CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761094Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date:	August 20, 2018
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Merry Christie, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research III
Application:	BLA 761094
Applicant:	Dompé farmaceutici S.p.A.
Submission Date:	May 31, 2017
Product:	Oxervate (cenegermin-bkbj)
Dosage form:	Ophthalmic solution
Strength and Container-Closure:	0.002% solution in multiple-dose vial
Indication, dose, route, and frequency of administration:	for the treatment of (b) (4) neurotrophic keratitis: one drop in (b) (4) the affected eye(s), 6 times a day at 2 hourly intervals, starting from the morning and within 12 hours. Treatment should be continued for eight weeks.
Background and Summary Description:	The Applicant submitted a biologics license application for the treatment of (b) (4) neurotrophic keratitis
Recommendations:	The prescribing information, patient information labeling, instructions for use, container labels, and carton labeling submitted on August 9, 2018 are acceptable from an OBP labeling perspective.

Materials Considered for this Label and Labeling Review	
Materials Reviewed	**Appendix Section**
Proposed Labels and Labeling	A
Other	B (n/a)
Evaluation Tables	C
Acceptable Labels and Labeling	D (n/a)

n/a = not applicable for this review

DISCUSSION and CONCLUSION

We evaluated the proposed labels and labeling for compliance to the applicable requirements in the Code of Federal Regulations, FDA guidance, and United States Pharmacopeia (USP) standards (see Appendix C).

The prescribing information, patient information labeling, instructions for use, container labels, and carton labeling for Oxervate (cenegermin-bkbj) ophthalmic solution, 0.002% in multiple dose vials were reviewed and found to comply with relevant regulations (21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100), and USP standards and labeling recommendations.

The prescribing information, patient information labeling, instructions for use, container labels, and carton labeling submitted on August 9, 2018 are acceptable from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling
Prescribing Information (submitted December 22, 2017 \\cdsesub1\evsprod\bla761094\0007\m1\us\114-labeling\114a-draft-label\uspi.docx and March 2, 2018 \\cdsesub1\evsprod\bla761094\0016\m1\us\114-labeling\114a-draft-label\uspi.docx)

Patient Information/Instructions for Use (submitted December 22, 2017 \\cdsesub1\evsprod\bla761094\0007\m1\us\114-labeling\114a-draft-label\patient-leaflet.doc and March 2, 2018 \\cdsesub1\evsprod\bla761094\0016\m1\us\114-labeling\114a-draft-label\patient-leaflet.pdf)

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Appendix C: Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Regulations, Guidance and CDER Best Labeling Practices	Conforms
Proper Name (21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10) *for container of a product capable of bearing a full label* **Comment/Recommendation:** *considered a partial label*	☐ No ☐ Yes ☒ N/A
Manufacturer name, address, and license number (21 CFR 610.60) *for container of a product capable of bearing a full label* **Comment/Recommendation:** *considered a partial label*	☐ No ☐ Yes ☒ N/A
Lot number or other lot identification (21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100) **Comment/Recommendation:** *considered a partial label*	☐ No ☐ Yes ☒ N/A
Expiration date (21 CFR 610.60, 21 CFR 201.17) **Comment/Recommendation:** *considered a partial label*	☐ No ☐ Yes ☒ N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.60 **Comment/Recommendation:** *considered a partial label*	☐ No ☐ Yes ☒ N/A
Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24	☐ No ☐ Yes ☒ N/A
No Package for container 21 CFR 610.60	☐ No ☐ Yes ☒ N/A
Partial label 21 CFR 610.60 21 CFR 201.10	☒ No ☐ Yes ☐ N/A

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Comment/Recommendation:
Add the manufacturer name and U.S. license number (See 21 CFR 610.60(c)) as follows:
Dompé farmaceutici S.p.A.
U.S. License No. xxxx

The applicant revised as requested

No container label 21 CFR 610.60	☐ No ☐ Yes ☒ N/A
Ferrule and cap overseal	☒ No ☐ Yes ☐ N/A

Comment/Recommendation:
FOR VIALS: Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals).

DTOP did not send the recommendation per DTOP email dated 18Jul18 General Chapters: <7> refers to injectable products and cenegermin is not injectable.

OBP labeling determined that although this USP General Chapters <7> refers to injectable products, OBP labeling applies this concept across all products supplied in vials in support of a systematic approach to the labeling of vials to reserve the ferrule and the cap for cautionary statements.

Visual inspection 21 CFR 610.60	☒ No ☐ Yes ☐ N/A

Comment/Recommendation:
FOR VIALS: Confirm there is sufficient area on the container to allow for visual inspection when the label is affixed to the vial and indicate where the visual area of inspection is located per 21 CFR 610.60(e).

DTOP did not send the recommendation per DTOP email dated 18Jul18 "Since these patients are visually impaired due to neurotrophic keratitis, their assessment of the drug product by visual inspection would be unreliable at best. 21 CFR 610.60(e) does not require identification of the visual area for inspection."

OBP labeling determined that this is important information especially for small container closures where the label may overlap and not provide sufficient area for visual inspection prior to application in the eye.

NDC numbers 21 CFR 201.2 21 CFR 207.35	☐ No ☒ Yes ☐ N/A

Comment/Recommendation: *Not required for partial labels per 21 CFR 610.60(c).*

Route of administration 21 CFR 201.5 21 CFR 201.100	☐ No ☐ Yes ☒ N/A

Comment/Recommendation: *container label lacks space*	
Preparation instructions 21 CFR 201.5	☐ No ☐ Yes ☒ N/A
Package type term 21 CFR 201.5	☐ No ☐ Yes ☒ N/A
Comment/Recommendation: *partial label*	
Drugs **Misleading statements** 21 CFR 201.6	☐ No ☐ Yes ☒ N/A
Strength 21 CFR 201.10 21CFR 201.100	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: Revise the strength from 20 mcg/mL to 0.002% to represent the strength as percent weight in volume (% w/v). The strength presentation of most FDA approved solutions for ophthalmic use are expressed as percent, and these products are typically ordered as percent strength and administered as drops. *The applicant revised as requested*	
Drugs **Prominence of required label statements** 21 CFR 201.15	☐ No ☒ Yes ☐ N/A
Spanish-language (Drugs) 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
Bar code label requirements 21 CFR 201.25 21CFR 610.67	☐ No ☒ Yes ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
Net quantity 21 CFR 201.51	☐ No ☒ Yes ☐ N/A

Usual dosage statement 21 CFR 201.55 21 CFR 201.100 **Comment/Recommendation:** *container label lacks space*	☐ No ☐ Yes ☒ N/A
Inactive ingredients 21 CFR 201.100 **Comment/Recommendation:** *container label lacks space*	☐ No ☐ Yes ☒ N/A
Storage requirements	☐ No ☐ Yes ☒ N/A
Dispensing container 21 CFR 201.100	☐ No ☐ Yes ☒ N/A

Package Label[5] Evaluation

Regulations, Guidance and CDER Best Labeling Practices	Conforms
Proper name (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10)	☒ No ☐ Yes ☐ N/A

Comment/Recommendation:

For the kit carton: On the top panel (principal display), add the proper name to appear underneath the proprietary name and include the dosage form and route of administration statement as follows:

Oxervate
(cenegermin)
Ophthalmic Solution
0.002%
For topical application in the eye

The applicant revised as requested and included the mcg/mL strength in parenthesis but did not include the statement "for topical application in the eye". OBP labeling determined this is acceptable since the kit carton includes other components than just the drug product in vial.

For the weekly vial carton: On the top panel (principal display), remove (b) (4) and revise the proprietary name, proper name, dosage form, strength, and route of administration statement to appear as follows:

Oxervate
(cenegermin)
Ophthalmic Solution
0.002%
For topical application in the eye

[5] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus this includes the carton, prescribing information, and patient labeling.

The applicant revised as requested and included the mcg/mL strength in parenthesis. OBP labeling determined this is acceptable

For the diary card: remove [redacted] (b) (4) and revise the proprietary name, proper name, dosage form, strength, and route of administration statement to appear as follows:
Oxervate
(cenegermin)
Ophthalmic Solution
0.002%
For topical application in the eye

The applicant revised as requested and included the mcg/mL strength in parenthesis but did not include the statement "for topical application in the eye". OBP labeling determined this is acceptable since the diary card is for documentation of administration.

