.55)	Yes. USUAL DOSAGE: See accompanying Prescribing Information.	Acceptable.
"Keep out of reach of children" (optional for Rx, required for OTC)	Yes. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN	**Acceptable.**
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Oral Solution	**Acceptable.**

Conclusion: Acceptable. The final revised carton label will reflect all the above information.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: Acceptable. The final revised package insert, bottle and carton labels will reflect all the above information.

Rao V. Kambhampati, Ph.D.
Senior Chemist/ONDP/DNDP I/PMAB I

Secondary Review Comments and Concurrence: I concur.

Wendy I. Wilson-Lee, Ph.D.
Branch Chief (Acting), Branch 1/DNDP1/ONDP/OPQ
March 21, 2016

II. List of Deficiencies To Be Communicated

None.

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

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**
Assay	• Formulation • Container closure • Raw materials • Process parameters Scale/equipment/site	Low	Final product testing at release and on stability	Acceptable	
Physical Stability (phase separation)	See above	Low	Controlled as part of final product visual inspection at release and on stability	Acceptable	
Solid state – polymorphic form	See above	Low	No known polymorphs identified	Acceptable	
Dosing accuracy	See above Dosing device	Low	Final product testing for deliverable volume	Acceptable	Formulation changes that impact viscosity should be evaluated against impact to dosing accuracy
Palatability	• Formulation • Container closure • Raw materials • Process parameters Scale/equipment/site	Medium		Acceptable	Formulation changes, (b) (4) (b) (4) should be evaluated against impact to palatability
Microbial Limits	See above	Low	Final product testing at release and on stability	Acceptable	
Leachables	See above	Medium	Leachables evaluated at low and high pH for both primary container and label ink	Acceptable	Changes to primary container and label ink should be evaluated for potential leachables