CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214965Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214965
Assessment # 1

Drug Product Name	Verkazia (cyclosporine ophthalmic emulsion)
Dosage Form	Ophthalmic emulsion
Strength	0.1%
Route of Administration	Topical ophthalmic
Rx/OTC Dispensed	Rx
Applicant	Santen, Inc.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Aug. 26, 2020	All disciplines
Labeling	Sep 2, 2020	Drug product
Quality Amendment	Sep 8, 2020	Manufacturing and facility
Quality Amendment	Sep 23, 2020	Quality microbiology
Quality Amendment	Sep 30, 2020	Manufacturing and facility
Quality Amendment	Oct 30, 2020	Drug product and quality microbiology
Quality Amendment	Nov 30, 2020	Manufacturing and facility
Quality Amendment	Dec 2, 2021	Manufacturing and facility
Quality Amendment	Feb 12, 2021	Drug product, manufacturing and facility
Quality Amendment	Feb 19, 2021	Manufacturing and facility
Quality Amendment	Mar 22, 2021	Drug product
Quality Amendment	Mar 24, 2021	Biopharmaceutics
Quality Amendment	Apr 15, 2021	Drug product
Quality Amendment	May 5, 2021	Drug product
Quality Amendment	May 6, 2021	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Zhengfu Wang	Suong Tran
Drug Product	Milton Sloan	Chunchun Zhang
Manufacturing	Laurie Nelson	Vidya Pai
Microbiology	Sallie Crenshaw	Erika Pfeiler
Biopharmaceutics	Joan Zhao	Poonam Delvadia
Regulatory Business Process Manager	Kelly Ballard	
Application Technical Lead	Chunchun Zhang	
Laboratory (OTR)	NA	
Environmental	Milton Sloan	Chunchun Zhang

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	02/02/2021	
	III			Adequate	5/16/2011	

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	70502	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology	Complete	Adequate	2/3/2021	Erin Ruhland
CDRH				
Clinical				
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 214965, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product Verkazia (cyclosporine ophthalmic emulsion), 0.1%. All information requests and review issues have been addressed.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued an overall acceptable recommendation for all the facilities on 3/17/2021.

Therefore, NDA 214965 is recommended for approval from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

A comparability protocol was submitted to facilitate an additional cetalkonium chloride (CKC) manufacturer and was found acceptable with the proposed reporting category of CBE-30. However, we recommend the following general comment should be communicated to the applicant in the action letter:

We acknowledge you plan to include an additional manufacturer for cetalkonium chloride (CKC) with the proposed reporting category of CBE-30. However, we remind you the additional manufacturer should be registered with FDA and in good GMP standing.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product cyclosporine ophthalmic emulsion, 0.1% is a sterile, unpreserved, (b) (4) (b) (4) emulsion drug product packaged in single-dose (b) (4) low density polyethylene (LDPE) containers and then in in a conventional sealed (b) (4) aluminum pouch.

Proposed Indication(s) including Intended Patient Population	For the treatment of (b) (4) vernal keratoconjunctivitis for children from 4 through 18 years of age.
Duration of Treatment	Instill one drop of Verkazia ophthalmic emulsion 4 times daily (morning, noon, afternoon, and evening) into each affected eye.
Maximum Daily Dose	As above (see the package insert for details)

Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The applicant cross-referenced the CMC information for the drug substance Cyclosporine to DMF [redacted]. DMF [redacted] was found adequate by Dr. Zhengfu Wang on 2/2/2021.

Drug Product: Adequate

Verkazia is a sterile, unpreserved, [redacted] topical ophthalmic emulsion containing cyclosporine USP 1 mg/mL (0.1% w/w). All the other excipients are compendial except cetalkonium chloride (CKC), CKC is a novel excipient, however it is considered as a low risk [redacted] The applicant provided adequate CMC information on CKC. A comparability protocol was submitted to facilitate an additional CKC manufacturer and was found acceptable with the proposed reporting category of CBE-30. The revised drug product specifications are acceptable and include the following quality attributes: appearance, ID, pH, osmolality, zeta potential, mean droplet sizes, assay, sterility, content uniformity, degradation products. All the analytical methods are adequately validated. Evaluation of the risk assessment of the elemental impurities was performed and indicates the results are lower than the permitted daily exposure (PDE) as noted in ICH Q3D guidance. CoAs for two phase 3 clinical batches and fine primary stability batches are provided.

The applicant has submitted 5 primary stability batches with 36 months stability data when stored at long term storage condition (25°C/40%RH) and 6 months at accelerated condition (40°C/25%RH). All the quality attributes met the specifications. Only a slight increase trend was observed in the mean droplet size. Extractable/leachable studies were performed and there are no safety concerns for the potential leachables. Therefore, the expiration date of 36 months is granted when stored at 20 °C- 25 °C.