Manufacturer name, address, and license number 21CFR 610.61	☒ No ☐ Yes ☐ N/A

Comment/Recommendation:
For both the weekly vial carton and the kit carton: Add the U.S. license number to appear with the manufacturer name and address (See 21 CFR 610.61(b)) as follows:
Manufactured by: Dompé farmaceutici S.p.A.
Via Campo di Pile – 67100 L'Aquila, Italy
U.S. License No. xxxx

The applicant revised as requested

Lot number or other lot identification 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Expiration date 21 CFR 610.61 21 CFR 201.17	☐ No ☒ Yes ☐ N/A
Preservative 21 CFR 610.61	☒ No ☐ Yes ☐ N/A

Comment/Recommendation:
For both the weekly vial carton and the kit carton: If no preservative, add the statement "No preservative" on the carton labeling per 21 CFR 610.61 (e).

The applicant revised as requested

Number of containers 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Strength/volume 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100	☒ No ☐ Yes ☐ N/A

Comment/Recommendation:

For both the weekly vial carton and the kit carton: Revise the strength from 20 mcg/mL to 0.002% to represent the strength as percent weight in volume (% w/v). The strength presentation of most FDA approved solutions for ophthalmic use are expressed as percent, and these products are typically ordered as percent strength and administered as drops.

The applicant revised as requested and included the mcg/mL strength in parenthesis. OBP determined this is acceptable.

Storage temperature/requirements
21 CFR 610.61

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
For the weekly vial carton: revise the storage statement to appear as follows:
Storage Instructions for Pharmacist: Store the weekly carton containing 7 OXERVATE vials in the freezer at or below -20°C (-4°F) until time of dispensing.
Storage Instructions for Patients: You may thaw only the number of frozen OXERVATE vials required for use over the course of a single day received from the pharmacy at room temperature up to 25°C (77 °F). It may take approximately 30 minutes to thaw. Store the remaining vials in the carton refrigerated between 2°C to 8°C (36°F to 46°F) for up to 14 days or until time of use. Do Not Refreeze the vials.

Opened vials may be stored in the refrigerator for up to 12 hours or at room temperature up to 25°C (77°F) for up to 12 hours. Discard any unused portion after 12 hours.

For the kit carton:
Include instructions for pharmacist as follows:
"**Instructions for Pharmacist**:

- **Storage:** Store the weekly carton containing 7 OXERVATE vials in the freezer at or below -20°C (-4°F) until time of dispensing.
- **Dispense:** Dispense the weekly vial carton in the insulated pack provided in the Delivery System Kit
- Instruct the patient to only administer OXERVATE using vial adapters, pipettes, and sterile alcohol wipes provided in the Delivery System Kit.
- Discuss the storage requirements with the patient.

"Storage Instructions for Patient:

- Remove the weekly carton containing 7 OXERVATE vials from the insulated pack in the Delivery System Kit within 5 hours of leaving the pharmacy and store the weekly carton containing 7 OXERVATE vials in the refrigerator between 2°C to 8°C (36°F to 46°F) for up to 14 days.
- You may thaw only the number of frozen OXERVATE vials required for use over the course of a single day received from the pharmacy at room temperature up to 25°C (77 °F). It may take approximately 30 minutes to thaw.
- Do not refreeze the vial. Do not shake the vial.
- Opened vials may be kept in the original carton in the refrigerator between 2°C to 8°C (36°F to 46°F) for up to 12 hours. Discard unused portion after 12 hours.
- If needed, opened vials may be stored at room temperature up to 25°C (77 °F) for up to 12 hours. Remove only the number of OXERVATE vials required for use over the course of a single day from the refrigerator. Discard any unused portion after 12 hours.

If these changes are incorporated, then you may delete the following from the side panels of the kit carton:

1. "For the pharmacist: Supply to the patient in combination with oxervate. (b) (4)
2. (b) (4)
3. "Store this delivery system kit at room temperature (do not freeze)."

Prior to sending OBP labeling recommendations to the applicant, DTOP revised OBP labeling recommendations for the weekly carton and the kit carton labeling to not include instruction for only thawing the number of frozen vials required for use and the temperature and time required to thaw (highlighted in grey above). The applicant revised per DTOP's recommendation, however, OBP labeling determined that this is important storage and handling information for ease of accessibility for immediate dosing required upon returning from the pharmacy.

However, since this information is accessible in the IFU which will be included in the delivery system kit carton, OBP labeling determined that this is acceptable.

Handling: "Shake Well", "Do not Freeze" or equivalent
(21 CFR 610.61)

☒ No
☐ Yes
☐ N/A

Comment/Recommendation: For both the weekly vial carton and the kit carton: Add the statement "Do Not Shake" to ensure instructions for handling, as appropriate based on the character of the product, appear on the carton labeling per 21 CFR 610.61 (i). [see recommendation above to add "Do Not Shake" statement on the kit carton.]

The applicant revised as requested

Multiple dose containers (recommended individual dose)
21 CFR 610.61

☐ No
☒ Yes
☐ N/A

Route of administration
21CFR 610.61
21 CFR 201.5
21 CFR 201.100

☒ No
☐ Yes
☐ N/A

Comment/Recommendation: The weekly vial carton includes the statement "For topical application in the eye"; for kit carton see recommendation above to add the route of administration statement

Prior to sending OBP labeling recommendations to the applicant, DTOP revised OBP labeling recommendations for the kit carton labeling and did not include the recommendation to add the route of administration. The route of administration statement "For topical application in the eye" is important to consistently convey across all labeling since the container closure system is a vial and the delivery device is similar in appearance to a syringe.

OBP labeling determined this is acceptable since the kit carton includes other components than just the drug product in vial.

Known sensitizing substances 21CFR 610.61	☐ No ☐ Yes ☒ N/A
Inactive ingredients 21 CFR 610.61 21 CFR 201.100	☐ No ☒ Yes ☐ N/A

Comment/Recommendation: For the weekly vial carton: Revise the list of inactive ingredients to appear in alphabetical order (see USP Chapter <1091>) as follows: Each mL of solution contains 20 mcg of cenegermin (0.002% w/v), disodium hydrogen phosphate anhydrous, hydroxypropylmethylcellulose, L-methionine, mannitol, polyethylene glycol 6000, sodium dihydrogen phosphate dihydrate, and trehalose dihydrate in Water for Injection, USP.

The applicant revised to appear in alphabetical order as requested; however, sodium dihydrogen phosphate dihydrate was misspelled. Revise from "sodium dihydrogen phosphate dehydrate" to read "sodium dihydrogen phosphate dihydrate" and add "USP" to read "Water for Injection, USP". The applicant revised as requested

Source of the product 21 CFR 610.61	☐ No ☐ Yes ☒ N/A
Minimum potency of product 21 CFR 610.61	☒ No ☐ Yes ☐ N/A

Comment/Recommendation: For the weekly vial carton ensure that the minimum potency of the drug product expressed in terms of official standard of potency, or if potency is a factor and no US standard of potency has been prescribed, the words "No U.S. standard of potency" per 21 CFR 610.61 (r).

The applicant revised as requested

Rx only 21CFR 610.61 21 CFR 201.100	☒ No ☐ Yes ☐ N/A

Comment/Recommendation: For the kit carton, ensure the statement "Rx only" appears per 21 CFR 610.61(s).

The applicant revised as requested

Divided manufacturing 21 CFR 610.63	☐ No ☐ Yes ☒ N/A
Distributor 21 CFR 610.64	☐ No ☒ Yes ☐ N/A
Bar code 21 CFR 610.67 21 CFR 201.25	☒ No ☐ Yes ☐ N/A

Comment/Recommendation: For the kit carton, ensure that a linear barcode appears. *The applicant revised as requested*	
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
NDC numbers 21 CFR 201.2 21 CFR 207.35	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: For the kit carton, ensure that a NDC code appears. Clarify if the weekly carton containing the vials and the Delivery System Kit carton will have different NDC numbers (See 21 CFR 207.33 to 37) *The applicant revised with different NDC numbers. OBP labeling determined this to be acceptable.*	
Preparation instructions 21 CFR 201.5 **Comment/Recommendation:** see recommendation above for storage and handling	☒ No ☐ Yes ☐ N/A
Package type term 21 CFR 201.5 **Comment/Recommendation:** Revise from "multidose vial" to "multiple-dose vial". *The applicant revised as requested*	☒ No ☐ Yes ☐ N/A
Drugs **Misleading statements** 21 CFR 201.6	☐ No ☒ Yes ☐ N/A
Drugs **Prominence of required label statements** 21 CFR 201.15	☐ No ☒ Yes ☐ N/A
Spanish-language (Drugs) 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
Net quantity 21 CFR 201.51	☐ No ☒ Yes

	☐ N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100 **Comment/Recommendation:** For the weekly vial carton and the kit carton: Remove the statement [redacted] *The applicant revised as requested*	☐ No ☒ Yes ☐ N/A
Dispensing container 21 CFR 201.100 **Comment/Recommendation:** *statement was requested to be revised [see storage recommendations above]*	☐ No ☒ Yes ☐ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24	☐ No ☐ Yes ☒ N/A
Other: For the weekly vial carton: Revise the statement from "ATTENTION: Use only with the vial adapters, pipettes, and disinfectant wipes provided separately." To read as follows: "ATTENTION: Use only with the vial adapters, pipettes, and sterile alcohol wipes provided in the Delivery System Kit." *The applicant revised as requested* For the kit carton: Revise the contents statement to read as follows: "Delivery System Kit Contents: [redacted] vial adapters [redacted] pipettes [redacted] sterile [redacted] wipes 1 dose card *The applicant revised as requested* For the kit carton: Revise the statement from "Use only with oxervate eye drop" to read: "For use with Oxervate Ophthalmic Solution Only" *The applicant revised as requested*	☒ No ☐ Yes ☐ N/A

Prescribing Information and Patient Labeling Evaluation

Regulations	Conforms
PRESCRIBING INFORMATION	
Highlights of prescribing information	
PRODUCT TITLE 21 CFR 201.57(a)(2)	☐ No ☒ Yes ☐ N/A
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: OBP labeling recommends using consistent terminology for the kit throughout all labels and labeling. "Delivery System Kit" is used on the proposed kit carton *The applicant revised as requested*	
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: We revised to the appropriate dosage form "Ophthalmic solution" and to be consistent with the product title. *The applicant revised as requested* Revise the strength from 20 µg/mL to 0.002% to represent the strength as percent weight in volume (% w/v) to be consistent with currently marketed ophthalmic solutions. (see internal email dated May 8, 2018) *The applicant revised as requested* The primary presentation of strength (0.002%) should appear alone here or if the mcg/mL strength is to be included then it can appear in parenthesis (e.g., 0.002% (20 mcg/mL) The strength presentation of most FDA approved solutions for ophthalmic use are expressed as percent and these products are typically ordered as percent strength and administered as drops *The applicant revised as requested* We added the package type term "multiple-dose vial" *The applicant revised as requested*	
Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: We added instructions for refrigerated storage conditions upon receipt from the pharmacy *The applicant revised as requested* We added thaw temperature (room temperature) and expected thaw time (30 minutes) for frozen product received from the pharmacy *The applicant revised as requested*	

We added the visual inspection instructions ("Visually inspect the solution in the vial for particulate matter and discoloration prior to use. Discard the vial if any particulate matter or discoloration is observed in the solution").
This recommendation was not accepted by DTOP during team labeling review. OBP labeling applies this concept across all products supplied in vials in support of a systematic approach to the labeling of vials. OBP labeling determined that the regulatory requirement for the verbatim statement applies to parenteral products and thus is not required information for this section.

We added "do not shake" statement
The applicant revised as requested

We added storage and handling conditions for the opened vials and time to discard
The applicant revised as requested

3 DOSAGE FORMS AND STRENGTHS
21 CFR 201.57(c)(4)

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
we added the dosage form and identifying characteristics of the dosage form per 21 CFR 201.57(c)(4) and the package type term
The applicant revised as requested

We revised the primary presentation of strength to appear as 0.002%. OBP labeling recommends that if the mcg/mL strength is to be included then it can appear in parenthesis (e.g., 0.002% (20 mcg/mL). The vial labels and carton labeling will have the % strength as primary presentation
The applicant revised as requested

6.2 IMMUNOGENICITY
Draft Guidance for Industry: Labeling for Biosimilar Products

☐ No
☐ Yes
☒ N/A

11 DESCRIPTION
(21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q))

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
We deleted the proprietary name since this first paragraph discusses the drug substance
This recommendation was not accepted by DTOP during team labeling review.

OBP labeling removed the dosage form from within the parenthesis in the second paragraph since the dosage form is not part of the proper name
The applicant revised as requested

We added the route of administration to the second paragraph per 21 CFR 201.57(c)(12)
The applicant revised as requested

OBP labeling revised the list of inactive ingredients to appear in alphabetical order (see USP Chapter <1091>) followed by their quantitative information that is deliverable in 1 mL using the metric system of weight in parenthesis (x mg) except for those inactive ingredients added to adjust pH or tonicity or water for injection

The applicant revised as requested

16 HOW SUPPLIED/ STORAGE AND HANDLING
21 CFR 201.57(c)(17)

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
The applicant revised the weekly carton and the Delivery System Kit will have different NDC numbers as requested

OBP relocated storage instructions for the patient to section 17 as information that the healthcare provider should convey to the patient (when to remove the carton from the insulated pack and place in refrigerator, storage conditions for the frozen vial(s) for immediate use, visual inspection instructions, do not shake instructions, storage conditions for the opened vial, and discard time)
The applicant revised as requested

We added information about how long (14 days) the patient can store unopened vials of cenegermin refrigerated at 2-8°C
The applicant revised as requested

OBP labeling notes that although section 16 provides information for the supplied product, summary statement for the opened vial may be included in section 16 with a cross-reference to the detailed storage instructions for the opened vial in section 2 (Dosage and Administration)
The applicant revised as requested

We added the statement "do not refreeze"
The applicant revised as requested

MANUFACTURER INFORMATION
21 CFR 610.61, 21 CFR 610.64

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
Per 21 CFR 610.61(b) Revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h and add a placeholder for the US license number
The applicant revised as requested

INSTRUCTIONS FOR USE AND PATIENT INFORMATION

TITLE (NAMES AND DOSAGE FORM)

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
For Patient Information and Instructions for Use: For BLAs the dosage form is not a part of the proper name and thus should appear outside of the parenthesis and be consistent with the prescribing information
The applicant revised as requested

STORAGE AND HANDLING

☒ No
☐ Yes
☐ N/A

Comment/Recommendation: For Instructions for Use: We revised the how supplied information to clarify that the weekly carton is included in the Delivery System Kit
The applicant revised as requested

For Instructions for Use: We added the storage time period for the unopened vials and clarified the temperature for the thaw time for the frozen vial(s).
The applicant revised as requested

For Instructions for Use: We added the storage conditions and times for the opened vials
The applicant revised as requested

INGREDIENTS

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
For Patient Information: List all inactive ingredients in alphabetical order (see USP Chapter <1091>)
The applicant revised as requested

MANUFACTURER INFORMATION
21 CFR 610.61, 21 CFR 610.64

☒ No
☐ Yes
☐ N/A

Comment/Recommendation:
For Patient Information and Instructions for Use: Per 21 CFR 610.61(b) Revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h and add a placeholder for the US license number
The applicant revised as requested

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Vicky Borders-Hemphill

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Date: 8/20/2018 03:55:09PM
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Merry Christie

Digitally signed by Merry Christie
Date: 8/21/2018 02:58:48PM
GUID: 564632fe005f32f02e279baa8e984e30

First Approval for Breakthrough Review: Yes

Recommendation: Approval

BLA/NDA Number:761094
Review Number:1
Review Date:7/7/2017

Drug Name/Dosage Form	Oxervate (cenegermin)
Strength/Potency	20 ug/ml or 0.002% (w/v)
Route of Administration	Ophthalmic drops
Rx/OTC dispensed	Rx
Indication	Neurotrophic keratitis
Applicant/Sponsor	Dompe Pharmaceutici S.p.A.
US agent, if applicable	Robert McCormack, Creative Regulatory Solutions

Product Overview

Oxervate (cengermin) is an *E. coli* expressed 118 KDa recombinant human Nerve Growth Factor (NGF) proposed for the treatment of neurotrophic keratitis, an ocular degenerative disease caused by impairment of trigeminal innervation. Oxervate is active as a non-covalent homodimer. Oxervate is provided as an opthalmic solution in a multiple dose vial. It is dosed at one drop in the affected eye or eyes, 6 times per day at 2-hour intervals, for eight weeks.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Merry Christie	OBP/DBRR III
Drug Product	Merry Christie	OBP/DBRR III
Immunogenicity	Merry Christie and Joao Pedras Vasconcelos	OBP/DBRR III
Labeling	Vickie Borders Hemphill	OBP
Facility	Wayne Seifert	OPF/DIA
Microbiology (DS)	Max Van Tassell	OPF/DMA
Microbiology (DP)	Virginia Carroll	OPF/DMA
Microbiology QAL	Maria Jose Lopez Barragan	OPF/DMA
Application Team Lead	Maria Cecilia Tami	OBP/DBRR III
Tertiary Review	Susan Kirshner	OBP/DBRR III
RBPM	Melinda Bauerlien	OPRO

Mutidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Derek Alberding	DTOP
Cross-disciplinary Team Lead	William Boyd	DTOP

Medical Officer	Rhea Lloyd	DTOP
Pharm/Tox	Aaron Ruhland	DTOP
Clinical Pharmacology	Abhay Joshi	OCP
Statistics	Qing Zhou	OB

1. Names:
   a. Proprietary Name: Oxervate
   b. Trade Name: Oxervate
   c. Non-Proprietary Name/USAN: cenegermin
   d. CAS Name: 1772578-74-1
   e. OBP systematic name (tentative): RPROT P01138 (NGF_HUMAN) Beta-nerve growth factor (rhNGF)
   f. Other names: none

Submissions Reviewed:

Submission:	Date sent	Date Received:	Review Completed (yes or no)
STN003	6/24/2017	7/12/2017	Y
STN002	1/31/2017	6/23/2017	Y
STN005	9/18/2017	10/31/2017	Y
STN010	1/10/2018	1/16/2018	Y
STN014	12/13/2017	1/30/2018	Y
STN015	2/5/2018	2/15/2018	Y
STN018	3/14/2018	3/19/208	Y
STN019	3/15/2018	3/20/2018	Y
STN020	3/8/2018	3/27/2018	Y
STN022	3/27/2018	4/10/2018	Y
STN025	4/13/2018	4/20/2018	Y
STN026	4/13/2018	5/2/2018	Y
STN027	4/13/2018	5/7/2018	Y
STN029	5/4/2018	5/9/2018	Y
STN030	4/30/2018	5/11/2018	Y
STN031	5/11/2018	5/16/208	Y
STN033	5/21/2018	5/25/2018	Y
STN035	5/25/2018	5/29/2018	Y
STN036	5/16/2018	5/30/2018	Y
STN037	5/18/2018	5/31/2018	Y
STN038	5/25/2018	6/4/2018	Y
STN 040	6/5/2018	6/14/2018	Y
STN 041	6/6/2018	6/14/2018	Y
STN 041	6/8/2018	6/22/2018	Y
STN 043	7/3/2018	7/6/2018	Y
STN 046	7/17/2018	7/20/2018	Y
STN 047	7/25/2018	7/26/2018	Y

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]
(b) (4)	III		(b) (4)	3	N/A
	III			3	N/A
	III			3	Adequate

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application; therefore, the DMF did not need to be reviewed.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Approval

The Office of Product Quality, CDER, recommends approval of STN 761094 for Oxervate (cenegermin) manufactured by Dompe Pharmaceutici S.p.A. The data submitted in this application are adequate to support the conclusion that the manufacture of Oxervate is adequately-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

Manufacturing location:

- Drug Substance: Dompe Pharmaceutici S.p.A.
- Drug Product: (b) (4)

- Fill size and dosage form: topical ophthalmic solution, 1 mL cenegermin 20 µg/mL.
- Dating period:
  - Drug Product: 12 months at -20±5 °C
  - Drug Substance: (b) (4)
  - Intermediate Substance: N/A
  - For packaged products: "Not packaged"
  - Stability Option (select one below):
    - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and/or drug product under 21 CFR 601.12.
- Exempt from lot release
  - Yes
    Rationale, if exempted: Per FR notice 95-29960, well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products are exempted from 21 CFR 601.2a lot release requirements.

  - Dompé Farmaceutici s.p.a. (Dompé) requested a categorical exclusion from the need to prepare an environmental assessment in accordance with 21 CFR 25.31. The request is based on an action that increases the use of the active moiety, but the active concentrations of the substance at the point of entry into the aquatic environment will be less than 1 part per billion.
    A calculation is provided showing that the levels will be not exceeded and uses a formula presented in *Guidance for Industry-Environmental Assessment of human Drug and Biologics Applications, dated July 1998*. Therefore, approval of this submission will not increase the overall use of the active moiety.
    The claim of a categorical exclusion is accepted.

B. Benefit/Risk Considerations:

The overall control strategy includes control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. The control strategy combined with in-process, release, and stability testing ensure process consistency and drug substance and drug product with appropriate quality attributes and free of adventitious agents.

Post-marketing commitments are being requested to enhance the control strategy of the product to better ensure robust process control and product performance over time regarding: completion of real time shipping validation studies under worst case conditions; leachables assessment at release in the final DP container closures to confirm the risk assessment conclusions; (b) (4) development of a two tier RS system; enhancements to the potency assay; revision of the bioburden assay to use a 10 ml test volume; and to conduct endotoxin method qualification using two additional DS batches. The Oxervate DS and DP manufacturing processes and controls are acceptable.

C. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

1- To perform a leachable study to evaluate leachables from the manufacturing process and the container closure system in OXERVATE (cenegermin) drug product. The analysis will be performed using one drug product lot analyzed at release. Appropriate methods will be used to detect, identify, and quantify organic non-volatile, volatile and semi-volatile species, and metals. Complete data and the risk evaluation for potential impact of leachables on product safety and quality will be provided in the final study report.

2- To perform real time shipping validation studies to support the stability of OXERVATE (cenegermin) drug product vials shipped from the DP manufacturing site in Italy to the US. The shipping study should evaluate product quality before and after shipping using worst-case shipping conditions of distance, duration, temperature, mode of transportation and vibration. The study should be performed with drug product manufactured with a process representative of the commercial process, same formulation and packaged in the same container closure system as that proposed for commercial batches.
The final study report(s) will be submitted in accordance with 21 CFR 601.12.

3- To establish a two-tiered reference material system for OXEVATE, comprised of primary and secondary (working) reference materials prepared from lot(s) representative of production and clinical materials. The final study report(s) will be submitted in accordance with 21 CFR 601.12.

4- To conduct structure-function studies to better understand whether all critical aspects of NGF biological function relevant to receptor binding are adequately controlled by the current TF-1 cell based assay, that only assesses NGF activity through binding the TrkA.

5- To implement a control reference material for the potency assay to improve control over the assay variability and provide additional assurance that the RS is performing as expected during routine potency testing. The potency assay control material should perform within established acceptance criteria relative to the reference standard. The final study report(s) will be submitted in accordance with 21 CFR 601.12.

6- To conduct the bioburden test with a 10 mL sample volume. The revised bioburden method should be qualified using three batches of in-process intermediates and bulk drug substance.

7- To conduct the endotoxin method qualification using two additional batches of the bulk drug substance.
8- Provide the shipping validation summary report for drug product distribution to the US, performed in the actual shipping lanes under worst-case conditions (summer). (b) (4)

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

CQAs were identified during process development and formulation studies. When defining CQAs, the Sponsor considered cenegermin's formulation, route of administration, dosage, safety profile, and biological activity.

(b) (4)

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
Potency	Efficacy	Intrinsic	Release and stability testing	Assay only measures activation through the TrkA receptor. (b) (4) . A PMC to implement a control reference material for the potency assay will improve the control over the assay variability and ensure consistent performance of the assay during routine testing.
Hydrophobic variants -product related variants	Immunogenicity		Formulation	(b) (4)

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(b) (4)

- Description:
  NGF is a 118 amino acid, 13kDa protein with 3 disulfide bonds that forms a cysteine knot structure made up of twisted beta strands linked by the disulfide bonds. In humans, NGF is expressed as a pro-peptide that is secreted into the endoplasmic reticulum and cleaved by furin protease.[1] Similarly, cenegermin is produced as proNGF and includes a 130 amino acid leader

[1] Kliemannel M et al. (2007) *The pro-peptide of proNGF: Structure Formation and Intramolecular Association with NGF*. Protein Sci. 16:3; 411-419

sequence. During manufacture [redacted] (b) (4) [redacted]. Physiologically active NGF or cenegermin exist as a non-covalent homodimers. Cenegermin, is expressed in *E.coli* and its sequence contains two changes at the furin cleavage site, R101V and K103A to enhance the consistency of the cleavage reaction. The following figure provides a 3D representation of the NGF homodimer.