The storage statement is “Store at 20°C-25°C (68°F-77°F). Do not freeze.” and will be finalized at the OND’s labeling meeting.

Labeling: Adequate

Labeling recommendations from the Product Quality perspective will be communicated to the OND PM.

Manufacturing: Adequate

The manufacturing process includes: (b) (4) (b) (4) The proposed process control is found adequate. The facilities associated with the application appear acceptable to support the manufacture of Verkazia (cyclosporine ophthalmic emulsion), 0.1%. No Pre-Approval Inspection are recommended.

Biopharmaceutics: N/A

Biopharmaceutics' general recommendation shown below was communicated to the applicant on 3/18/2021 and received the acknowledgment on 3/24/2021. This is satisfactory and no action is needed from the applicant at this time.

The rate and extent of drug release from ophthalmic drug products are quality criteria that may reflect aspects related to formulation and process variations that are important to control to ensure consistent quality. In vitro drug release test (IVRT) is also deemed as a useful test to assess product sameness under certain post approval changes, and thus we recommend you consider developing an IVRT for your proposed VERKAZIA (cyclosporine) ophthalmic emulsion. However, other approaches are acceptable such as using one or more other critical quality attributes (CQAs) which are sensitive to the formulation and process variations, if adequate scientific justifications are provided for how the proposed control strategy will assure consistent product quality.

If the proposed control strategy does not assure consistent product quality, we recommend you develop an IVRT and have the following recommendations regarding the IVRT development report for your future submission (e.g., supplement).

- *Identify key physicochemical properties that affect drug release and ocular bioavailability.*
- *A detailed description of the optimal methodology and the developmental parameters (i.e., solubility data for the drug substance on the ocular surface, pH, selection of the equipment/apparatus, in vitro release media, agitation/rotation speed, assay, etc.) that were used to identify the selected method as most appropriate should be included in the report. Ideally, the in vitro release method should be physiologically relevant (e.g., mimicking physiological factors).*
- *The drug release profile should be complete and cover at least 80% of drug released or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend using at least twelve samples per testing variable.*
- *The drug release data (individual, mean, SD, profiles) should be reported as the cumulative percentage of drug being released with time.*
- *Include the testing conducted to demonstrate the discriminating capability of the selected test as well as the validation data for the test method (i.e., method*

robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.). The chosen method should be discriminating and sensitive enough to reject non-target lots that would have less than acceptable clinical performance. Include data/information including multi-point in vitro release profile supporting the discriminating ability of the method with respect to the most relevant critical material attributes (CMAs), critical formulation variables (CFVs), and critical process parameters (CPPs).

- *If feasible, collect in vitro release profile on pivotal clinical and registration batches that would serve as reference product for comparison purposes to support future post approval changes.*

Microbiology (if applicable): Adequate

The applicant has provided adequate sterility assurance. The process is (b) (4)

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment Site	H	(b) (4)	L	Post-approval stability protocol will test sterility.
Assay (API), stability	• Formulation • Container closure • Raw materials	L	(b) (4)	L	
Content Uniformity	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M		L	

			(b) (4)		
Mean droplet sizes	• Formulation • Container closure[1] • Process parameters • Scale/equipment	M		L	
pH	• Formulation • Container closure • Process parameters • Scale/equipment	L		L	
Extractables/ leachables	• Formulation • Container closure	M		L	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

NA

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

NA

4. Labeling Deficiencies

5. Manufacturing Deficiencies

NA

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

NA

8. Other Deficiencies *(Specify discipline, such as Environmental)*

NA

Application Technical Lead Name and Date:

Chunchun Zhang, Ph. D., May 11,2021

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CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

R REGIONAL INFORMATION

Environmental

Santen Inc. claims that the Verkazia NDA qualifies for a categorical exclusion in accordance with 21 CFR 25.31(b) and that, to the best of the applicant's knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment. The requested categorical exclusion is based on the following estimate of the concentration of cyclosporine at the point of entry into the aquatic environment. The expected introduction concentration (EIC) of cyclosporine was calculated as:

EIC-Aquatic (ppb) = A x B x C x D where

(b) (4)

Assessment: ***Adequate***

The claim of categorical exclusion is acceptable and no additional information is required.