- Mechanism of Action (MoA):
  Although aspects of the MoA of NGF are known, how they contribute to efficacy is unclear. Neurotrophic keratitis (NK) is a degenerative disease caused by impairment of trigeminal innervation, such as a lesion to the trigeminal nerve. Nerve growth factor (NGF) is essential for the survival and growth of sympathetic and sensory neurons and for the differentiation of neurons in the central nervous system. NGF induces neurite sprouting by neural cells and restores the function of injured neurons.[2] Exogenous NGF has been shown to reverse damage to peripheral nerves and heal corneal epithelial defects such as those observed in NK.[3] NGF also has important functions on non-neuronal cells, for example, it is an autocrine survival factor for memory B lymphocytes.[4] Neurotrophins act via two classes of transmembrane receptors that may, but do not need to interact for function: the low-affinity receptor $P75^{NTR}$ and the high-affinity neurotrophin receptors of the tyrosine kinase (Trk) family TrkA. Neurotrophin Trk binding leads to activation of intracellular signaling pathways, including those controlled by Ras, the Cdc42/Rac/RhoG protein family, MAPK, PI3K, and PLC-γ.[5] NGF receptors are expressed on anterior segments of the eye including iris, ciliary body, lens, cornea, and conjunctiva, by the lacrimal gland, and by all the intra-ocular tissues. The Trk receptors are responsible for most of the survival and growth properties of the neurotrophin family.[6] The neurotrophins and their receptors have been identified in and on many different human tissues, including in the cornea, the central and peripheral nervous system, and immune cells.[7,8,9] In NK clinical trials cenegermin did not induce nerve growth. Therefore, the mechanism of cenegermin efficacy for treating NK is not clear.

- Potency Assay:

[2] Bonini S et al. (2000) *Topical Treatment with Nerve Growth Factor for Neurotrophic Keratitis.* Opthalmology. 107: 1347-1351
[3] Aloe L et al. (2008) *The Topical Application of Nerve Growth Factor as a Pharmacological Tool for Human Corneal and Skin Ulcers.* Pharmacol Res. 57: 253-258
[4] Torcia M et al. (1996) *Nerve Growth Factor is an Autocrine Survival Factor for Memory B Lymphocytes.* Cell. 85:345-356
[5] Patapoutian A and Reichardt LF (2001) *Trk Receptors: Mediators of Neurotrophin Action.* Current Opinion in Neurobiology. 11: 272-280
[6] Nakagawara A (2001) *Trk Receptor Tyrosine Kinases: A Bridge Between Cancer and Neural Development.* Cancer Letters. 2: 107-114
[7] Leon A et al. (1997) *The Sage of the Nerve Growth Factor: Mast Cells Synthesize, Store, and Release Nerve Growth Factor.* World Scientific Series in 20th Century Biology Volume 3. 445-449
[8] Muller LJ et al. (2003) *Corneal Nerves: Structure, Contents and Function.* Experimental Eye Research. 76:5; 521-542
[9] Kokaia A et al. (1993) *Coexpression of Neurotrophins and their Receptors in Neurons of the Central Nervous System.* PNAS. 90:14; 6711-6715

Cenegermin biological activity is controlled with a TF-1 cell-based potency assay. TF-1 cells proliferate in response to NGF[10] and are erythroblast cells that express neutrophin receptor TrkA, but not p75.[11] For the cell-based potency assay, TF-1 cells are plated and a reagent containing MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) and PES (phenazine ethosulfate, serves as an electron acceptor) is added. NADPH or NADH, produced by dehydrogenase enzymes in metabolically active cells, reduces MTS to a purple formazan compound. The quantity of formazan produced is measured by absorbance at 490 nm and is proportional to the number of viable cells present. Potency is reported as relative to a reference standard.

(b) (4)

- Reference Materials:

(b) (4)

- Critical starting materials or intermediates:

(b) (4)

[10] Ma L and Zou Y (2013) TF-1 Cell Proliferation Assay Method for Estimating Bioactivity of Nerve Growth Factor. *Journal of Applied Virology*. 2:2; 32-37

[11] Chevalier S et al. (1994) Expression and Functionality of the trkA Proto-Oncogene Product/NGF Receptor in Undifferentiated Hematopoietic Cells. *Blood*. 83:6; 1479-1485

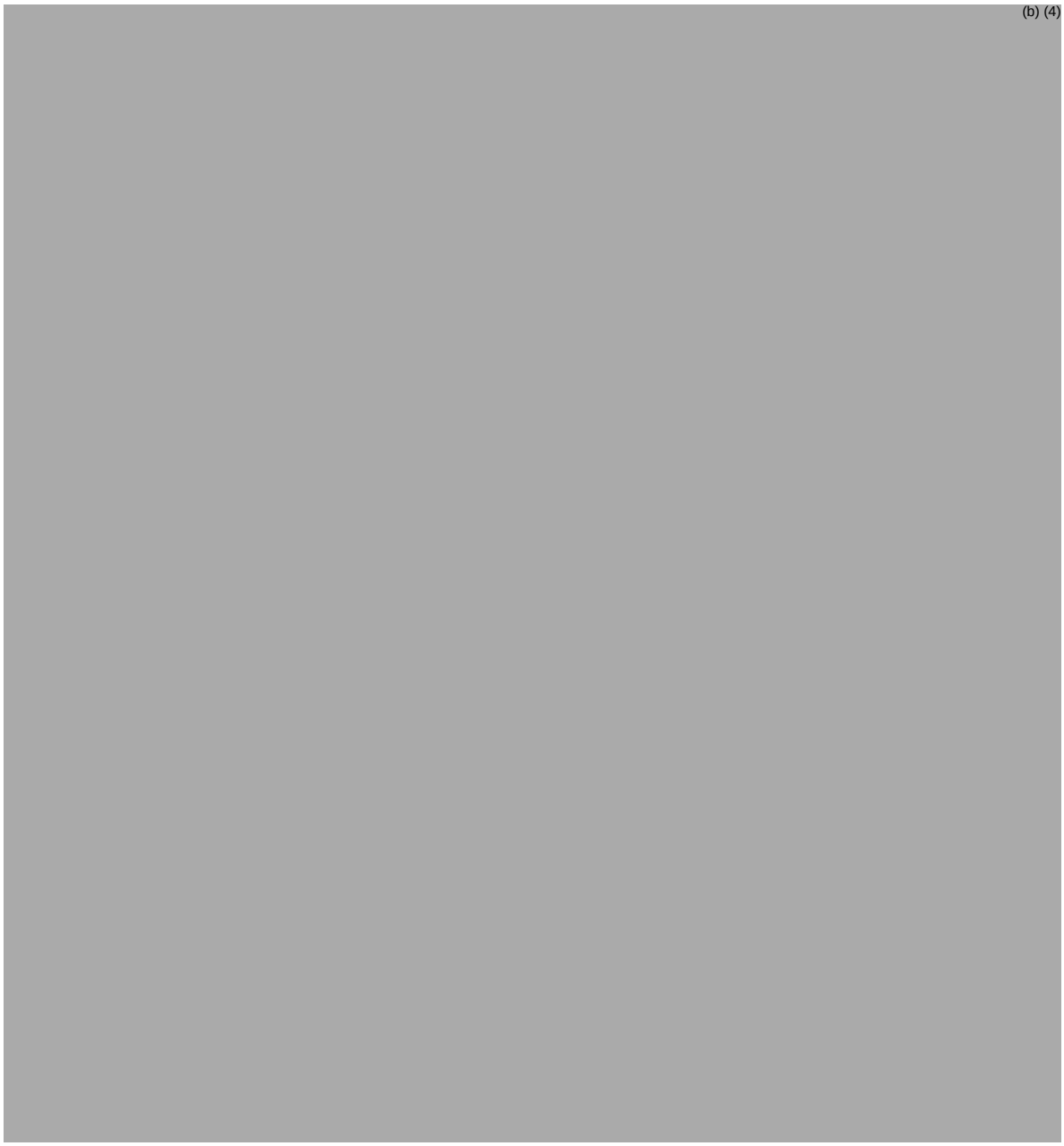
(b) (4)

- Manufacturing process summary:

(b) (4)

[12] The appearance of Impurity (b) (4)

(b) (4)



- Container closure:

(b) (4)

- Dating period and storage conditions:

The commercial expiration date for cenegermin DS is (b) (4) months at (b) (4) C. The Sponsor did not provide sufficient stability data to support the proposed dating period of (b) (4) months at (b) (4) °C. We approved a stability protocol as part of the license application (b) (4) .

C. Drug Product [Established Name] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy	Other
Appearance of solution	Safety and Efficacy	(b) (4)		
pH	Stability			
Osmolality	Stability and Safety			
Subvisible particles	Safety			
Protein content	Efficacy			
Sterility	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)			
Container closure integrity (maintenance of sterility during shelf-life)	Safety (failure in closure integrity may lead to contamination through a loss of sterility or evaporation/leakage impacting concentration or content)			

- Potency and Strength:
  Oxervate is a 0.002% (w/v or 0.02 mg/ml) sterile preservative-free ophthalmic solution

- Summary of Product Design:
  DP is packaged in multi-dose (b) (4) vials with a rubber stopper and an aluminum seal with a polypropylene flip-off cap containing 1.0 mL Oxervate. Each vial is designed to deliver one day's worth of treatment of six (b) (4) µL drops one eye and discarded at the end of the day.

Each vial contains 1.0 mL solution. Considering that each drop is approximately (b) (4) ul and that 6 doses are administered/day, the vial includes an overfill of approximately (b) (4) ul. However, the fill volume is acceptable for the following reasons:

- As per the instructions of use, when drawing the solution from the vial, the plunger must reach the stop point, what represents a volume of at least (b) (4) ul per dose (approximately (b) (4) ul/day).
- The instructions say (b) (4)
- Doses are 6 times/day, however, the instructions of use state that (b) (4) Therefore, there is the possibility that additional product is needed to deliver the 6 doses/day.

Therefore, the excessive volume is needed to deliver the expected daily doses. In addition, the instructions for use provide adequate instructions to prevent misuse of the product.

- List of Excipients:
  Disodium hydrogen phosphate anhydrous (2.87 mg), hydroxypropylmethyl cellulose (1.0 mg), L-methionine (0.01 mg), mannitol (12.22 mg), polyethylene glycol 6000 (10.0 mg), sodium dihydrogen phosphate dehydrate (1.22 mg), trehalose dihydrate (47.03 mg), Water for Injection, and hydrochloric acid and/or sodium hydroxide to adjust pH.

- Reference Materials:
  The same reference material is used for DS and DP.

- Manufacturing process summary:
  (b) (4)

(b) (4)

- Container closure:
  Three ml (b) (4) vial with a rubber stopper and an aluminum seal with a polypropylene flip-off cap.

- Dating period and storage conditions:
  Oxervate dating period is 12 months at (b) (4) °C.

(b) (4)

- List of co-package components, if applicable:
  Vial-adapter, disposable pipettes, and disinfectant wipes, weekly dose recording card

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H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
1. Annual Stability Protocol;
2. Qualification and Requalification of Working Cell Banks
3. Requalification of Reference Material

ii. Outstanding review issues/residual risk:
Post-marketing commitments to complete shipping validation studies under summertime conditions; assess leachables at release in the final DS container closure; (b) (4) develop a two-tier RS system; enhance the potency assay; revise the bioburden assay to use a 10 ml test volume; and to conduct endotoxin method qualification using two additional DS batches are being requested.

iii. Future inspection points to consider:
(b) (4)

b. Drug Product

i. Protocols approved:
1. Annual Stability Protocol
2. Requalification of Reference Material (same as DS)

ii. Outstanding review issues/residual risk:
Post-marketing commitments to complete real time shipping validation studies to support product stability of OXERVATE (cenegermin) drug product vials shipped from Italy to the US and complete shipping validation studies under summertime conditions, assess leachables from the manufacturing process and the container closure system at release of DP, develop a two-tier RS system (same as DS); enhance the potency assay (same as DS);

Future inspection points to consider:

(b) (4)

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
	Product Type				
1.	Recombinant Product		X		
2.	Naturally Derived Product			X	
3.	Botanical			X	
4.	Human Cell Substrate/source material			X	
5.	Non-Human Primate Cell Substrate/Source Material			X	
6.	Non-Primate Mammalian Cell Substrate/source material			X	
7.	Non-Mammalian Cell Substrate/Source Material		X		
8.	Transgenic Animal source			X	
9.	Transgenic Plant source			X	
10.	New Molecular Entity		X		
11.	PEPFAR drug			X	
12.	PET drug			X	
13.	Sterile Drug Product		X		
14.	Other: [fill in information]			X	
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			X	
16.	Comparability Protocol(s)			X	
17.	End of Phase II/Pre-NDA Agreements tem			X	
18.	SPOTS (special products on-line tracking system)			X	
19.	USAN assigned name			X	
20.	Other [fill in]			X	
	Quality Considerations				
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements			X	
27.	Real Time release testing (RTRT)			X	
28.	Parametric release in lieu of Sterility testing			X	
29.	Alternative Microbiological test methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial analytical procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other {fill-in}			X	

Maria Cecilia Tami

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Susan Kirshner

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Patricia Hughes Troost

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Zhihao Peter Qiu

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BLA 761094

Cenegermin

Dompe Pharmaceutici S.p.A

CMC Review Addendum

Merry Christie, Ph.D.
Maria Cecilia Tami, Ph.D.
Susan Kirshner, Ph.D.

Division of Biotechnology Review and Research III

Addendum to primary CMC review of original BLA 761094

Review Date: June 30, 2018
PDUFA action date: August 22, 2018 (priority review)

6. **Submissions Reviewed**:

Submission:	Date sent	Date Received:	Review Completed (yes or no)
STN 040 (response to IR 12)	6/5/2018	6/14/2018	Y
STN 041 (response to IR 13)	6/6/2018	6/14/2018	Y
STN 041 (response to IR 14)	6/8/2018	6/22/2018	Y
STN 043 (response to IR 15)	7/3/2018	7/6/2018	Y
STN 046 (response to IR 16)	7/17/2018	7/20/2018	Y
STN 047 (response to IR 17)	7/25/2018	7/26/2018	Y

Background: By the time this review memo was uploaded in Panorama, the responses to IR12, IR13 and IR14 had not be received. During the review of the responses to these IRs, additional information was requested in an IR dated July 3, 2018 (IR15). The responses to IR12, IR13 and IR14 as well as the responses to IR15 are reviewed and discussed in this memo.

Information requests IR12-15 requested that the Sponsor address the following CMC related issues:

1- Establish an adequately qualified commercial reference standard (RS) by requalifying the current RS material (b) (4) to more accurately assign its potency and protein concentration using (b) (4) as a comparator. (b) (4) was used in pivotal clinical studies and process validation
2- Submit an adequate protocol for requalification of existing RS.
3- Update the DS and DP release and stability specifications to improve control over purity
4- Revise the WCB qualification protocol to include a comparability assessment of drug substance manufactured at full scale using the approved and proposed working cell banks

Overall Reviewer Conclusion: *The Sponsor's responses to information requests dated June 5, June 6, June 8 and July 3, July 17 and July 25, 2018 are acceptable. The Sponsor adequately addressed all outstanding CMC related issues. Therefore, from a CMC perspective, BLA 761094 is recommended for approval. The following CMC items will be addressed post marketing:*

1- To develop a two-tier in-house reference material system consisting of primary and working reference materials. Each subsequent working or primary reference material (b) (4) characterized that is representative of production and clinical materials (ICH Q6B).
2- To better understand whether all critical aspects of NGF biological function relevant to receptor binding are adequately controlled by the current TF-1 cell based assay, that only assesses NGF activity through binding the TrkA
3- To performs leachables studies at release of DP to evaluate the leachates from the manufacturing process into the product. Because the DP is frozen, leachables data collected at the end of the shelf life are not needed.

4- To perform shipping validation studies to support the stability of oxervate during (b) (4) shipping distance and conditions from Italy to the US.
5- To implement a control reference material for the potency assay to improve control over the assay variability and provide additional assurance that the RS is performing as expected during routine potency testing.

Reviewer comment: *The visual inspection results of the PPQ batches showed high rejection rates due to defects in the vials such as bubbles and scratches in the glass, and cracks in the neck, bottom, and body of the vial. Identification of the root cause of this high visual inspection rejection rates and implementation of adequate CAPAs will be assessed in the next inspection of Oxervate DP manufacturing facility. This issue will not be addressed as a post marketing commitment.*

REVIEW OF RESPONSES TO PENDING INFORMATION REQUESTS

Control of Drug Substance and Drug Product

(b) (4)

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Maria Cecilia Tami

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
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Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewer: Virginia Carroll, Ph.D.
Acting Quality Assessment Lead: Maria Jose Lopez-Barragan, Ph.D.
Branch Chief: Patricia Hughes, Ph.D.