Primary Drug Product Assessor Name and Date:
Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div3/Branch 6

Secondary Assessor Name and Date (and Secondary Summary, as needed)
Chunchun Zhang, Ph.D.,
Quality Assessment Lead,
OPQ/ONDP/Div3/Branch 6

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Verkazia™	Acceptable
Established name(s)	Cyclosporine	Acceptable
Route(s) of administration	Topical Ophthalmic	Acceptable
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	ophthalmic emulsion, 0.1%	Acceptable
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2 FULL PRESCRIBING INFORMATION

Section 2 (DOSAGE AND ADMINISTRATION)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	Agrees with DMEPA Labeling review recommends adding statement to "gently shake" in Section 2

Section 3 (DOSAGE FORMS AND STRENGTHS)

Ophthalmic emulsion containing cyclosporine 1.0 mg/mL

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Ophthalmic emulsion	Acceptable
Strength(s) in metric system	0.1%	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

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Section 11 (DESCRIPTION)

(b) (4)

Structural Formula

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	Acceptable
Dosage form(s) and route(s) of administration	Yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	Recommend consider listing inactives listed as alphabetical order (per LRT).
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	No	Recommend adding "sterile". See tracked changes
Pharmacological/ therapeutic class	Yes	
Chemical name, structural formula, molecular weight	Yes	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Yes	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	Yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Yes	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.		
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	N/A	

Other Sections of Labeling

Manufacturing Information After Section 17 (for drug products)

For NDAs include:
Manufactured for: Santen Inc
Manufactured by: ExcelVision

Distributed by:
Santen Inc.
6401 Hollis Street, Suite 125
Emeryville, CA 94608
United States

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Yes	Acceptable

PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

CARTON AND CONTAINER LABELING

3.1 Container Label

(Copy/paste or refer to a representative example of a proposed container)

3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes	
Dosage strength	Yes	
Route of administration	No	Add For Ophthalmic use
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	Yes	
"Rx only" displayed on the principal display		
NDC number		
Lot number and expiration date		
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	(b) (4)	Add temp equivalent on Celsius (b) (4) (DMEPA review) Accepted revision: Store at 20°C to 25°C (68°F to 77°F)
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	Recommend revising "(b) (4)" to single-dose for PI consistency
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code		

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor		
Medication Guide (if applicable)		
No text on Ferrule and Cap overseal		
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.		
And others, if space is available		

Assessment of Carton and Container Labeling: *Inadequate*

The established name is not at least half the size of the proprietary name (see DMEPA label review).

ITEMS FOR ADDITIONAL ASSESSMENT

The comments will be negotiated as part of the clinical labeling meeting(s).

Overall Assessment and Recommendation:

Adequate with revisions.

Primary Drug Product Assessor Name and Date:
Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div3/Branch 6

Secondary Assessor Name and Date (and Secondary Summary, as needed)
Chunchun Zhang, Ph.D.,
Quality Assessment Lead,
OPQ/ONDP/Div3/Branch 6

Milton Sloan

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Chunchun Zhang

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	214965
Assessment Cycle Number	MR01
Drug Product Name/Strength	Verkazia, 1.0 mg/mL
Route of Administration	Ophthalmic
Applicant Name	Santen Incorporated
Therapeutic Classification/ OND Division	CDER/OND/OSM/DO
Manufacturing Site	Excelvision 27 Rue de la Lombardière, ZI La Lombardière 07100 Annonay, France
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
Original Submission	**8/26/2020**
Response-to-CMC-information-request-09sep2020	**10/02/2020**
Response-to-cmc-information-request-16oct2020	**10/30/2020**
S0011-cover-letter-30nov2020	**11/30/2020**

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

Remarks: The drug product is a single-dose, non-preserved, sterile emulsion for ophthalmic administration for the treatment of (b) (4) vernal keratoconjunctivitis for children from 4 through 18 years of age.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents: N/A

S DRUG SUBSTANCE-N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product-** A sterile, unpreserved, [redacted] drug product that is milky white in appearance. The ophthalmic emulsion is packaged in low density polyethylene (LDPE) single-dose vials sealed by [redacted] with a nominal fill volume of 0.3 mL.

- **Drug product composition-**
  Section 3.2.P.1, "description-and-composition" document.

Table 1: Composition of Verkazia Ophthalmic Emulsion

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)	
		%w/w[a]	mg/mL
Cyclosporine (USP)	Drug substance	0.10	1.0
Triglycerides, medium-chain (USP)	[redacted]		
Tyloxapol (USP)			
Cetalkonium chloride (In-house)			
Glycerol (USP)			
Poloxamer 188 (USP)			
Sodium Hydroxide (USP)	pH adjuster		
Water for Injection (USP)	[redacted]		
Total			

- **Description of container closure system-**
  Section 3.2.P.7 "Container Closure System" document.

- The drug product is filled into LDPE single dose containers [redacted]

  The single dose LDPE eye drop containers are provided in strips of five

which are labeled and packaged in a conventional sealed (b) (4) aluminum pouch.

Table 1: Low Density Polyethylene Manufacturer

Component	Manufacturer and supplier	Address
(b) (4)	(b) (4)	

Assessment: *Adequate*

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

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Assessment: *Adequate*

The applicant has met regulatory expectations with regard to the test method, acceptance criteria, and verification of the suitability of use of the sterility test that will be performed on the drug product prior to its release.