BLA:	761094/0
Applicant:	Dompe farmaceutici S.p.A.
US License Number:	2074
Submission Reviewed:	Original BLA
Product:	Oxervate (cenegermin ophthalmic solution, rhNGF)
Indication:	Treatment of (b) (4) neurotrophic keratitis
Dosage Form:	Eye drops, solution, 20 µg/mL
Manufacturing Sites:	Dompé farmaceutici S.p.A. L'Aquila, Italy (DS) (b) (4)
FDA Receipt Date:	12/22/2017
Action Date:	8/22/2018

Conclusion and Approvability Recommendation

The drug product part of the BLA was reviewed from a sterility assurance and quality microbiology perspective and is recommended for approval. There is one post-marketing commitment (PMC):

1. Provide the shipping validation summary report for drug product distribution to the US, performed in the actual shipping lanes under worst-case conditions (summer). (b) (4) .

Review Addendum

This review addendum is supplemental to the interim review completed 5/23/2018 for drug product (761094.rev.mem.micro.DP.interim.05.23.2018). The following information is reviewed herein: identification of co-packaged sterile disinfectant wipes, parameters for sterile filtration and clarifications on the media fill program.

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(b) (4)

SATISFACTORY

CGMP Status

The assessment of manufacturing facilities is documented in panorama.

Conclusion

I. The drug product part of the BLA was reviewed from a sterility assurance and product quality microbiology perspective and is recommended for approval. There is one post-marketing commitment.
II. Product quality aspects other than microbiology should be reviewed by OBP.

III. No inspection follow-up items were identified.

DP Quality Microbiology Information Requests Sent and Date

(b) (4)

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Maria Jose Lopez-Barragan

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Date: 6/28/2018 11:00:31AM
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Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum

Date: 06/05/2018

From: Wayne Seifert, OPQ/OPF/DIA

To: BLA File, STN 761094/0

Through: Zhihao (Peter) Qiu, Ph.D., Branch Chief, OPQ/OPF/DIA Branch 1

Subject: Inspection waiver memo for manufacture of rhNGF DP (b) (4) (b) (4)

Applicant: Dompé farmaceutici S.p.A.

Facility: (b) (4)

Product: Cenegermin (OXERVATE) (rhNGF)

Dosage: Ophthalmic (topical), Eye drops/solution, 20µg/ml

Indication: Treatment of moderate (b) (4) (b) (4) neurotrophic keratitis.

Waiver Recommendation

BLA STN 761094/0 proposes to manufacture Cenegermin (OXERVATE) (rhNGF) DP at (b) (4) The proposed manufacturing process is similar to other approved products produced in the (b) (4) Department.

A PAI of the (b) (4) facility was conducted by (b) (4) from (b) (4) for profile code (b) (4) that resulted in a VAI conclusion. A prior ORAHD level I inspection was conducted (b) (4) for profile codes (b) (4) that resulted in a NAI conclusion, with a PAI conducted by CDER-DIA (b) (4) for profile code (b) (4) with a classified VAI.

The fill line proposed for rhNGF DP manufacture is (b) (4) manufacturing area. The fill line is used for the commercial manufacture of a U.S licensed biological product, BLA (b) (4) profile class

(b) (4) Based on the compliance history of the firm, the current GMP status, and the fact that (b) (4) has been approved to manufacture other Agency approved and licensed products, we recommend that the pre-approval inspection for the facility be waived for BLA 761094/0 (action date 08/22/2018).

Summary

BLA STN 761094/0 proposes manufacture of rhNGF DS at Dompé farmaceutici S.p.A., L'Aquila, Abruzzo, Italy (FEI: 3004216297) and rhNGF DP (b) (4) (b) (4) This waiver recommendation is in regard to rhNGF DP manufacture at (b) (4)

Facility and Process Information

The proposed manufacture of rhNGF DP will be performed within the (b) (4) Department. A brief overview of the manufacturing process for rhNGF is as follows:

(b) (4)

Evaluation of criteria that may warrant inspection

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

   (b) (4) is registered as a DP manufacturer and currently produces products for U.S. distribution for the fill line proposed for rhNGF manufacture that includes BLA (b) (4)

2. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

Previous inspections have encompassed the profile code for the application under review and include (b) (4) and in all cases, have resulted in an acceptable NAI or VAI conclusion.

3. *The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities / buildings / areas.*

As noted in the response to Question 1, (b) (4) is registered as a DP manufacturer and currently produces products for U.S. distribution for the fill lines proposed for rhNGF manufacture.

4. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment.*

The manufacturing scheme for currently produced products for U.S. distribution (b) (4)

Signed:

Wayne Seifert., DIA/OPF Facility Reviewer Wayne E. Seifert -S DATE _____

Zhihao (Peter) Qiu, Ph.D., DIA/OPF, Branch Chief Zhihao Qiu -S DATE _____

Virginia Carroll, Ph.D., MABIV/DP Reviewer Virginia A. Carroll -S DATE _____

Maria Ceillia Tami, Ph.D., DBRRIII/OBP ATL Mariacecil Tami -S DATE _____

Merry Christie, Ph.D., DBRRIII/OBP CMC Reviewer Merry Christie -S DATE _____

Patricia Hughes, Ph.D., DMA/OPF Branch Chief Patricia F. Hughestroost -S DATE _____

Amy Rosenberg, M.D., DBRRIII/OBP, Division Director Amy S. Rosenberg -S DATE _____

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 06/01/2018
To: Administrative File, STN 761094/0
From: Wayne Seifert, Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Zhihao (Peter) Qiu, Ph.D., Supervisory Consumer Safety Officer
CDER/OPQ/OPF/DIA, Branch 1 Chief
Subject: New Biologic License Application (BLA)
US License: N/A
Applicant: Dompé farmaceutici S.p.A.
Mfg Facility: Drug Substance: Dompé farmaceutici S.p.A. (FEI: 3004216297)
Drug Product: (b) (4)
Product: rhNGF, OXERVATE (cenegermin)
Dosage: Eye drops, solution, 20 µg/ml, Ophthalmic (topical)
Indication: For the treatment of (b) (4)
neurotrophic keratitis.
Due Date: 08/22/2018

RECOMMENDATION: This submission is recommended for approval from a facilities assessment perspective.

SUMMARY

The subject BLA proposes manufacture of rhNGF DS at the Dompé farmaceutici S.p.A. L'Aquila, Abruzzo, Italy (FEI: 3004216297) and DP at (b) (4) The final dosage form for the 20 µg/ml presentation consists of a 2cc multi-dose (b) (4) vial closed with a rubber stopper and an aluminum seal, with a polypropylene flip-off cap.

rhNGF belongs to the pharmacotherapeutic group 'ophthalmologicals', with Anatomical Therapeutic Chemical (ATC) code S01XA24. (b) (4)

(b) (4)

(b) (4) The developed formulation is a sterile aqueous solution intended for ocular instillation (topical eye drop), containing rhNGF at a concentration of 20 µg/ml.

ASSESSMENT

3.2.S.2. DRUG SUBSTANCE FACILITIES

(b) (4)

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(b) (4)

CONCLUSION

Adequate descriptions were provided for the facilities proposed for pro-NGF IB Intermediate and rhNGF active substance and drug product manufacture. The subject BLA is recommended for approval from a facilities assessment perspective.

Wayne Seifert
Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1

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Zhihao (Peter) Qiu, Ph.D.,
Supervisory Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1 Chief

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewer: Virginia Carroll, Ph.D.
Acting Quality Assessment Lead: Maria Jose Lopez-Barragan, Ph.D.
Branch Chief: Patricia Hughes, Ph.D.

BLA:	761094/0
Applicant:	Dompe farmaceutici S.p.A.
US License Number:	2074
Submission Reviewed:	Original BLA
Product:	Oxervate (cenegermin ophthalmic solution, rhNGF)
Indication:	Treatment of (b) (4) neurotrophic keratitis
Dosage Form:	Eye drops, solution, 20 µg/mL
Manufacturing Sites:	Dompé farmaceutici S.p.A. L'Aquila, Italy (DS) (b) (4)
FDA Receipt Date:	
Action Date:	8/22/2018

Conclusion and Approvability Recommendation

The drug product part of the BLA was reviewed from a sterility assurance and quality microbiology perspective and is recommended for approval pending the review of the following additional information and data:

(b) (4)

filtration parameters validated during the microbial retention study. The study should be performed with actual drug product or appropriate surrogate solution and with similar equipment setup (tubing, filter, pump) as routine production.

b. Adjust the routine sterile filtration parameters to fall within the validated parameters for flow rate and/or differential pressure, if necessary.
c. Currently the flow rate or differential pressure during sterilize filtration is not monitored. Implement direct monitoring of flow rate and/or pressure across the sterilizing filter using a flow meter or pressure gauges. Provide a completion date for this implementation.