P.7 CONTAINER CLOSURE

Summary Table of the Container Closure System Proposed

Assessment: See Section P.1 of this review.

P.8.1 STABILITY SUMMARY AND CONCLUSION

Section 3.2.P.8.1, pg. 11 of "Stability Summary and Conclusion" document.

Proposed Expiry: 36 months

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

Section 3.2.P.8.1, "Stability Summary and Conclusion" document and Section 3.2.P.8.2, "Post-Approval Stability Protocol and Stability Commitment" document.

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Sterility	USP<71>	Sterile

During routine manufacture, (b) (4) (b) (4) (b) (4) The testing schedule in the post-approval commercial stability protocol (pg. 6 of "Stability Summary and Conclusion" document) is as follows:

Long Term stability storage conditions: 25°C ± 2°C/40% RH ± 5% RH

Test	Time (Months)						
	0	3	6	12	18	24	36
Sterility	X			X		X	X

Intermediate stability storage conditions[a]: 30°C ± 2°C/65% RH ± 5% RH

Test	Time (Months)						
	0	3	6	12	18	24	36
Sterility	X			X		X	X

[a]Batches 9E45 and 9E46 were not tested under intermediate conditions

Accelerated stability storage conditions: 40°C ± 2°C/≤25% RH

Test	Time (Months)		
	0	3	6
Sterility	X		X

Post Approval Stability Commitment

The applicant states that at least one batch of the drug product will be placed on stability testing annually under "real time" conditions.
The applicant commits to placing the first three commercial lots of the subject drug product into their long term (25°C) and accelerated (40°C) stability program. Thereafter, on an annual basis, a minimum of one production lot will be added to the stability program at the long-term conditions in an inverted position.

The following information request was sent to the applicant on 10/16/2020.

9. *We acknowledge the information provided in Section 3.2.P.8.2, in the "Post-Approval Stability Protocol and Stability Commitment" document. Please define the "real time" conditions that will be utilized for annual stability testing. Additionally, please commit to placing the first three commercial lots of the drug product into the stability program.*

Response dated 10/30/2020

The applicant committed to placing the first three commercial lots of the drug product onto their long-term stability program and to place at least one batch on the long-term stability program annually after that.

Assessment: *Adequate*

Although the applicant did not define the "real time" conditions utilized for annual stability testing, as they committed to placing their first three commercial lots (and one batch annually thereafter) on long-term stability conditions, it can be assumed that the long-term conditions (25°C ± 2°C/40% RH ± 5% RH) are representative of the "real time" conditions for annual stability testing. Therefore, 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.

P.8.3 STABILITY DATA

Section 3.2.P.8.3, "Stability Data" document

Stability data for three exhibit lots of drug product (Z036, Z037, and Z038) manufactured in the original aluminum pouch until the end of 2017 and 2 exhibit lots of drug product (9E45 and 9E46) manufactured in the current aluminum package was provided. Exhibit batches Z036, Z037, and Z038 were stored for up to 36 months at long term and intermediate conditions and up to 6 months at accelerated conditions. Exhibit batches 9E45 and 9E46 were stored for up to 36 months at long term conditions and up to 6 months at accelerated conditions. Sterility testing performed at all time points met the established acceptance criteria.

Assessment: *Adequate*

The stability data submitted to date support the microbiological quality of the subject drug product.

APPENDICES

Assessment: N/A

R REGIONAL INFORMATION

Executed Batch Records

Executed lot #s: 6J12, X528, and 2A44. Executed batch records provided are not in English.

The following information request was sent to the applicant on 10/16/2020.

10. *We acknowledge the information provided in Section 3.2.R for executed batches 6J12, X528, and 2A44. However, all of the executed batch records provided are in French. Please provide executed batch records for batches 6J12, X528, and 2A44 in English.*

Response dated 10/30/2020

The applicant committed to providing translated batch records by 11/30/2020 for batches 6J12, X528, and 2A44.

Response dated 11/30/2020

The applicant provided translated executed batch records [redacted] for lots 2A44, 6J12, and X528. The batch records confirm that validated drug product [redacted] were used for the manufacture of the exhibit batches.

Assessment: *Adequate*

The batch records confirm that [redacted] and [redacted] were used for the manufacture of the exhibit batches.

Comparability Protocols

N/A

Assessment: N/A

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

2.A. Prescribing Information

[redacted]

Assessment: *Adequate*

The package insert provides adequate instructions concerning the storage and administration of the subject drug product.

MICROBIOLOGY LIST OF DEFICIENCIES: N/A

Primary Microbiology Assessor Name and Date: Sallie Crenshaw, Ph.D., 12/1/2020

Secondary Assessor Name and Date: Erika Pfeiler, Ph.D., 12/1/2020

Sallie Crenshaw

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Erika Pfeiler

Digitally signed by Erika Pfeiler
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Laurie Nelson

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