2. Media fills should be representative of the conditions under which actual manufacturing operations are conducted. (b) (4) Use of anaerobic growth medium (e.g. fluid thioglycollate medium) should be considered. (b) (4)
3. Submission of the shipping validation report for distribution of finished drug product to the United States is expected by August 2018 (see amendment 0030).
4. Sterile disinfectant wipes to support the delivery of sterile drug product should be provided in the delivery system kit. A supplier and information about sterile disinfectant wipes is pending.

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0002	6/23/2017	Original BLA (Module 3)
0010	1/16/2018	Response to IR
0015	2/15/2018	Response to IR
0022	4/10/2018	Response to IR
0026	5/2/2018	Response to IR
0030	5/11/2018	Response to IR

Module 3.2

P.1 Description and Composition of the Drug Product

rhNGF (recombinant human Nerve Growth Factor) drug product is a sterile preservative-free ophthalmic solution containing 0.02 mg/mL of drug substance. There is a (b) (4)% overage to ensure the label claim. The DP is packaged in multi-dose (b) (4) vials with rubber stopper and aluminum seal with polypropylene flip-off cap. Each vial contains 1.0 mL of

solution. Seven multi-dose vials are packaged per box in combination with a kit of delivery system devices, including one vial-adapter, disposable pipettes (used to withdraw from the vial and administer one ocular drop of (b) (4) µl) and non-sterile disinfectant wipes. The flip-off is removed and the vial adapter is connected to the glass vial immediately before use. To administer the product, a pipette is attached to the vial adapter, secured (b) (4)

Reviewer's comment: An information request was sent to the applicant on 2/5/2018 to provide sterile disinfectant wipes instead of non-sterile disinfectant wipes. In the response (0015), the applicant agreed to find a supplier of sterile disinfectant wipes. In a teleconference on 5/17/2018, the FDA clinical review team emphasized that sterile disinfectant wipes must be included in the kit. The identification of a supplier of sterile wipes is pending.

PENDING

The composition of the rhNGF DP is copied below:

Table 1 Composition of rhNGF Drug Product

Ingredient	Quantity		Function	Quality Reference
	mg/ml	mg/drop*		
Active Ingredient(s)				
rhNGF Drug Substance	0.02**	0.00078	Active ingredient	Internal monograph
Excipients				
Trehalose dihydrate	47.03	1.834	(b) (4)	EP/USP current ed.
Mannitol	12.22	0.477		EP/USP current ed.
Na_2HPO_4 anhydrous	2.87	0.112		EP/USP current ed.
NaH_2PO_4 Dihydrate	1.22	0.048		EP/USP current ed.
Hypromellose	1.00	0.039		EP/USP current ed.
Macrogol 6000 (PEG 6000)	10.00	0.390		EP/USP current ed.
L-methionine	0.01	0.00039		EP/USP current ed.
Hydrochloric acid	up to pH 7.1-7.3			Ph. Eur. current ed.
Sodium hydroxide	up to pH 7.1-7.3			Ph. Eur. current ed.
Nitrogen	-			Ph. Eur. current ed.
(b) (4)				EP/USP current ed.

(b) (4)

P.2 Pharmaceutical Development

P.2.4 Container Closure System

The primary container closure system is a 2R vial, described in P.7.

The delivery system allows multiple uses over the daily treatments (6 withdrawals over 12 hours). It consists of a swabable vial adapter with self-sealing valve to be connected to the vial without opening the stopper, single-use 0.1 mL disposable pipettes to withdraw and instill single drops to the eye, and disinfectant swabs to clean the vial adapter valve before each use. (b) (4)

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(b) (4)

SATISFACTORY

CGMP Status

The assessment of manufacturing facilities is documented in panorama.

Conclusion

I. The BLA was reviewed from a sterility assurance and product quality microbiology perspective. The approvability recommendation is pending the review of additional information to be submitted by the applicant. The information will be reviewed in an addendum to this review memo.

II. Product quality aspects other than microbiology should be reviewed by OBP and CDRH.

III. The following inspection follow-up items were identified:

1. (b) (4)
2. The acceptance criteria for rate of rejected units after visual inspection should be established. A high rejection rate should result in an investigation.
3. (b) (4)

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Virginia Carroll

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Patricia Hughes Troost

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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

To: Administrative File, **STN 761094**
From: Maxwell Van Tassell, Ph.D., DMA Branch IV
Through: Maria Jose Lopez-Barragan, Ph.D., Acting Qual. Assess. Lead, DMA Branch IV
Subject: New 351(a) Biologics License Application (BLA)
US License: 2074
Applicant: Dompé farmaceutici S.p.A.
Product: Oxervate (cenegermin)
Indication: Treatment of (b) (4) Neurotrophic Keratitis
Dosage: Topical ophthalmic solution, 20 µg/mL
Facility: Via Campo di Pile snc, 67100
L'Aquila, Italy (FEI: 3004216297)
Receipt Date: 12/22/2017
Action Date: 8/22/2018

Recommendation for Approvability: The drug substance section of BLA STN 761094, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval with the following post-marketing commitments:

1. To revise the bioburden method to include a sample volume of at least 10 mL and conduct bioburden method qualification using three batches of in-process intermediates and bulk drug substance.
2. To conduct the endotoxin method qualification using (b) (4) batches of the bulk drug substance.

Review Summary

Dompé farmaceutici S.p.A. has submitted 351(a) BLA 761094 to obtain licensure of Oxervate (cenegermin). Oxervate is designed for the treatment of neurotrophic keratitis in adults by stimulating the proliferation and differentiation of sympathetic and sensory neurons in the eye.

BLA 761094 was submitted in eCTD on December 22, 2018. This review contains the assessment of the drug substance portion of the BLA from a microbiological quality perspective. For review of drug product microbiological aspects of the application, please see the review by Virginia Carroll, Ph.D.

Drug Substance Quality Microbiology Information Reviewed

Sequence number	Date	Description
eCTD 0002	06/23/2017	Quality Information Submission
eCTD 0014	01/30/2018	CMC Information Update
eCTD 0015	02/15/2018	Response to Information Request
eCTD 0031	05/16/2018	Response to Information Request

Review Assessment

3.2.S DRUG SUBSTANCE

3.2.S.1 GENERAL INFORMATION

The Oxervate (cenegermin) active substance is a recombinant human Nerve Growth Factor (rhNGF), optimized for expression in *E. coli* as ProNGF, which is identical to human NGF following enzymatic hydrolysis. rhNGF forms a noncovalent homodimer from 118 amino acid monomers of approximately 13 kDa each. (b) (4)

3.2.S.2 MANUFACTURE

3.2.S.2.1 Manufacturer(s)

(b) (4)

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The post-approval stability program incorporates bioburden and endotoxin testing to the same specifications as for DS release testing.

Information Request Submitted 03/27/18, Item #4:
Eliminate bioburden and endotoxin testing from the drug substance stability program, as microbial testing of a frozen bulk does not need to be monitored.

Applicant Response in eCTD SN0022:
The applicant agreed, but indicated that the testing could not be eliminated due to request from the EMA to monitor these parameters during the API shelf-life.

Reviewer Comment
Microbial testing of the frozen bulk DS is not required per current FDA expectations because microbial growth is not expected to occur in a frozen bulk.

SATISFACTORY

cGMP Status
Refer to Panorama for cGMP status of the relevant facilities.

Conclusion

I. The drug substance section of this BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval with the following post-marketing commitments that have been communicated to the sponsor:
   a. To revise the bioburden method to include a sample volume of at least 10 mL and conduct bioburden method qualification using three batches for each in-process intermediates and the bulk drug substance.
   b. To conduct the endotoxin method using (b) (4) batches of the bulk drug substance.

II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the appropriate division.

III. A pre-license inspection was conducted at Dompé farmaceutici S.p.A., L'Aquila, Italy, from April 16th-20th and April 23rd-24th, 2018 by OPF/DMA, OPF/DIA, and OBP (Refer to FACTS number 11835286). A seven-item Form FDA 483 was issued. Refer to Panorama for compliance status of the facilities.

Maxwell Van Tassell

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Maria Jose Lopez-Barragan

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